Gallos, I., Williams, H. M., Price, M. J., Merriel, A., Gee, H., Lissauer, D., ... Hofmeyr, G. J. (2015). Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Protocol). *Cochrane Database of Systematic Reviews*, (5). https://doi.org/10.1002/14651858.CD011689

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Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Protocol)

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Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis.
Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD011689.
DOI: 10.1002/14651858.CD011689.

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[Intervention Protocol]

Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis

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Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New, published in Issue 5, 2015.

Citation: Gallos ID, Williams HM, Price MJ, Merriel A, Gee H, Lissauer D, Moorthy V, Tunçalp Ö, Gülmezoglu AM, Deeks JJ, Hofmeyr GJ, Coomarasamy A. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2015, Issue 5. Art. No.: CD011689. DOI: 10.1002/14651858.CD011689.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

We aim to assess the clinical effectiveness and side-effect profile of uterotonic drugs to prevent PPH, and to generate a clinically useful ranking of available uterotonics according to their effectiveness and side-effects. We will explore the effects according to various key prognostic and treatment factors. The population of interest is women following a vaginal birth or a caesarean section in the hospital or the community setting. All uterotonic drugs considered by the WHO are eligible and the outcomes include blood loss-related outcomes and side-effects.

BACKGROUND

Description of the condition

An estimated 289,000 women died during childbirth in 2013 (WHO 2014). Almost all (99%) deaths occurred in developing countries where women give birth in communities with no medical support. Postpartum haemorrhage (PPH) is one of the leading causes of maternal death worldwide, accounting for up to a third of all deaths (Say 2014). Even when death is avoided, the need for blood transfusion, hysterectomy and the risks for morbidity are high, even in developed countries (Penney 2007).

The third stage of labour, defined as the period of time from birth until the delivery of the placenta, and the immediate postpartum period are the most hazardous periods of childbirth due to the risk

of PPH. The World Health Organization (WHO) defines PPH when blood loss after birth exceeds 500 mL in the first 24 hours (WHO 2012). Even though healthy women can easily cope with this amount of blood loss, for women of low-income countries who may be malnourished and anaemic it can cause considerable morbidity and mortality. The primary cause of PPH as defined by WHO is uterine atony, which accounts for 75% of cases (Weekes 1956). Even though risk factors for adverse maternal outcomes from severe haemorrhage have been identified (Souza 2013), often PPH is unpredictable as it occurs in the absence of identifiable clinical or historical risk factors (Combs 1991). Therefore, effective prevention of PPH is advocated for all women during childbirth (WHO 2012). The administration of uterotonic drugs routinely in the third stage of labour is a key intervention that prevents PPH, although there is uncertainty about which drug may be the most effective.

Description of the intervention

The administration of uterotonic drugs to prevent PPH is part of the active management of the third stage of labour, which can prevent two out of three events of PPH (Begley 2011). The active management of the third stage of labour refers to the administration of a uterotonic drug, early cord clamping, and controlled cord traction until delivery of the placenta. The WHO guideline development group recently revisited the evidence underpinning each component of the active management of third stage of labour and considered the use of uterotonics as the main intervention within this package (WHO 2012). Uterotonics are also essential for the treatment of PPH, but this is not considered in this review.

How the intervention might work

Many different uterotonic drugs have been used for preventing PPH. These include oxytocin, ergometrine, misoprostol, carbetocin, and others, alone or in combination.

Oxytocin

Oxytocin (Syntocinon®) is the most widely used uterotonic drug. At low doses, it produces rhythmic uterine contractions that are indistinguishable in frequency, force and duration from those observed during spontaneous labour, but at higher dosages, it causes sustained tetanic uterine contractions (MEDICINES.ORG.UK). It has a short half-life, approximately three to five minutes, and can be used as an infusion to maintain uterine contraction. When used intramuscularly, the latent phase lasts two to five minutes, but the uterine activity can last two to three hours (MEDICINES.ORG.UK). However, oxytocin cannot be used orally. It is unstable in ambient temperatures and it requires a cold chain through storage and transport. It should also not be given intravenously as a large bolus, because it can cause severe hypotension (Thomas 2007). Because of its anti-diuretic effect, water intoxication can occur with prolonged infusion of oxytocin (MEDICINES.ORG.UK). Oxytocin has a favourable side-effect profile and it is not significantly worse than placebo for common side-effects such as nausea and vomiting, but the evidence is scarce (Westhoff 2013).

Ergometrine

Ergometrine and methylergometrine are ergot alkaloids that increase the uterine muscle tone by causing continuous tetanic contractions. It has a latent phase of two to five minutes after intramuscular injection and the plasma half-life is 30 to 120 minutes (de Groot 1998). However, ergometrine and methylergometrine are unstable in heat with an unpredictable bioavailability, which precludes oral use (de Groot 1996). They are vasoconstrictive and increase the risk of hypertension postpartum (Liabsuetrakul 2007). Other side-effects with ergot alkaloids are pain after birth, nausea and vomiting (Liabsuetrakul 2007).

Misoprostol

Misoprostol is a prostaglandin E1 analogue, which is licensed for the prevention and treatment of gastric ulcers. It is well known for its off-label use as a uterotonic agent (Tuncalp 2012). It is water-soluble and heat stable (Davies 2001). It is absorbed after nine to 15 minutes after sublingual, oral, vaginal, and rectal use. The half-life is about 20 to 40 minutes. Oral and sublingual routes have the advantage of rapid onset of action, while the vaginal and rectal routes result in prolonged activity and greater bioavailability (Schaff 2005). However, it is associated with side-effects such as diarrhoea, abdominal pain, nausea and vomiting, shivering and pyrexia (Tuncalp 2012). Other prostaglandins are available in injectable form such as PGF2alpha analogues (carboprost). However, PGF2alpha analogues are only used to treat PPH when it is not controlled by other methods due their cost and availability.

Carbetocin

Carbetocin is a newer long-acting synthetic analogue of oxytocin with agonist properties. After intravenous injection, it produces tetanic uterine contractions within two minutes, lasting for approximately six minutes followed by rhythmic contractions for 60 minutes (Hunter 1992). When carbetocin is administered by an intramuscular injection the tetanic contractions last for approximately 11 minutes and the rhythmic contractions for 120 minutes (Hunter 1992). Carbetocin is heat stable and the side-effect profile appears to be similar to oxytocin (Su 2012).

Combination drugs

The use of combinations of uterotonic drugs is also popular and the most commonly used preparation is oxytocin plus ergometrine (syntometrine®). This combination is associated with a statistically significant reduction of PPH above 500 mL when compared with oxytocin alone, attributable to the additive ergometrine effect (odds ratio (OR) 0.82, 95% confidence interval (CI) 0.71, 0.95) (McDonald 2004). Another combination is oxytocin plus misoprostol that is also found to be associated with a small reduction in PPH above 500 mL (risk ratio (RR) 0.71, 95% CI 0.53, 0.95) (Tuncalp 2012). However, both these combinations are associated with significant side-effects and despite the small difference in PPH, there is no difference found for severe PPH when compared to oxytocin. This has led the WHO to recommend oxytocin over these combinations (WHO 2012).

The WHO recommends that all women giving birth should be offered uterotonics during the third stage of labour for the prevention of PPH; oxytocin (intramuscular/intravenous, 10 international units (IU) is the uterotonic drug of choice (WHO 2012). Other injectable uterotonics and misoprostol are recommended as alternatives for the prevention of PPH in settings where oxytocin is not available. Carbetocin is found to reduce the need for additional uterotonics (RR 0.62; 95% CI 0.44, 0.88), but it is more expensive and not better than oxytocin for preventing PPH above 1000 mL (WHO 2012).

Why it is important to do this review

Several Cochrane reviews have compared individual uterotonic drugs with other uterotonic drugs or with placebo or no treatment (Begley 2011; Liabsuetrakul 2007; McDonald 2004; Su 2012; Tuncalp 2012; Westhoff 2013). A standard pairwise meta-analysis however, can only compare two drugs that have been directly compared in head-to-head trials (direct evidence). In the absence of a single high-quality, randomised controlled trial comparing all available uterotonic drugs, uncertainty remains about which is the most effective drug for preventing PPH. A network meta-analysis allows evidence synthesis when there is a range of interventions available, in order to make comparisons across all pairs of interventions using direct and indirect trial data in a coherent manner. Indirect evidence is obtained by inferring the relative effectiveness of two competing treatments through a common comparator (Lumley 2002). Thus a network meta-analysis produces estimates of relative effects for each treatment compared with every other in the network, even though some pairs may not have been directly compared, and has the potential to reduce the uncertainty in effect estimates (Caldwell 2005). It also allows the calculation of the probability that each treatment is the best for any given outcome and can be used to identify gaps in the evidence base, thus informing future research agendas.

OBJECTIVES

We aim to assess the clinical effectiveness and side-effect profile of uterotonic drugs to prevent PPH, and to generate a clinically useful ranking of available uterotonics according to their effectiveness and side-effects. We will explore the effects according to various key prognostic and treatment factors. The population of interest is women following a vaginal birth or a caesarean section in the hospital or the community setting. All uterotonic drugs considered by the WHO are eligible and the outcomes include blood loss-related outcomes and side-effects.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled comparisons or cluster trials of effectiveness or side-effects of uterotonic drugs for preventing PPH will be included. Quasi-randomised trials and cross-over trials will be excluded.

Types of participants

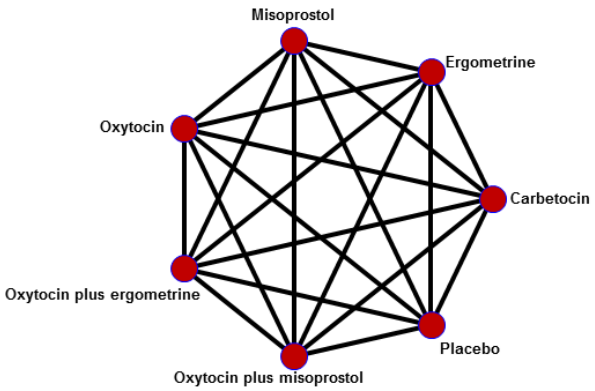
The review will consider studies including pregnant women following a vaginal birth or caesarean section conducted in both hospital and community settings.

Types of interventions

We will consider trials of uterotonics described by WHO (WHO 2012) (oxytocin, ergometrine, misoprostol, carbetocin, or combinations of uterotonics) administered prophylactically by healthcare professionals for preventing PPH via any systemic route (sublingual, subcutaneous, intramuscular, rectal, oral, intravenous bolus and/or infusion) compared with another uterotonic or with placebo or no treatment. If we identify in the included studies interventions that we are not aware of, we will consider them as eligible and include them in the network after assessing their comparability with those named above. We will include trials in which non-pharmacologic co-interventions such as controlled cord traction, cord clamping, or uterine massage was performed as a randomised intervention in all arms of the trial. We will stratify all drugs according to mode of birth, prior risk of PPH, healthcare setting, specific dosage, regimen and route, to detect inequalities in subgroups that could affect comparative effectiveness.

Figure 1 shows the overall network of eligible comparisons in the review at a drug level.

Figure 1. Overall network of eligible comparisons at a class level.



Multi-arm trials that compare different dosages, regimens or routes of one uterotonic drug, but also compare those versus another uterotonic drug, will be included. Intervention arms of different dosages, regimens or routes of the same uterotonic drug will be merged together for the global analysis of all outcomes and treated as separate independent comparisons only for the relevant subgroup analysis according to dosage, regimen and route of drug administration, while taking into account the correlation between the comparisons. We will exclude trials comparing exclusively different dosages, regimens or routes of administration of the same uterotonic drug. The review will be restricted to studies evaluating uterotonic drugs administered systemically at the birth of the baby for preventing PPH. Studies considering non-uterotonic drugs, uterotonic drugs administered locally (for example, via intraumbilical or intrauterine routes) or at a later stage of delivery (for example, for the treatment of PPH or for retained placenta) will be excluded.

We assume that any patient that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the eligible uterotonic drugs.

Types of outcome measures

We will estimate the relative effects and ranking of the competing interventions according to the following outcomes.

Primary outcomes

The primary outcomes of the review are:

1. primary PPH above or equal to 500 mL; and
2. primary PPH above or equal to 1000 mL.

Secondary outcomes

The secondary outcomes of the review are:

1. maternal death;
2. maternal deaths or severe morbidity events adapted from WHO "near miss" criteria (WHO 2011) to include major surgery (laparotomy, uterine artery ligation, internal iliac artery ligation, B-Lynch suture, hysterectomy, extensive vaginal repair, admission to the intensive care unit, or vital organ failure (temporary or permanent);
3. additional uterotonics requirement;
4. transfusion requirement;
5. manual removal of the placenta;
6. mean volumes of blood loss (mL);
7. mean durations of the third stage of labour (minutes);
8. change in haemoglobin measurements before and after birth (g/L);
9. clinical signs of blood loss;
10. neonatal unit admission requirement;
11. breastfeeding at discharge; and
12. side-effects such as nausea, vomiting, hypertension, headache, tachycardia, hypotension, abdominal pain, fever and shivering in the first 24 hours postpartum.

Search methods for identification of studies

The following methods section of this protocol is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register.

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator 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;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the 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 can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we will search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished trial reports. The search terms we plan to use are given in Appendix 1 and any changes to this will be documented fully in the review.

Searching other resources

We will retrieve additional relevant references cited in papers identified through the above search strategy. We will search for the full texts of studies identified as abstracts.

We will seek information from primary authors to investigate whether these studies meet eligibility criteria, and to obtain outcome and study data. Trials that compare at least two of the drugs are eligible and we shall search for all possible comparisons formed by the drugs of interest.

We will not apply any language or date restrictions.

Data collection and analysis

Selection of studies

Two review authors will retrieve and independently assess for inclusion all the potential studies we identify. We will resolve any disagreement through discussion or, if required, in consultation with a third person.

We will create a Study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into a Microsoft Access document and Review Manager Software (RevMan 2014) and check for accuracy. When information is unclear, we will attempt to contact authors of the original reports to provide further details. The following data will be extracted.

Outcome data

From each included study we will extract: the number of participants, the gestational age and the parity of participants, and any exclusion criteria. We will also extract: the interventions being compared, and their respective primary and secondary outcomes. All relevant arm level data will be extracted (e.g. number of events and number of patients for binary outcomes).

Data on potential effect modifiers

From each included study we will extract the following study, intervention and population characteristics that may act as effect modifiers.

1. mode of delivery (vaginal delivery or caesarean section);
2. prior risk of PPH (as defined by trialists and categorised as low, high, mixed or not stated);
3. dosage, regimen, and route of drug administration (sublingual, subcutaneous, intramuscular, rectal, oral, intravenous bolus and/or infusion); and
4. setting of the study (community or hospital).

Other data

From each included study we will extract the following additional information.

1. country or countries in which the study was performed;
2. date of publication;
3. type of publication (full text publication, abstract publication, unpublished data); and
4. trial registration reference.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

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

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the methods as:

- 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); or
- unclear risk of bias.

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

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess the methods as:

- 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); or
- unclear risk of bias.

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

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess the methods as:

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

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

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess methods used to blind outcome assessment as:

- 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)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state 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 is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups and less than 10% of missing outcome data);
- 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 or more than 10% of missing outcome data); or
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk of bias.

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

We will describe for each included study any important concerns about other possible sources of bias, such as the source of funding and potential conflicts of interest.
We will assess these interests as:

- low risk of other bias (public funding or no funding and no significant conflicts of interest identified);
- high risk of other bias (industry funding or significant conflicts of interest identified); or
- unclear risk of other bias.

Another source of bias could be generated by the method of measuring blood loss. We will assess the method described in each study and classify it as at:

- low risk of other bias (objective measurements such as weighing sponges, measurements in drapes, volumetric assessment, tagged red cells, etc);
- high risk of other bias (subjective measurement such as clinical or visual estimates); or
- unclear risk of other bias (unspecified methods of measurement).

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis for information about how the risk of bias will be incorporated in the sensitivity analysis.

Measures of treatment effect

Relative treatment effects

We will summarise relative treatment effects for dichotomous outcomes as the posterior median odds ratio (MOR) and 95% credible intervals (CrIs). For continuous scales of measurement we will use the posterior mean difference (MD), or the standardised mean difference (SMD) with 95% CrIs if different scales have been used. Where the target parameter is the effect of treatment on the change in a continuous measure, such as the change in haemoglobin between baseline and postpartum we will, where possible, account for the within-patient correlation between baseline and postpartum estimates (Dias 2013).

Relative treatment ranking

We will also estimate the ranking probabilities for all treatments of being at each possible rank for each intervention (conditional on the model and specified vague priors). Then, we will obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA). SUCRA can also be expressed as a percentage interpreted as the percentage of effectiveness or side-effects of a treatment that would be ranked first without uncertainty. For primary outcomes, we will assess the robustness of these findings in sensitivity analysis by considering estimates of mean rank with 95% CrIs.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their standard errors using the methods described in the *Handbook* [Section 16.3.4 or 16.3.6] using an estimate of the intracluster correlation co-efficient (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. However, we will perform sensitivity analysis to assess the validity of this assumption for primary outcomes.

Cross-over trials

This type of trial is not appropriate for this intervention.

Multi-arm trials

Multi-arm trials will be included and we will account for the correlation between the effect sizes in the network meta-analysis. We will treat multi-arm studies as multiple independent comparisons in pairwise meta-analyses.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of clinical and methodological heterogeneity within treatment comparisons

To evaluate the presence of clinical heterogeneity, we will generate descriptive statistics for trial and study population characteristics across all eligible trials that compare each pair of interventions. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics.

Assessment of transitivity across treatment comparisons

We will assess the assumption of transitivity by comparing the distribution of potential effect modifiers across the different pairwise comparisons. In this context we expect that the transitivity assumption will hold assuming the following.

1. The common treatment used to compare different uterotonics indirectly is similar when it appears in different trials (e.g., oxytocin is administered in a similar way in oxytocin versus misoprostol trials and in oxytocin versus oxytocin plus ergometrine trials).
2. All pairwise comparisons do not differ with respect to the distribution of effect modifiers (e.g., the design and study characteristics of oxytocin versus misoprostol trials are similar to oxytocin versus oxytocin plus ergometrine trials).

The assumption of transitivity will be evaluated epidemiologically by comparing the clinical and methodological characteristics of sets of studies grouped by treatment comparisons.

Assessment of reporting biases

We will assess potential reporting bias for the primary outcomes by assessing the sensitivity of results to exclusion of studies with fewer than 400 participants.

Data synthesis

Methods for direct treatment comparisons

Initially, we will perform standard pairwise meta-analyses using a random-effects model in WinBUGS for every treatment comparison with at least two studies. Review Manager Software (RevMan 2014) will be used to compute the I^2 statistic.

Methods for indirect and mixed comparisons

We will perform a network meta-analysis within a Bayesian framework using WinBUGS 1.4.3 (Lunn 2000). Our *a priori* belief is that a random-effects model is more appropriate because we expect a degree of clinical heterogeneity between trials. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity

In standard pairwise meta-analyses we will estimate different heterogeneity variances for each pairwise comparison. In network meta-analysis we will assume a common estimate for the heterogeneity variance across the different comparisons. Non-informative priors will be used as described in the NICE technical support document 2 (Dias 2014).

Measures and tests for heterogeneity

We will assess statistically the presence of heterogeneity within each pairwise comparison for the primary outcomes using the I^2 statistic and its 95% CI that measures the percentage of variability that cannot be attributed to random error.

The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter (τ^2) estimated from the network meta-analysis models. For dichotomous outcomes the magnitude of the heterogeneity variance will be compared with the empirical distribution as derived by Turner (Turner 2012). For the primary outcomes, we will also estimate a total I^2 value for heterogeneity in the network as described elsewhere.

Assessment of statistical inconsistency

The statistical agreement between the various sources of evidence in a network of interventions (consistency) will be evaluated by global and local approaches to complement the evaluation of transitivity.

Local approaches for evaluating inconsistency

To evaluate the presence of inconsistency locally we will use the node-splitting approach within the Bayesian framework. This technique allows us to split the information contributing to estimates of a parameter (node), into two distinct components: the "direct" evidence from direct comparison trials or multi-arm trials that contain this contrast, and the "indirect" based on all the remaining evidence. This process will be applied to all contrasts in the network. We will use node splitting to also generate intuitive graphics showing the difference between the "direct", "indirect" and the combined information.

Global approaches for evaluating inconsistency

To check the assumption of consistency in the entire network we will use the 'Lu & Ades' (Lu 2006) model. Model comparison will be based on the Deviance Information Criterion (DIC) statistic, with a difference of five or more being considered meaningful (Spiegelhalter 2002). In addition, the fit of the network meta-analysis models will be assessed using the posterior mean residual deviance. If there is a difference of five or more between the number of data points and the posterior mean residual deviance then a more detailed investigation will be performed to attempt to identify the reasons for poor fit. In a well-fitting model, the posterior mean deviance should be approximately the same as the number of unconstrained data points (Dempster 1997). Due to the way the residual deviance is calculated, if there are zero events in one of the arms of a trial there may be computational difficulties and the residual deviance may be artificially inflated. Therefore, for the purposes of assessing model fit, the contribution of these trials to the residual deviance and the number of independent data points, will not be included. We will also provide plots of the individual contributions to the deviance of each data point for the network meta-analysis compared to the 'Lu & Ades' model. If inconsistency cannot be explained or modelled, then the network meta-analysis will not be performed for that outcome.

Investigation of heterogeneity and inconsistency

If we find important heterogeneity and/or inconsistency, we will explore the possible sources for both primary and secondary outcomes. If sufficient studies are available, we will perform meta-regression or subgroup analyses by using the following potential effect modifiers as possible sources of inconsistency and/or heterogeneity.

- Mistakes and inconsistencies in data extraction and entry.
- Population: prior risk of PPH (high versus low), mode of delivery (vaginal delivery versus caesarean section), setting (hospital versus community).
- Intervention: dose, regimen or route.
- Quality of the studies: studies will be ranked as "low risk of bias" if they are double-blinded, and have allocation concealment with little loss to follow-up (less than 10%). The concealed studies with assessor blinding and little loss to follow-up (less than 10%) will be ranked as "intermediate risk of bias" and the rest as "high risk of bias". We consider that assessor blinding is likely to be very important, in order to eliminate any risk of bias in subjective measurements or estimates of blood loss (not all studies measure this outcome objectively). We consider protocol publication in advance of the results to be an unsuitable criterion for sensitivity analyses, because protocol publication only became widespread in recent years.
- Funding source (high versus low risk of bias).
- Whether an objective method of outcome assessment was employed (objective versus subjective). Objective methods of blood loss measurement are considered to be all methods that employ a measurement of the blood loss. This is in contrast to subjective methods where a healthcare professional is estimating the blood loss, usually visually.
- Trial size (excluding small studies, in recognition of the greater likelihood for small studies than large or multi-centre studies to suffer publication bias). In terms of trial size, there is evidence that smaller studies can exaggerate estimated benefits (Nüesch 2010). However, the cut-off for deciding the definition of a small study can vary between research topics. For this topic, it appears that trials with more than 400 participants are more likely to be of higher quality, prospectively registered and overall at low risk of bias.
- Randomisation unit (cluster versus individual).

Subgroup analysis

For the primary outcomes we will carry out the following subgroup analyses.

- Population: prior risk of PPH (high versus low), mode of delivery (vaginal delivery versus caesarean section), setting (hospital versus community).
- Intervention: dose, regimen or route.

We will assess subgroup differences by evaluating the relative effects and assessment of model fit.

Sensitivity analysis

For the primary outcomes we will perform sensitivity analysis for the following.

- Quality of the studies as described previously.
- Funding source as described previously.

- Whether an objective method of outcome assessment was employed (objective versus subjective).
- Trial size as described previously.
- Randomisation unit (cluster versus individual).
- Choice of relative effect measure (risk ratio versus odds ratio).
- Use of fixed-effect versus random-effects model.
- Choice of prior distribution.

Differences will be assessed by evaluating the relative effects and assessment of model fit.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this protocol has been commented on by five peers (an editor and four referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Advisers.

This review is undertaken as part of independent research funded by the UK National Institute for Health Research (Health Technology Assessment Project 14/139/17 Uterotonic drugs for preventing postpartum haemorrhage: a network meta-analysis and cost-effectiveness analysis). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

The World Health Organization and Ioannis D Gallos, Helen M Williams, Malcolm J Price, Abi Merriel, Harold Gee, David Lissauer, Vidhya Moorthy, Jonathan J Deeks, G Justus Hofmeyr and Arri Coomarasamy retain copyright and all other rights in their respective contributions to the manuscript of this Review as submitted for publication.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search terms

ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP)
Third stage AND labo(u)r AND oxytocin
Third stage AND labo(u)r AND misoprostol
Third stage AND labo(u)r AND carbetocin
Third stage AND labo(u)r AND ergometrine
uterotonic* AND oxytocin
uterotonic* AND misoprostol
uterotonic* AND carbetocin
uterotonic* AND ergometrine
uterotonic* AND labo(u)r
uterotonic* AND h(a)emorrhage
h(a)emorrhage AND postpartum AND ergometrine
h(a)emorrhage AND postpartum AND oxytocin
h(a)emorrhage AND postpartum AND carbetocin
h(a)emorrhage AND postpartum AND misoprostol

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Ioannis D Gallos (IDG) and Arri Coomarasamy (AC) conceived the idea for this study. IDG, Helen M Williams (HMW), Malcolm J Price (MP), Abi Merriel (AM), Harold Gee (HG), David Lissauer (DL), Vidhya Moorthy (VM), Özge Tunçalp (OT), A Metin Gülmezoglu (AMG), Jonathan J Deeks (JJD), G Justus Hofmeyr (GJH) and AC designed the meta-analysis. MP and JJD provided statistical advice and input. IDG drafted the protocol. HMW, MP, AM, HG, DL, OT, AMG, JJD, GJH and AC reviewed the protocol and provided critical feedback.

DECLARATIONS OF INTEREST

Ioannis D Gallos (IDG): is a co-applicant to the UK National Institute for Health Research HTA Project Award 14/139/17 entitled "Uterotonic drugs for preventing postpartum haemorrhage: a network meta-analysis and cost-effectiveness analysis".

Helen M Williams (HMW): is part-funded by the Birmingham Women's NHS Foundation Trust, and a co-applicant to the UK National Institute for Health Research HTA Project Award 14/139/17 entitled "Uterotonic drugs for preventing postpartum haemorrhage: a network meta-analysis and cost-effectiveness analysis".

Malcolm J Price (MP) is funded as a research fellow by the UK Medical Research Council (MRC) Project Award MR/J013595/1, and a co-applicant to the UK National Institute for Health Research HTA Project Award 14/139/17 entitled "Uterotonic drugs for preventing postpartum haemorrhage: a network meta-analysis and cost-effectiveness analysis".

Abi Merriel (AM): is part-funded by Ammalife (UK Registered Charity 1120236) and the Birmingham Women's NHS Foundation Trust.

Harold Gee (HG): is a Trustee of Ammalife (UK Registered Charity 1120236).

David Lissauer (DL): is a Trustee of Ammalife (UK Registered Charity 1120236).

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IDG, OT, AMG, GJH, and AC have been involved in one or more previous or ongoing trials related to the use of uterotonics for the prevention of PPH that could potentially be eligible for inclusion in this review. Ferring Pharmaceuticals and Novartis have supplied carbetocin and oxytocin to these studies, and an ongoing study is additionally supported by Merck for Mothers. IDG, OT, AMG, GJH, and AC will not participate in decisions regarding inclusion of these trials in this review or any tasks related to them such as data extraction or quality assessment.

SOURCES OF SUPPORT

Internal sources

- University of Birmingham, UK.

The authors of this review are employed by the institutions indicated by their respective affiliations except where otherwise stated.

- World Health Organization, Switzerland.

The authors of this review are employed by the institutions indicated by their respective affiliations except where otherwise stated.

- Sandwell and West Birmingham NHS Trust, UK.

The authors of this review are employed by the institutions indicated by their respective affiliations except where otherwise stated.

- University of the Witwatersrand, South Africa.

The authors of this review are employed by the institutions indicated by their respective affiliations except where otherwise stated.

External sources

- National Institute for Health Research, UK.

This review is undertaken as part of independent research funded by the UK National Institute for Health Research (Health Technology Assessment Project 14/139/17 Uterotonic drugs for preventing postpartum haemorrhage: a network meta-analysis and cost-effectiveness analysis).

- Birmingham Women's NHS Foundation Trust, UK.

Additional financial support to meet the employment costs of Helen M Willliams (HMW) and Abi Merriel (AM) is provided by Birmingham Women's NHS Foundation Trust.

- Medical Research Council, UK.

Additional financial support to meet the employment costs of Malcolm J Price (MP) is provided by the Medical Research Council (Project MR/J013595/1).

- Ammalife, UK.

Additional financial support to meet the employment costs of Abi Merriel (AM) is provided by Ammalife (UK Registered Charity 1120236).