Uterotonic drugs to prevent postpartum haemorrhage: a network meta-analysis

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Declared competing interests of authors: Ioannis Gallos, Metin Gülmezoglu, Justus Hofmeyr and Arri Coomarasamy have been involved in one or more previous or ongoing trials related to the use of uterotonics for the prevention of postpartum haemorrhage that were considered for inclusion in this review. Ferring Pharmaceuticals (Saint-Prex, Switzerland) and Novartis Pharmaceuticals UK Ltd (Surrey, UK) have supplied carbetocin and oxytocin to these studies. Ioannis Gallos, Metin Gülmezoglu, Justus Hofmeyr and Arri Coomarasamy have not participated in decisions regarding inclusion of these trials in this review or any tasks related to them such as data extraction or quality assessment. Arri Coomarasamy is involved in a World Health Organization-sponsored randomised controlled trial of carbetocin versus oxytocin, supported by Merck for Mothers (Merck & Co., Inc., Kenilworth, NJ, USA). Metin Gülmezoglu was involved in a large multicentre trial included in the review as part of the central co-ordination unit. As part of the central co-ordination unit, he is also involved in an ongoing World Health Organization-sponsored randomised controlled trial of carbetocin versus oxytocin supported by Merck for Mothers. Abi Merriel is part-funded by Ammalife (a UK-registered charity 1120236) and the Birmingham Women's NHS Foundation Trust. Harry Gee and Arri Coomarasamy are trustees of Ammalife. Jonathan Deeks is a member of the Health Technology Assessment (HTA) Commissioning Board and the HTA Efficient Study and Designs Board.

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Scientific summary

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Background

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality worldwide. Prophylactic uterotonic drugs can reduce blood loss and are recommended for routine use. There are several different uterotonic drugs for preventing PPH. These drugs include ergometrine, misoprostol (Cytotec®; Pfizer Inc., New York, NY, USA), misoprostol plus oxytocin (Syntocinon®; Novartis International AG, Basel, Switzerland), carbetocin (Pabal®; Ferring Pharmaceuticals, Saint-Prex, Switzerland), ergometrine plus oxytocin and oxytocin when used alone. Currently, oxytocin [given intramuscularly/intravenously at a dose of 10 international units (IU)] is the uterotonic drug of choice. Several pairwise meta-analyses have compared two drugs at a time already, but there is no single global analysis to examine the relative effects and ranking of all available drugs based on all relevant evidence.

Objectives

- To identify the most effective and cost-effective uterotonic drug(s) to prevent PPH, and to generate a clinically useful ranking of available uterotonics according to their effectiveness and side-effect profile.
- To develop a decision model to evaluate the cost-effectiveness of the different drugs and combinations thereof for preventing PPH in the UK and, when evidence is available, to explore effectiveness and cost-effectiveness in different treatment subgroups (different dosages, regimens and routes of administration of each uterotonic drug) and population subgroups (prior risk of PPH, mode of birth and health-care setting).

Methods

A systematic review was performed of randomised trials of pregnant women following a vaginal birth or caesarean section conducted in hospital and community settings. Included were trials of uterotonics administered prophylactically by health-care 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. All drugs were stratified according to the mode of birth, prior risk of PPH, health-care setting, specific dosage, regimen and route of drug administration, to detect inequalities in subgroups that could affect comparative effectiveness. The study estimated relative effects and ranking of the competing interventions according to the prevention of PPH blood loss of $\geq$ 500 ml and $\geq$ 1000 ml as primary outcomes. Secondary outcomes included maternal mortality or morbidity, requirement for additional uterotonics, transfusion or manual removal of placenta, mean volumes of blood loss, mean durations of the third stage, changes in haemoglobin (Hb) measurements and patient-reported outcomes, such as clinical signs of excessive blood loss and side effects such as nausea, vomiting, hypertension, headache, tachycardia, hypotension, abdominal pain, fever and shivering in the first 24 hours post partum.

The Pregnancy and Childbirth Trials Register, ClinicalTrials.gov and the World Health Organization (WHO)'s International Clinical Trials Registry Platform (ICTRP) were searched for published and unpublished trial reports until September 2015 (updated October 2017). Additional references, cited in papers, were identified through the above search strategy and the full texts of the studies identified as relevant were obtained. No language or date restrictions were applied. Information was sought from primary authors to investigate whether or not these studies met the study's eligibility criteria, and to obtain outcome and

study data. Three review authors retrieved trials, independently assessed potential trials for inclusion, independently extracted data from included trials and assessed the risk of bias for each trial using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. Oxford: The Cochrane Collaboration; 2011).

For this review, it was assumed that any woman who meets the inclusion criteria is, in principle, equally likely to be randomised to any of the eligible uterotonic drugs. A standard pairwise meta-analysis was performed using a random-effects model and network meta-analysis (NMA) within a frequentist framework using multivariate random-effects meta-analysis models in Stata® (StataCorp LP, College Station, TX, USA), exploiting the direct and indirect randomised evidence to determine the relative effects and ranking. The probability that each treatment is the most effective was computed, as well as the cumulative probabilities of a strategy being ranked at least first, second or third.

Results

The study comprised 137 randomised trials, involving 87,466 women in the NMA and compared six drugs among themselves and with placebo or no treatment for the prevention of PPH. The most effective drug strategies for prevention of PPH blood loss of ≥ 500 ml were ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin. All three strategies were found to reduce the risk of PPH blood loss of ≥ 500 ml compared with the standard drug, oxytocin [ergometrine plus oxytocin: risk ratio (RR) 0.69, 95% confidence interval (CI) 0.57 to 0.83; carbetocin: RR 0.72, 95% CI 0.52 to 1.00; misoprostol plus oxytocin: RR 0.73, 95% CI 0.6 to 0.9]. Each of these three strategies had an almost 100% cumulative probability of being ranked the first, second or third most effective drug. Oxytocin was ranked fourth, with an almost 0% cumulative probability of being ranked in the top three. Similar rankings of these three strategies were noted for the reduction of PPH blood loss to ≥ 1000 ml, but the CIs were wider as this outcome is more rare (ergometrine plus oxytocin: RR 0.77, 95% CI 0.61 to 0.95; carbetocin: RR 0.70, 95% CI 0.38 to 1.28; misoprostol plus oxytocin: RR 0.90, 95% CI 0.72 to 1.14). However, again these three strategies had an almost 80% probability of being ranked the first, second or third most effective drug. Oxytocin was ranked fourth, with an approximately 20% probability of being ranked in the top three for this outcome.

For the majority of the secondary outcomes, such as requirement for additional uterotonics, transfusion, change in Hb concentration and blood loss as a continuous outcome, again, ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were the three most effective strategies. Oxytocin was consistently ranked fourth behind these three strategies.

In terms of side effects, ergometrine and ergometrine plus oxytocin had the poorest ranking for nausea, vomiting, hypertension and headache. Misoprostol and misoprostol plus oxytocin had the poorest ranking for fever and shivering. Carbetocin and oxytocin had the fewest side effects, similar to the placebo or no treatment.

The subgroup analyses of primary outcomes by mode of birth, prior risk of PPH, health-care setting and by dose and route of the drugs had limited power and were unstable, but generally were in agreement with the overall results. However, in the sensitivity analyses, when the analysis was restricted to high-quality studies or studies rated as being at a low risk of bias, carbetocin lost its ranking and was comparable with oxytocin. However, ergometrine plus oxytocin was still ranked higher than oxytocin for both primary outcomes. When the analysis was restricted to large studies, it was found that there were no studies investigating carbetocin and, again, ergometrine plus oxytocin and misoprostol plus oxytocin were ranked higher than oxytocin.

Alongside the NMA, a cost-effectiveness analysis was performed to identify the most cost-effective uterotonic drug for the prevention of PPH from the UK perspective. The results of the cost-effectiveness analysis for vaginal birth, without considering side effects, showed that ergometrine plus oxytocin and carbetocin were the leading strategies. The estimated incremental cost-effectiveness ratio (ICER) for prevention with carbetocin compared with ergometrine plus oxytocin was £1888.75 per case of PPH blood loss of ≥ 500 ml avoided. When side effects were included in the analysis, the dominant strategies were carbetocin and oxytocin. The estimated ICER for prevention with carbetocin compared with oxytocin was £927.65 per case of PPH blood loss of ≥ 500 ml avoided. The results for birth by caesarean section were mixed because of a large number of missing data. The probability of PPH for ergometrine and ergometrine plus oxytocin was unavailable as no trials were found using these drugs for preventing PPH in caesareans, so these drugs were excluded from the analysis. In caesareans, misoprostol plus oxytocin and carbetocin were the leading strategies. When side effects were excluded from the analysis, misoprostol plus oxytocin dominated all other strategies for the primary outcome of cost per case of PPH blood loss of ≥ 500 ml avoided in women undergoing caesarean sections. When side effects were included in the analysis, the estimated ICER for prevention with misoprostol plus oxytocin compared with carbetocin was £2480.19 per case of PPH blood loss of ≥ 500 ml avoided. In the sensitivity analysis, ergometrine and ergometrine plus oxytocin were also included, by making assumptions about the effectiveness of these strategies from the overall NMA, and found that ergometrine plus oxytocin dominated all other strategies. The results of the probabilistic sensitivity analysis show moderate uncertainty in the input parameters. This reflects the differing results shown in the principal analysis.

Conclusions

This NMA found that ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin are more effective uterotonic drug strategies for preventing PPH than the current standard drug of oxytocin. However, ergometrine plus oxytocin and misoprostol plus that of oxytocin cause significant side effects. Carbetocin has a favourable side-effect profile similar to oxytocin and the placebo or the control. Carbetocin is also more cost-effective than oxytocin, being the least costly in all but one of the cost-effectiveness analyses, despite the unit cost for carbetocin being relatively more expensive. However, carbetocin trials are small and of poor quality and when the analysis is restricted to high-quality trials, carbetocin loses its top ranking and does not appear to be more effective than oxytocin for both primary outcomes; however, there is significant uncertainty around the effect estimate. There is a need for a large high-quality trial comparing carbetocin with the current standard treatment of oxytocin for the prevention of PPH; such a trial is currently being conducted by the WHO.

Study registration

The study is registered as PROSPERO CRD42015020005; Cochrane Pregnancy and Childbirth Group (substudy) reference number 0871; PROSPERO–Cochrane (substudy) reference number CRD42015026568; and sponsor reference number ERN_13–1414 (University of Birmingham, Birmingham, UK).

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