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[Intervention Review]

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

Ioannis D Gallos[1], Helen M Williams[1], Malcolm J Price[2], Abi Merriel[3], Harold Gee[4], David Lissauer[5], Vidhya Moorthy[6], Aurelio Tobias[1], Jonathan J Deeks[7], Mariana Widmer[8], Özge Tunçalp[8], Ahmet Metin Gülmezoglu[8], G Justus Hofmeyr[9], Arri Coomarasamy[1]

[1]Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK. [2]School of Health and Population Sciences, University of Birmingham, Birmingham, UK. [3]Bristol Medical School, University of Bristol, Southmead Hospital, UK. [4]Birmingham, UK. [5]School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK. [6]Department of Obstetrics and Gynaecology, Sandwell and West Birmingham NHS Trust, Birmingham, UK. [7]Institute of Applied Health Research, University of Birmingham, Birmingham, UK. [8]UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland. [9]Walter Sisulu University, University of the Witwatersrand, Eastern Cape Department of Health, East London, South Africa

**Contact address:** Ioannis D Gallos, Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research, University of Birmingham, C/o Academic Unit, 3rd Floor, Birmingham Women's Hospital Foundation Trust, Mindelsohn Way, Birmingham, B15 2TG, UK. i.d.gallos@bham.ac.uk, gallosioannis@gmail.com.

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## ABSTRACT

### Background

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality worldwide. Prophylactic uterotonic drugs can prevent PPH, and are routinely recommended. There are several uterotonic drugs for preventing PPH but it is still debatable which drug is best.

### Objectives

To identify the most effective uterotonic drug(s) to prevent PPH, and generate a ranking according to their effectiveness and side-effect profile.

### Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register (1 June 2015), ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for unpublished trial reports (30 June 2015) and reference lists of retrieved studies.

### Selection criteria

All randomised controlled comparisons or cluster trials of effectiveness or side-effects of uterotonic drugs for preventing PPH.

Quasi-randomised trials and cross-over trials are not eligible for inclusion in this review.

### Data collection and analysis

At least three review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We estimated the relative effects and rankings for preventing PPH ≥ 500 mL and PPH ≥ 1000 mL as primary outcomes. We performed pairwise meta-analyses and network meta-analysis to determine the relative effects and rankings of all available drugs. We stratified our primary

outcomes according to mode of birth, prior risk of PPH, healthcare setting, dosage, regimen and route of drug administration, to detect subgroup effects.The absolute risks in the oxytocin are based on meta-analyses of proportions from the studies included in this review and the risks in the intervention groups were based on the assumed risk in the oxytocin group and the relative effects of the interventions.

**Main results**

This network meta-analysis included 140 randomised trials with data from 88,947 women. There are two large ongoing studies. The trials were mostly carried out in hospital settings and recruited women who were predominantly more than 37 weeks of gestation having a vaginal birth. The majority of trials were assessed to have uncertain risk of bias due to poor reporting of study design. This primarily impacted on our confidence in comparisons involving carbetocin trials more than other uterotonics.

The three most effective drugs for prevention of PPH ≥ 500 mL were ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination. These three options were more effective at preventing PPH ≥ 500 mL compared with oxytocin, the drug currently recommended by the WHO (ergometrine plus oxytocin risk ratio (RR) 0.69 (95% confidence interval (CI) 0.57 to 0.83), moderate-quality evidence; carbetocin RR 0.72 (95% CI 0.52 to 1.00), very low-quality evidence; misoprostol plus oxytocin RR 0.73 (95% CI 0.60 to 0.90), moderate-quality evidence). Based on these results, about 10.5% women given oxytocin would experience a PPH of ≥ 500 mL compared with 7.2% given ergometrine plus oxytocin combination, 7.6% given carbetocin, and 7.7% given misoprostol plus oxytocin. Oxytocin was ranked fourth with close to 0% cumulative probability of being ranked in the top three for PPH ≥ 500 mL.

The outcomes and rankings for the outcome of PPH ≥ 1000 mL were similar to those of PPH ≥ 500 mL. with the evidence for ergometrine plus oxytocin combination being more effective than oxytocin (RR 0.77 (95% CI 0.61 to 0.95), high-quality evidence) being more certain than that for carbetocin (RR 0.70 (95% CI 0.38 to 1.28), low-quality evidence), or misoprostol plus oxytocin combination (RR 0.90 (95% CI 0.72 to 1.14), moderate-quality evidence)

There were no meaningful differences between all drugs for maternal deaths or severe morbidity as these outcomes were so rare in the included randomised trials.

Two combination regimens had the poorest rankings for side-effects. Specifically, the ergometrine plus oxytocin combination had the higher risk for vomiting (RR 3.10 (95% CI 2.11 to 4.56), high-quality evidence; 1.9% versus 0.6%) and hypertension [RR 1.77 (95% CI 0.55 to 5.66), low-quality evidence; 1.2% versus 0.7%), while the misoprostol plus oxytocin combination had the higher risk for fever (RR 3.18 (95% CI 2.22 to 4.55), moderate-quality evidence; 11.4% versus 3.6%) when compared with oxytocin. Carbetocin had similar risk for side-effects compared with oxytocin although the quality evidence was very low for vomiting and for fever, and was low for hypertension.

**Authors' conclusions**

Ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination were more effective for preventing PPH ≥ 500 mL than the current standard oxytocin. Ergometrine plus oxytocin combination was more effective for preventing PPH ≥ 1000 mL than oxytocin. Misoprostol plus oxytocin combination evidence is less consistent and may relate to different routes and doses of misoprostol used in the studies. Carbetocin had the most favourable side-effect profile amongst the top three options; however, most carbetocin trials were small and at high risk of bias.

Amongst the 11 ongoing studies listed in this review there are two key studies that will inform a future update of this review. The first is a WHO-led multi-centre study comparing the effectiveness of a room temperature stable carbetocin versus oxytocin (administered intramuscularly) for preventing PPH in women having a vaginal birth. The trial includes around 30,000 women from 10 countries. The other is a UK-based trial recruiting more than 6000 women to a three-arm trial comparing carbetocin, oxytocin and ergometrine plus oxytocin combination. Both trials are expected to report in 2018.

Consultation with our consumer group demonstrated the need for more research into PPH outcomes identified as priorities for women and their families, such as women's views regarding the drugs used, clinical signs of excessive blood loss, neonatal unit admissions and breastfeeding at discharge. To date, trials have rarely investigated these outcomes. Consumers also considered the side-effects of uterotonic drugs to be important but these were often not reported. A forthcoming set of core outcomes relating to PPH will identify outcomes to prioritise in trial reporting and will inform futures updates of this review. We urge all trialists to consider measuring these outcomes for each drug in all future randomised trials. Lastly, future evidence synthesis research could compare the effects of different dosages and routes of administration for the most effective drugs.

## PLAIN LANGUAGE SUMMARY

**Which drug is best for reducing excessive blood loss after birth?**

**What is the issue?**

The aim of this Cochrane review was to find out which drug is most effective in preventing excessive blood loss at childbirth and has the least side-effects. We collected and analysed all the relevant studies to answer this question.

**Why is this important?**

Bleeding after birth is the most common reason why mothers die in childbirth worldwide. Although most healthy women can cope well with some bleeding at childbirth, others do not, and this can pose a serious risk to their health and even life. To reduce excessive bleeding at childbirth, the routine administration of a drug to contract the uterus (uterotonic) has become standard practice across the world. The aim of this research was to identify which drug is most effective in preventing excessive bleeding after childbirth with the least side-effects.

Different drugs given routinely at childbirth have been used for preventing excessive bleeding. They include oxytocin, misoprostol, ergometrine, carbetocin, and combinations of these drugs, each with different effectiveness and side-effects. Some of the side-effects identified include: vomiting, high blood pressure and fever. We analysed all the available evidence to compare all of these drugs and calculated a ranking among them, providing robust effectiveness and side-effect profiles for each drug.

**What evidence did we find?**

We searched for evidence in June 2015 and found 140 studies involving a total of 88,947 women. The results suggest that an ergometrine plus oxytocin combination, carbetocin, and a misoprostol plus oxytocin combination are the most effective drugs for preventing excessive bleeding after childbirth and are more effective than the drug oxytocin currently recommended by the World Health Organization (WHO). However, ergometrine plus oxytocin and misoprostol plus oxytocin were the worst drugs for side-effects, with carbetocin having the most favourable side-effect profile (less vomiting, high blood pressure and fever). More effective drugs could probably prevent one out of three women from bleeding excessively after childbirth compared to oxytocin. However, existing carbetocin studies were small and of poor quality.

**What does this mean?**

We found that ergometrine plus oxytocin, misoprostol plus oxytocin, and carbetocin were more effective drugs for reducing excessive bleeding at childbirth than oxytocin which is the current standard drug used to prevent this condition. Carbetocin has the least side-effects among the top three drug options, but to date studies of carbetocin were small and of poor quality.

There are some ongoing studies that are not yet complete, including two key studies. One is a large study (involving around 30,000 women across 10 different countries) comparing the effectiveness of carbetocin versus oxytocin for preventing PPH among women having a vaginal birth. The other is a UK-based trial (involving more than 6000 women) comparing carbetocin, oxytocin and ergometrine plus oxytocin combination. Both trials are expected to report in 2018 and these results will be incorporated when this review is updated.

Consultation with our consumer group has demonstrated a need for more research into PPH outcomes identified as priorities for women and their families, such as women's views regarding the drugs used, clinical signs of excessive blood loss, neonatal unit admissions and breastfeeding at discharge. Trials to date have rarely investigated these outcomes. Consumers also considered the side-effects of uterotonic drugs to be important and these were often not reported. A set of standardised PPH outcomes are being developed and will be incorporated in future updates of this review. We would hope that future trials would also consider adopting those outcomes. Finally, future systematic reviews could compare the effects of different doses and ways of administering the most effective drugs.