UNIVERSITY OF BIRMINGHAM

# Strategies to Manage Postpartum Haemorrhage

by

**William Rhys Parry-Smith**

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College of Medical and Dental Sciences

University of Birmingham

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# Abstract

Postpartum haemorrhage (PPH) is a global problem and the solutions to reducing it are complex. This thesis uses a mixture of research methods to investigate strategies that might improve the burden of blood loss following childbirth.

The main findings are:

1. The use of contraception medication prior to pregnancy warrants further research as progesterone only contraception in particular might be associated with an increase in the risk of subsequent PPH;
2. The use of antidepressant medication during late pregnancy does not appear to increase the risk of PPH;
3. Following childbirth, a preventative uterotonic drug may not need to be given immediately; a delay of up to 5 minutes does not appear to increase the risk of bleeding;
4. There is little evidence to recommend the use of oxytocin, carbetocin, or misoprostol over each other for use as a first line drug to treat PPH;
5. Less than half of patients who had a PPH of 500mL received treatment uterotonic medication;
6. There is no appreciable long-term effect of PPH on mental health, but there is an increased risk of developing postnatal depression and post traumatic stress disorder;
7. There is no appreciable effect of PPH on cardiovascular health.

# Dedication

This thesis is dedicated to my family, and in particular my wife, Fiona. Arthur, our son, was born as I started my doctorate, and Edith, our daughter, some 21 months later. The tireless support, love, and faith they have shown me have allowed this thesis to be completed.

# Acknowledgments

I would like to thank my primary supervisor and mentor, Professor Coomarasamy. He has guided, supported, and encouraged me every step of the way. The opportunity to work with him and acquire new skills has been invaluable.

My second supervisors Dr Nirantharakumar, and Dr Sumilo have been steadfast in their encouragement and patience, I thank them for their forbearance. Dr Nirantharakumar's group have been generous with their time, expertise, and feedback. I would like to thank Anuradhaa Subramanian, Krishna Gokhale, and Kelvin Okoth.

I would like to thank Associate Professor Tobias for his guidance and support with statistics. Dr Gallos and Dr Papadopoulou were invaluable in supporting the Cochrane review that forms a key chapter in this thesis along with the other co-authors listed.

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Final thanks must go to the women who consented to be involved with research during the most precious moments of their lives, as they become mothers. This thesis would not have been possible without them.

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## Abbrevations

| | |
|---|---|
| BMI | Body mass index |
| COCP | Combined oral contraceptive pill |
| CVD | Cardiovascular disease |
| HES | Hospital episode statistics |
| HTN | Hypertension |
| mTOR | Mammalian target of rapamycin |
| NICE | National institute for health and clinical excellence |
| POP | Progesterone only pill |
| PPH | Postpartum haemorrhage |
| PR | Progesterone receptor |
| PTSD | post traumatic stress disorder |
| SSRI | Selective serotonin reuptake inhibitor |
| THIN | The health improvement network |
| WHO | World health organisation |

# Chapter 1 - Thesis Introduction

## An introduction to postpartum haemorrhage

Postpartum haemorrhage (PPH) is broadly characterised as excessive bleeding following childbirth, primary haemorrhage within the first 24 hours, and secondary haemorrhage from 24 hours to six weeks after childbirth. Many clinicians would regard blood loss of 500 mL as the tipping point for progression to treatment (1). However, clinicians report that they start treatment as soon as they are unhappy with the rate of bleeding, rather than waiting for any specific volume of loss (2). The widely used definition of PPH is blood loss in excess of 500 mL following birth (3). The poor association of 500 mL loss with morbidity has led others to use 1000 mL or even PPH-related morbidity to define PPH (4). Blood loss in excess of 500 mL is commonly regarded as a key metric by which PPH is defined, and a key outcome measure to record. The international core outcome sets for prevention and treatment of PPH include blood loss as an outcome measure (5).

Across the world, maternal mortality remains unacceptably high. In recent years a rise in the number of deaths from PPH in developed healthcare settings highlight that PPH is a global problem, requiring on-going effort (6). Since 1990 the number of maternal deaths worldwide has dropped by 44%, and yet an estimated 303,000 women died in childbirth worldwide in 2015 (7). If death is avoided, the risk of morbidity is significant (8). The morbidity up to a month following a PPH includes sepsis, anaemia, and prolonged mechanical ventilation (9). The morbidity up to six

months can include both a psychological burden of; anxiety, depression, post-traumatic stress disorder, and the physical problems of exhaustion and headache (9).

The approach to addressing postpartum haemorrhage (PPH) can be divided into three phases. The first is prevention to avoid PPH in the first place and identification of risk factors. The second is treatment should prevention fail. The third is management of the complications following PPH. Figure 1 sets out the approach the thesis takes to better understanding strategies to manage postpartum haemorrhage.

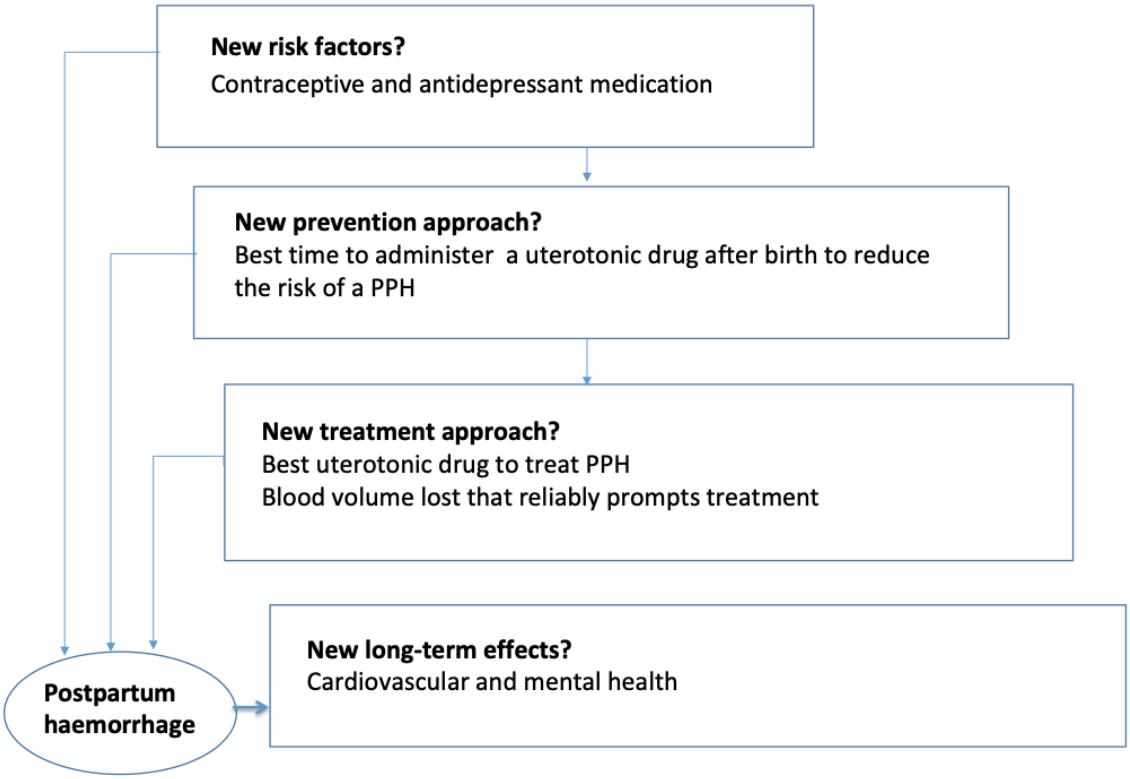


**Figure 1** Strategies to manage PPH

## Risk factors for PPH: antidepressant and contraceptive medication

The contribution of PPH to maternal mortality is well recognised and documented. In developed countries and sub-Saharan Africa haemorrhage accounts for 13.4% and 33.9%, respectively, of the overall causes of maternal mortality (10). The morbidity associated with PPH is also widely reported and captured in the maternal morbidity outcome indicator (11). The decline in PPH in low resource countries is welcomed, and credit goes largely to the impact of the millennium development goals in reducing maternal mortality (12). The incidence of atonic PPH is, however, increasing in many well-resourced countries, for example, in Canada the rate of PPH increased from 4.8% to 6.3% from 2001 to 2009 (6). The paradox of decreasing PPH in low resource settings and increase in well-resourced settings requires investigation, not least to ensure that gains made in low resource settings are maintained as the resource levels improve. Maternal obesity, nulliparity, gestational weight, and ethnicity have all been demonstrated to contribute to the increased risk of PPH in a New Zealand cohort study (13). In the USA, a large population based study of 8.5 million hospital deliveries demonstrated the following risk factors for increased rate of PPH; increased maternal age, fibroids, preeclampsia, amnionitis, placenta praevia or abruption, cervical laceration, instrumental delivery, caesarean delivery, and fetal macrosomia (14). Despite the contribution of these recognised risk factors the doubling of severe PPH in a decade was not explained by a mirrored change in the risk factors (14).

An approach to identifying potential novel risk factors for PPH would be contingent on a plausible biological explanation. The increase in atonic PPH could be viewed through the prism of smooth muscle dysfunction. The role of smooth muscle in uterine contraction is well described despite the underlying mechanisms being incompletely understood (15). The detrimental effects of obesity on levels of oestrogen, progesterone, and myometrium contractility, and the complex pathobiology at work have been well described (16). The use of contraceptive medication prior to pregnancy and a potential role in PPH is a question addressed in Chapter 2.

An explanation for the increase in PPH observed in well-resourced settings has been sought after. Speculation exists that the increased use of selective serotonin reuptake inhibitors (SSRIs) might cause novel drug interactions that lead to modulation of vascular tone and platelet aggregation causing PPH (17). Investigation of the role of antidepressant medication as a risk factor for PPH is addressed in Chapter 3.

## Timing of uterotonic medication

The timing of when to give uterotonic medication is covered in a number of guidelines (3,18). The International Federation of Gynecology and Obstetrics, as well as the World Health Organization (WHO) and the National Institute for Health and Care Excellence (NICE) recommend a uterotonic drug to be given ‘immediately after all births’, and advocates active management of the third stage of labour (19). However,

the evidence base for exactly when to administer the prevention/prophylactic uterotonic medication in PPH is limited.

The Cochrane Collaboration reviewed timing of uterotonic medication in 2010 and concluded that administration of oxytocin either before or after delivery of the placenta did not have a significant effect on key outcomes such as incidence of PPH or postpartum blood loss (20). A review of the literature identified that few papers have addressed timing of uterotonic medication. The two most recent papers demonstrated little clinical effect of relevance and were of poor quality. Fidan and colleagues found no statistically significant difference in the levels of haemoglobin and haematocrit if oxytocin was administered immediately or after placental separation (21). Orhan and colleagues demonstrated no difference in postpartum blood loss between administration of oxytocin with delivery of the anterior shoulder or after delivery is completed (22).

It might be argued that the literature regarding timing of uterotonic drug administration is sparse, due to the fact that researchers have accepted the national guidance on timing and widespread clinical practice, and as a result have focused their efforts elsewhere. There is clinical equipoise regarding the timing of uterotonic administration. An intrapartum clinical trial conducted at Birmingham Women's Hospital as part of the WHO CHAMPION study allows investigation of the uterotonic timing question, and is investigated in Chapter 4.

## Medication to treat PPH

Which uterotonics drug to use, should prevention fail and treatment be required, is a key strategy to manage PPH.

PPH treatment is characterised by interventions to remedy the cardinal cause, or causes, of haemorrhage. The treatment particularly focuses on uterine tone, as well as steps to exclude and repair any trauma, remove the placenta and membranes in entirety, and correct the clotting cascade (23). In clinical practice uterotonic medication is primarily used to treat PPH while other causes are excluded or managed. Interventions including surgery, embolization and/or uterine compression have been described in addition to medication. (I have co-authored during my doctorate two book chapters that summarise intervention for the management of massive haemorrhage. They have been reproduced in appendix 1 with permission from the editor.)

Uterotonic drugs work by increasing the contractility of the uterus, thereby compressing the blood vessels of the myometrium and reducing bleeding. Each class of medication has its own unique side effect profile and mode of action, although the end effect is increased uterine tone.

Oxytocin, a nine-amino-acid peptide, is widely regarded as the gold standard treatment of PPH, although the optimal dose and route of administration in treatment

is far from clear (3). Furthermore, there is clinical and laboratory evidence that whilst the first dose of oxytocin is effective, repeated doses become increasingly ineffective (24).

Carbetocin, an analogue of oxytocin, which produces sustained rather than rhythmic contraction of the uterus, is also used for the treatment of PPH, but has been evaluated for prevention only (25).Misoprostol is a synthetic analogue of prostaglandin E1 with methylation at C16; and causes uterine contractions. The use of misoprostol to treat PPH is recognised, although the optimum route and dosage is a matter of contention (26). Carboprost, another synthetic prostaglandin analogue of PGF2 with uterotonic properties, is often used in cases where oxytocin has already been used and a further uterotonic is indicated (27).

Ergot alkaloids, such as ergometrine, increase the muscle tone of the uterus; the optimum dose and route is open to discussion (28). Ergometrine has long been used in both treatment and prevention of PPH.

Syntometrine, a combination of oxytocin and ergometrine, has been advocated in the treatment of PPH for many years (1). The Cochrane review in Chapter 5 will outline the best drug to use for the treatment of PPH.

## Blood loss threshold at which treatment is started for PPH

It is recognised that management of PPH rests on early identification and treatment. The earlier treatment is given and bleeding stopped the better (29). It is known,

however, that recognition of PPH is challenging and blood loss can be underestimated by as much as 49% of the total volume loss (30).

The decision to treat excessive blood loss following delivery is dynamic and the practitioner uses a range of information including clinical assessment, blood loss estimation, and speed of flow (31). The use of a drape placed under the patient following delivery is a recognised technique to quantify blood loss accurately, but seems not to reduce the incidence of PPH (32). The CHAMPION study used a drape to collect blood loss following delivery (33). The study is well placed to accurately record blood loss and identify the blood loss threshold that triggers the administration of treatment uterotonics (as opposed to prevention uterotonics) following delivery.

The aim of PPH diagnosis and treatment in a timely fashion has been the subject of much research and recently bundles of care have been suggested, because even in well trained and resourced settings deaths continue to occur (34). However, a package of care, bundle, and increased training all relies on appropriate initiation of care in the first instance. It is most important to establish at what blood loss threshold clinicians recognise blood loss is sufficient enough to diagnose PPH and commence treatment. Chapter 6 will address this question.

## The consequences of PPH on mental and cardiovascular health

The investigation of psychological and physical health after PPH is limited. In a recent systematic review of psychological and physical health after PPH, just six studies were included, in stark contrast to the many papers addressing prevention,

treatment and risk factors for PPH (9). The long term consequences of PPH beyond a year, and health implications aside from future fertility and mental health have been little studied to date (35,36). The effect of PPH on mental health is explored in Chapter 7.

The interplay between vascular smooth muscle and vascular endothelium is complex and dysfunction of their relationship is thought to be implicated in first steps of pathogenesis contributing to cardiovascular disease, peripheral vascular disease, stoke and chronic kidney disease (37). What effect PPH has on long-term cardiovascular health is investigated in Chapter 8.

## Aims and objectives of this thesis

In this thesis I aim to investigate strategies to manage PPH, outlined in Table 1. The first objective is to investigate if novel risk factors increase the chance of developing a PPH. I therefore carried out a case control study in women exposed to contraceptive medication, which is reported in Chapter 2. I also carried out a case control study of women exposed to antidepressant medication, which is reported in Chapter 3.

The second objective is to understand if administration of a preventative uterotonic drug after childbirth is given at the optimum time. I carried out a cohort study, which is reported in Chapter 4.

The third objective is to establish which is the best uterotonic drug for treatment of PPH. I carried out a systematic review and meta-analysis, which is reported in Chapter 5.

The fourth objective is to establish the volume of postpartum blood loss that prompts administration of a treatment uterotonic drug. I carried out a cohort study, which is reported in Chapter 6.

The final objective is to establish the long-term effects of PPH. I carried out a cohort study investigating mental health outcomes, which is reported in Chapter 7. I also carried out a cohort study investigating cardiovascular outcomes, which is reported in Chapter 8.

**Table 1-** Outline of thesis

| | Objective | Population studied | Design | Outcome of interest |
|---|---|---|---|---|
| **Chapter 2** | To examine the association between contraceptive prescribing prior to pregnancy and PPH | Women aged 15-49 years old that had a live birth between 2005-17 in the UK 'THIN' database | Nested case-control study | Postpartum haemorrhage |
| **Chapter 3** | To examine the association between selective serotonin reuptake inhibitor prescribing during pregnancy and PPH | Women between the ages of 15 and 49 years old with a history or previous episode of anxiety or depression that had a live birth between 2005-17 in the UK 'THIN' database | Nested case-control study | Postpartum haemorrhage |
| **Chapter 4** | To examine the best time to administer uterotonic medication after delivery to reduce blood loss | Women enrolled in the UK site of the Champion trial | Cohort study (secondary analysis of primary data derived from the UK data of the Champion trial) | Total blood loss volume one hour following delivery and time of prevention uterotonic administration |

| | | | | |
|---|---|---|---|---|
| Chapter 5 | To identify the most effective and safe uterotonic drug for PPH treatment | All randomised controlled trials comparing the effectiveness and side effects of uterotonic drugs with other uterotonic drugs for the treatment of PPH | Systematic review and network meta-analysis | Ranking all available drugs according to their relative effectiveness and side effect profiles |
| Chapter 6 | To investigate the blood loss threshold that prompts administration of a treatment uterotonic drug | Women enrolled in the UK site of the Champion trial | Cohort study (secondary analysis of primary data derived from the UK data of the Champion trial) | Blood loss volume following delivery |
| Chapter 7 | To investigate the association between PPH and subsequent mental health disease | Women aged between 16 and 46 who had a record of delivery in 'HES' between 1990 and 2018 | Cohort study | Mental health disease following PPH |
| Chapter 8 | To investigate the association between PPH and subsequent cardiovascular disease | Women aged between 16 and 46 who had a record of delivery in 'HES' between 1990 and 2018 | Cohort study | Cardiovascular disease following PPH |

# Chapter 2 - Does oral contraceptive use increase the risk of Postpartum Haemorrhage? A nested case control study.

### *Preamble to Chapter 2*

In Chapter 1, I introduced the thesis and the key questions related to strategies that might improve the burden of blood loss following childbirth. I outlined the rise in incidence of PPH seen throughout the developed world and the need to identify new risk factors that might be contributing to this observation. The role of contraceptive medication and association with PPH is the hypothesis addressed in Chapter 2.

### *Contributions*

Dr. Parry-Smith conceived the idea, made substantial contribution to the design, acquisition, analysis and interpretation of the data, and wrote the manuscript.

Dr. Krish Nirantharakumar contributed to the design, interpretation of data, and provided substantial edits to the manuscript.

Dr. Dana Sumilo contributed to the design, interpretation of data, and provided substantial edits to the manuscript.

Dr. Anuradhaa Subramanian, Mr Krisha Gokhale, and Mr Kelvin Okoth contributed to the acquisition, analysis and interpretation of data.

Prof. Coomarasamy proofread the manuscript and provided substantial edits.

## Abstract

### *Introduction*

The incidence of postpartum haemorrhage (PPH) is increasing in the developed world without a clear reason. Investigation of novel risk factors that might be driving the rise in PPH is required.

### *Methods*

We conducted a nested case-control study utilising linked primary (The Health Improvement Network (THIN)) and English secondary care (Hospital Episode Statistics (HES)) databases, from 1st January 1997 to 31st January 2018. A total of 28,246 records were included in the study with 10,206 (36.13%) episodes of PPH recorded. 20,214 women were exposed to oral contraceptives; 14,319 women to COCP, 1,629 to POP, and 4,203 to both COCP and POP matched to 8,032 controls. Odds ratio for PPH in those women exposed to oral contraceptives and unexposed within 30 months of delivery were estimated after controlling for covariates using conditional logistic regression.

### *Results*

A prescription for COCP most recently within the 30-month exposure window prior to delivery was not associated with an increased risk of PPH OR=0.96 (95% CI 0.91-1.03, *p*=0.27). A prescription for POP most recently within the 30-month exposure window prior to delivery was associated with an increased risk of PPH OR=1.17 (95% CI 1.08-1.27, *p*=0.000).

### *Conclusion*

Progesterone-only contraceptive use prior to conception should be investigated further as a promising novel factor involved with PPH risk.

## Introduction

The incidence of atonic PPH is increasing in many well-resourced countries, for example, in Canada the rate increased from 4.8% to 6.3% from 2001 to 2009 (6). In the UK, PPH occurred in 13.8% of all deliveries 2013-14, with a doubling of PPH reported between 2003 and 2013 (38,39). The Hospital Episode Statistics (HES) 2017-18 data records that there were over 117,000 (19%) episodes of PPH in the more than 625,000 women delivering a baby in England that year (40). The contribution of PPH to maternal mortality is well recognised and documented in developed countries and in sub-Saharan Africa, where haemorrhage accounts for 13.4% and 33.9% respectively of the overall causes of maternal mortality (10). The decline in PPH in low resource countries is welcomed and driven by a decrease in the number of pregnancies per women, increased income per head, higher maternal educational attainment, and increasing access to skilled birth attendants (12).

The paradox of decreasing PPH in low resource settings and increase in well-resourced settings requires investigation, not least to ensure that gains made in low resource settings are maintained as the resource levels improve. An explanation of the increase in PPH observed in well-resourced settings has been sought but few new risk factors have been identified nor a rise in known risk factors which would account for the on-going increase in PPH seen year on year (13,14,41).

In 2015 and 2016 in the UK, over 7 million prescriptions were dispensed in community pharmacies for oral contraceptives (42). Oestrogen and progesterone in relation to pregnancy have recently been studied mainly in the context of pre-term birth (43). Oestrogen and progesterone levels in the context of obesity and their role in myometrium contractility and the complex pathobiology at work have been well

described (16). Progesterone has been used extensively in pre-term birth treatment; its' effect on the myometrium is to reduce contractility. Exposure to higher doses of the drug in oral contraceptives might well impact on PPH with modulation of oestrogen and progesterone receptors (44). The metabolic effects of the combined oral contraceptive pill and to a lesser extent progesterone only are profound, with a tendency towards higher cardiometabolic risk (45). Zhang and colleagues demonstrate both clinically and in vivo that obesity impairs uterine contractility, the effects of high circulating cholesterol are postulated as an explanation (46).

Our study examines for the first time the association between contraceptive prescribing prior to pregnancy and PPH in the UK setting using a population based primary and secondary care linked database for England.

## Methods

### Study design and data sources

We conducted a nested case-control study using data from The Health Improvement Network (THIN) database which is broadly representative of the UK population (47,48). THIN is a large population based database in the UK that contains electronic medical records of over 17 million patients from 787 general practices (163 of them linked to the HES database). THIN and HES databases, on their own and linked have been extensively used for epidemiological studies, including women with exposures during pregnancy (49–51). In addition to information recorded in primary care we used linked HES data, as diagnosis of PPH is largely made and recorded in hospital settings.

## Study population

Women between the ages of 15 and 49 years old that had a live birth between 2005-2017 were eligible to be included (source population). Patients were selected after they have been registered at their practice for at least 12 months and if their general practices have been using the electronic medical record (EMR) for at least 12 months before entry into the study. Women who had a record in THIN of abnormal placentation (placenta praevia, acreta, increta, and percreta), endometritis or secondary PPH were excluded as primary PPH was the mechanism of interest in this study. Women with a pregnancy code within 21 months of the current pregnancy were excluded to ensure adequate exposure to contraception and reduce the likelihood of two pregnancies within a three-year period. See Figure 2.

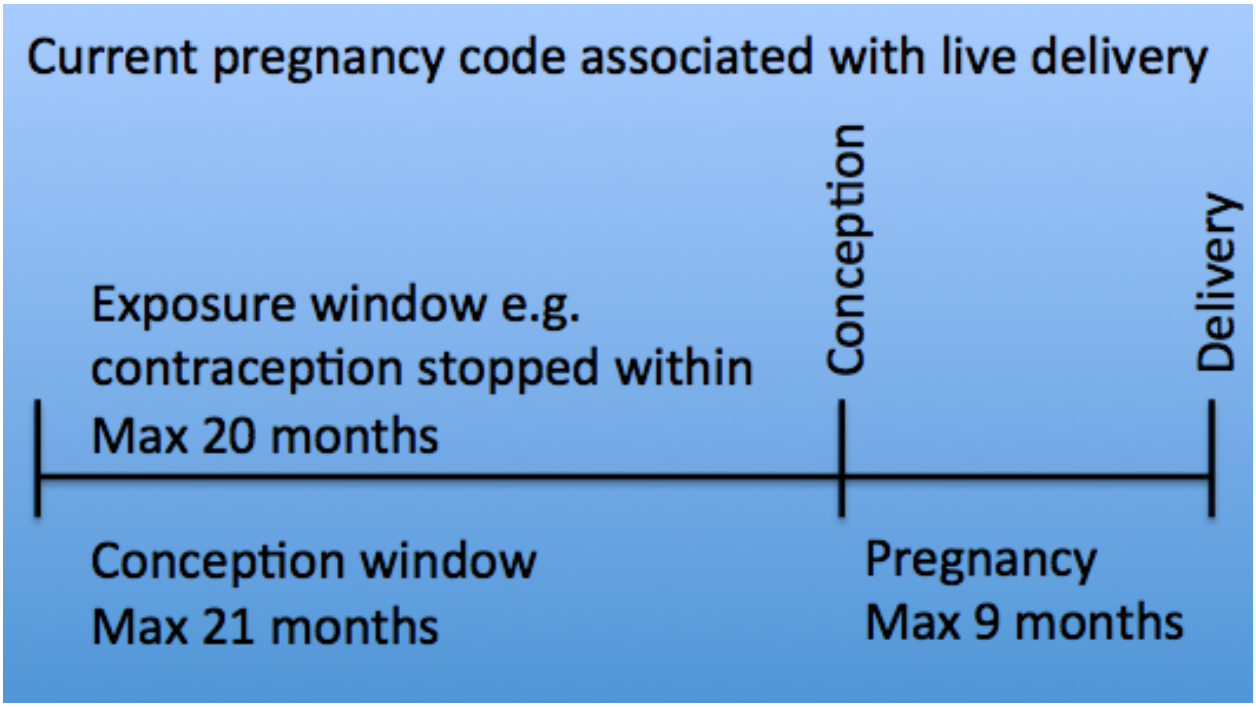


**Figure 2** Cohort exposure diagram

## Selection of cases and controls

All women who had a diagnosis of incident PPH documented in HES data were selected if they met the inclusion criteria. From the same cohort we randomly selected up to two controls matched for maternal age, Body Mass Index (BMI), parity, and Townsend score (a higher score implies greater deprivation) and delivery date within 6 months. Index date for each control was assigned to match the date of the first PPH diagnosis for the case.

## Exposures of interest

Prescription drug codes are recorded in the THIN database alongside the date of the prescription. Prescriptions 30 months prior to the index outcome of PPH were used to define exposure. Thirty months includes 9 months gestation and a 21 months conception window (including time for return of ovulation, following cessation of contraceptive). We have chosen 30 months to ensure that only one, term pregnancy can be likely achieved within the exposure timeframe.

In a sensitivity analysis we examined an additional exposure window period, defined as having a contraceptive prescription at 6 months prior to likely conception (taking gestation as 40 weeks), 6-12 months and 12-18 months. Prescription codes were divided into combined oral contraceptives (COCP), progesterone-only pills (POP).

## Covariates

Covariates that are independent predictors of PPH other than the exposure of interest were selected on the basis of biological plausibility, previous literature, and if they were reliably available in the database. These include maternal age, ethnicity, social deprivation, smoking status, BMI, parity, hypertension (pre-existing and pregnancy induced), pre-eclampsia, fibroids, diabetes (pre-existing and pregnancy

induced), anaemia, antepartum haemorrhage, fetal birth weight, mode of delivery (caesarean and instrumental), and chorioamnionitis.

### Data analysis

We used descriptive statistics to summarise baseline characteristics of cases and controls included in the study, reporting means (and standard deviations) for continuous variables and proportions for categorical variables. Conditional logistic regression was used to estimate Odds Ratios (OR) with 95% Confidence Intervals (CI), after adjustment for potential confounders. All analyses were performed in Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

## Results

A total of 28,246 records were included in the study with 10,206 (36.13%) episodes of PPH recorded. At baseline 30 months prior to delivery 20,214 women were exposed to oral contraceptives; 14,319 women to COCP, 1,629 to POP and 4,203 to both COCP and POP. In total 8,032 women were not exposed to oral contraceptive prescriptions.

In women who had most recently been exposed to a prescription for COCP, 5,641 (35.3%) had a PPH while 10,385 (64.8%) did not. In women who had most recently been exposed to a prescription for POP 1,712 (40.9%) had a PPH while 2,476 (59.1%) did not. In the control group exposed to a prescription for neither COCP nor POP 2,853 (35.5%) had a PPH while 5,179 (64.5%) did not. See Table 2.

**Table** 2- Crude and adjusted odds ratio for PPH among women exposed to oral contraceptive medication within a 30-month window prior to delivery compared to women unexposed to oral contraceptive medication.

| | | Case | Controls |
|---|---|---|---|
| **PPH with prescription of COCP within 30 months of delivery** | **Total *N*** | 16,026 | 8,032 |
| | **Outcomes *N (%)*** | 5,641 (35.20%) | 2,853 (35.53%) |
| | **Odds ratio (95%CI); *p*-value** | 0.93 (95% CI 0.87-0.99, *p*=0.030) | |
| | **Odds ratio ratio (95%CI); *p*-value^** | 0.96 (95% CI 0.91-1.03, *p*=0.27) | |
| **PPH with prescription of POP within 30 months of delivery** | **Total *N*** | 4,188 | 8,032 |
| | **Outcomes *N (%)*** | 1,712 (40.88%) | 2,853 (35.53%) |
| | **Odds ratio (95%CI); *p*-value** | 1.23 (95% CI 1.09-1.37, *p*=0.000) | |
| | **Adjusted Odds ratio (95%CI) ; *p*-value^** | 1.17 (95% CI 1.08-1.27, *p*=0.000) | |

^adjusted for age category, BMI category, smoking status, ethnicity, Townsend deprivation quintile, baseline record of hypertensive disorders of pregnancy (pregnancy induced hypertension and pre-eclampsia), diabetes (pre-existing and gestational), antepartum haemorrhage, fibroid uterus, chorioamnionitis, pre-delivery anaemia, birth weight and delivery method.

After adjusting for potential confounders, a prescription for COCP most recently within the 30-month exposure window prior to delivery was not associated with an increased risk of PPH OR=0.96 (95% CI 0.91-1.03, *p*=0.27). After adjusting for potential confounders, a prescription for POP most recently within the 30-month exposure window prior to delivery was associated with an increased risk of PPH OR=1.17 (95% CI 1.08-1.27, *p*=0.000). Covariates that increased the risk of PPH

were as follows: age (30-40 years) OR=1.27 (95% CI 1.09-1.48, *p*=0.002), BMI (25-30) OR=1.26 (95% CI 1.04-1.53, *p*=0.02), BMI (>30) OR=1.34 (95% CI 1.10-1.62, *p*=0.003), race (others) OR=1.17 (95% CI 1.02-1.36, *p*=0.03), chorioamnionitis OR=1.77 (95% CI 1.23-2.54, *p*=0.002), antenatal anaemia OR=1.70 (95% CI 1.54-1.88, *p*=0.000), birth weight (4-4.5kg) OR=1.81 (95% CI 1.66-01.97, p=0.000), birth weight (>4.5kg) OR=2.22 (95% CI 1.85-2.67, *p*=0.001), parity (2 or more babies) OR=1.56 (95% CI 1.33-1.82, *p*=0.000). Covariates that decreased the risk of PPH were as follows: age (15-20 years) OR=0.73 (95% CI 0.55-0.98, *p*=0.033), Townsend deprivation score 4 OR=0.90 (95% CI 0.83-0.98, *p*=0.014), Townsend deprivation score 5 OR=0.89 (95% CI 0.81-0.98, *p*=0.018), discontinued smoking OR=0.93 (95% CI 0.87-0.99, p=0.029), current smoking OR=0.82 (95% CI 0.76-0.88, *p*=0.000), birth weight (1.5-2.5kg) OR=0.75 (95% CI 0.66-0.86, *p*=0.000).

### Temporal trends

Dividing the datasets into prescription windows allowed a temporal analysis: 6 months prior to likely conception (taking gestation as 40 weeks), 6-12 months and 12-18 months. Exposure to COCP for 6 months or less prior to conception OR=0.89 (95% CI: 0.82-0.98, *p*=0.021). COCP at 6-12 months OR=0.90 (95% CI; 0.87-0.98, *p*=0.018). COCP at 12-18 months OR=0.97 (95% CI: 0.90-1.03, *p*=0.28). Exposure to POP for 6 months or less prior to conception OR=1.19 (95% CI: 1.04-1.37, *p*=0.009). POP at 6-12 months OR=1.27 (95% CI: 1.11-1.45, *p*=0.000). POP at 12-18 months OR=1.27 (95% CI: 1.17-1.37, *p*=0.000).

## Discussion

This is the first UK population-based case control study investigating the risk of PPH following exposure to oral contraceptive medication; it is the most comprehensive in

terms of adjustment for covariates to date in the literature. The study includes over 28,000 women with over 20,000 women exposed to oral contraceptive medication. In this large observational study, COCP use within 30-months prior to birth was not associated with an increase in the risk of PPH. The use of POP within 30-months prior to birth was associated with an increase risk of PPH. The exposure windows of contraceptive use within 6 months, 6-12 months, or longer than 12 months prior to conception do not show a convincing exposure duration response.

This study was designed to investigate a new hypothesis and generate further research into novel PPH risk factors and test previously known risk factors from the literature. The data supports the known association that increasing age, BMI, parity, and birth weight are risk factors for PPH, as was chorioamnionitis and antenatal anaemia (13,14,41). When testing a novel risk factor it is reassuring that the data supported the known associations with PPH. A reduction in the risk of PPH was seen in those aged 15-20 years, low birth weight, recent or current smoking, and increasing social deprivation scores. It is likely that these particular risk factors are confounded in part and co-dependent on a common mechanism such as increased risk of poor uteroplacental blood flow, which is often seen in the smoking population and low birth weight babies and/or the hypercoagulation effects of smoking reducing the risk of bleeding after birth (41,52).

## Comparison with previous studies

The role of oestrogen and progesterone in relation to pregnancy and labour has been extensively studied in animal work and only more recently begun to be understood in humans (53,54). Progesterone helps maintain uterine quiescence and suppress

uterine contractility, while being used for some time to reduce the risk of pre-term labour and birth (43). Foster and colleagues have demonstrated *in vitro* the importance of the mammalian target of rapamycin (mTOR) signalling components in the human myometrium during pregnancy and the key role progesterone plays in its regulation (53). Progesterone receptor (PR) isoform expression has a role in myometrial cell response, regulated by the interplay between the two major PR isoforms PR-A and PR-B(55). Exogenous progestin is thought to suppress uterine contractility acting through both genomic and non-genomic pathways (56). The role of oestrogen regarding uterine contraction and relaxation is less clear, though is thought to be excitatory and blocked by progesterone. Certainly in most mammals it is the fall in progesterone relative to oestrogen that precipitates labour and uterine contractions, a functional fall caused by change in progesterone, oestrogen, prostanoid, and oxytocin receptors is postulated in humans (57).

The effect of oral contraception on oestrogen and progesterone receptors prior to pregnancy is little known, but could result in receptor changes that might be a potential mechanism to explain the effect seen in this study. The functional status of uterine steroid receptors are changed by the action of exogenous oestrogen and progesterone in particular (58). One could speculate that different rates of PPH might be feasible if steroid receptor changes continued throughout pregnancy and birth. The precise mechanism that triggers labour and delivery is yet to be fully understood in humans despite extensive investigation. A clear mechanism to support the hypothesis generated by the data is unlikely to be forthcoming without further research.

## Strengths and limitations

Strengths of the study include its large sample size, using linked population wide primary and secondary care data. The strengths of the study are the multiple adjusted analyses in a large cohort of matched patients. However, due to the limitation of the database, the study did not adjust for previous PPH, induction of labour/augmentation of labour nor medication use such as low molecular weight heparin or aspirin which is a potential weakness, though mitigated in part by the matched trial design. The patients exposed to POP were matched two controls to one case, those exposed to COCP were matched to the same controls with two cases matched to one control. The lower matching ratio in the COCP group while pragmatic, is a weakness and may reduce the precision of the results but this is unlikely given the matched analysis conducted.

Measurement of blood loss and definition of PPH is a challenge with recognised underestimation of blood loss, however, by using linked hospital data we had access to the most complete routine data source available for case ascertainment (24). It is not clear what the cause of PPH is in the HES data and while the majority is likely to be secondary to uterine atony that is the mechanism of interest for this study, some PPH might not have been caused by atony. It is likely that each delivery suffered from a similar underestimation of blood loss across the study population, there being no particular reason why contraceptive prescription might predispose healthcare providers to overestimate blood loss at delivery. Contraceptives are primarily prescribed in primary care and well recorded in THIN database, however it does not capture prescribing outside primary care (59). A prescription issued for medication is

also not synonymous with taking the medication as prescribed. Equally prescription for contraceptives issues on repeat prescription, could have been stopped shortly after issue if conception was sought, making the time frame for exposure inaccurate.

## Implications for clinical practice and future research

The large number of prescriptions for oral contraceptives and widespread impact of PPH makes further investigation a key public health interest. This study and its' findings need further testing in other national data sets before firm recommendations for clinical practice can be suggested. Scandanavian and Canadian national databases and teams would have the capacity to do this work. I am working with collaborators in Canada McGill University Department of Epidemiology, Biostatistics and Occupational health to explore conducting a similar analysis with them. If similar findings are reported in other national databases the case for a prospective observational study could then be made to obtain funding. A prospective observational study would mitigate some of the concerns addressed above and would also allow for data to be collected on other relevant data such as induction of labour and cause of PPH.

The duration of contraceptive use did not increase risk of PPH which may be explained by further invitro progesterone receptor research and investigation of duration of receptor up/down regulation.

Until further research has been conducted implications for clinical practice should be limited, as causing concern over the use of contraceptive pills has historically led to a rise in pregnancy which undoubtedly increases the overall cases of PPH.

## Conclusion

Both progesterone-only and combined oral contraceptive use prior to conception should be investigated as a promising novel factor involved with PPH risk. The results of this study provide evidence to suggest that hormonal contraceptive use within 18 months of conception requires further research. The use of oral progesterone-only contraceptive medication within 18 months of conception might be associated with an as yet unproven increase in the risk of PPH.

## Ethics approval

The IQVIA Scientific Review Committee (SRC) and Independent Scientific Ethical Advisory Committee (ISEAC) approved this study. ISEAC Reference number: 18THIN035.

# Chapter 3 - Prescribing of selective serotonin reuptake inhibitors (SSRIs) in late pregnancy and the risk of postpartum haemorrhage (PPH): A nested case-control study using primary and secondary care linked data in England

### *Preamble to Chapter 3*

In Chapter 2, I shared the results of contraception medication and the association with PPH. In Chapter 3 I continue to explore new risk factors for PPH and investigate the emerging consensus that SSRI medication might be associated with PPH.

### *Contributions*

Dr. Parry-Smith - conceived the idea, made substantial contribution to the design, acquisition, analysis and interpretation of the data, and wrote the manuscript.

Dr. Krish Nirantharakumar - contributed to the design, interpretation of data, and provided substantial edits to the manuscript.

Dr. Dana Sumilo - contributed to the design, interpretation of data, and provided substantial edits to the manuscript.

Dr. Anuradhaa Subramanian, Mr Krisha Gokhale, and Mr Kelvin Okoth contributed to the acquisition, analysis and interpretation of data.

Prof. Coomarasamy proofread the manuscript and provided substantial edits.

## Abstract

### *Introduction*

The literature suggests that SSRI use during late pregnancy might increase the risk of PPH, but no studies have investigated this question in a UK population.

### *Methods*

We conducted a nested case-control study utilising linked primary (The Health Improvement Network (THIN)) and English secondary care (Hospital Episode Statistics (HES)) databases. Women aged 15-49 years who had anxiety and/or depression documented in medical records were included. Patients with a PPH diagnosis between 1997 and 2017 were matched with up to two controls by age, Body Mass Index (BMI), parity, deprivation, and delivery date. Odds ratios (ORs) for incident PPH and use of SSRI during pregnancy were estimated after controlling for covariates using conditional logistic regression.

### *Results*

A total of 3,403 cases of PPH and 6,784 controls were analysed. Prescribing of SSRI medication within the last three months and within the last two months prior to delivery was not associated with an increased risk of PPH (adjusted OR=0.97, 95% CI 0.82 to 1.14, *p*=0.69, and adjusted OR=0.99, 95% CI 0.84 to 1.17, *p*=0.94, respectively).

### *Conclusion*

In this large population based study using linked primary and secondary care data, SSRI prescribing within the last trimester of pregnancy was not associated with an increased risk of PPH.

## Introduction

Postpartum haemorrhage (PPH) is commonly defined as blood loss following birth in excess of 500 mL (3). It accounts for 13.4% of the overall causes of maternal mortality in high income countries (10). The incidence of PPH has been increasing in many well-resourced countries, with a doubling of PPH in the last decade reported in the UK (38,39).

Two recent systematic reviews have concluded that there may be an association between anti-depression medication and PPH, but the numbers of studies investigating the effect of selective serotonin reuptake inhibitors (SSRIs) as a separate antidepressant group were small, and none have been conducted in a UK setting (60,61). The most comprehensive study that was methodologically rigorous and had a large sample size, however, lacked important covariates such as body mass index (BMI) and used a low income Medicaid US database (62).

Prescriptions of newer antidepressants containing SSRIs have increased markedly concurrently with a rise in PPH (63). It has been suggested that the increased use of SSRIs might cause novel drug interactions that lead to modulation of vascular tone and platelet aggregation causing PPH (17). Serotonin receptors are present in the myometrium and their disruption by these anti-depressant drugs could contribute to poor uterine smooth muscle contraction and atonic PPH (64).

Our study aims to address the limitations in previous studies and for the first time will examine the association between SSRI prescribing during pregnancy and PPH in the

UK using a population based primary and secondary care linked database for England.

## Methods

### Study design and data sources

We conducted a nested case-control study using data from The Health Improvement Network (THIN) database which is broadly representative of the UK population (47,48). THIN is a large population-based database that contains electronic medical records of over 15 million patients registered with 787 general practices (163 of them linked to the Hospital Episodes Statistics (HES) database). In addition to information recorded in primary care we used linked HES data, as diagnosis of PPH is largely made and recorded in hospital settings. THIN and HES databases, on their own and linked have been extensively used for epidemiological studies, including to study exposures during pregnancy (49–51).

### Study population

Women between the ages of 15 and 49 years old with a history or previous episode of anxiety or depression that had a live birth between 1997 and 2017 were eligible to be included (source population). A history of mental ill health was essential to ensure all in the source population had an equal chance to be offered a prescription of SSRI (62). Patients were selected after they had been registered at their general practice for at least 12 months and if their practice had used electronic medical records and had acceptable mortality reporting for at least 12 months before entry into the study to ensure data quality (65). Women who had a record in THIN of abnormal placentation (placenta praevia, acreta, increta, and percreta) were excluded. Women

who had a record of secondary PPH were also excluded as primary PPH was the primary mechanism of interest in this study.

## Selection of cases and controls

All women who had a diagnosis of incident PPH documented in HES data using ICD-10 codes were selected if they met the inclusion criteria. From the source cohort we randomly selected up to two controls matched for maternal age, BMI, parity, Townsend score (a measure for deprivation), and delivery date within 6 months. Index date for cases and controls was the date of delivery.

## Exposure of interest

Prescription drug codes are recorded in the THIN database alongside the date of the prescription. Prescriptions within three months prior to delivery was the time window used to measure exposure. In UK general practice drugs are usually prescribed for up to three months and it is likely that this indicates current usage of medication. It appears the SSRI effect on platelet function starts within days of exposure to the medication and lasts for up to two weeks, reflecting the platelet turn over time of around 10 days (66).

In a sensitivity analysis we examined an additional exposure window period, defined as having an SSRI prescription recorded within two months. The metabolism and dosing across pregnancy is poorly understood and looking at two different exposure windows might be helpful to assess misclassification bias (67).

## Covariates

Covariates that are independent predictors of PPH other than the exposure of interest were selected on the basis of biological plausibility, previous literature and if they were reliably available in the database. These include maternal age, ethnicity,

social deprivation, smoking status, BMI, parity, hypertension (pre-existing and pregnancy induced), pre-eclampsia, fibroids, diabetes (pre-existing and pregnancy induced), anaemia, antepartum haemorrhage, fetal birth weight, and mode of delivery.

### Data analysis

We used descriptive statistics to summarise baseline characteristics of cases and controls included in the study, reporting means (and standard deviations) for continuous variables and proportions for categorical variables. Conditional logistic regression was used to estimate ORs with 95% CIs, after adjustment for potential confounders. All analysis were performed using Stata software (version 14.2).

## Results

A total of 3,403 PPH cases and 6,784 controls were included in the study (Figure 3). The mean age at delivery was 31.2 (*SD* 5.7) years for cases, and 31.2 (*SD* 5.6) years for controls. Similar proportions of the cases and controls had a record of depression and anxiety. Anxiety was documented in 2,018 (59.3%) of the cases and 3,945 (58.2%) of the controls. Depression was documented in 2,420 (71.1%) of the cases and 5,013 (73.9%) of the controls, see Table 3 for detailed baseline characteristics.

**Figure 3**- Flowchart of included patients with postpartum haemorrhage (PPH) and controls

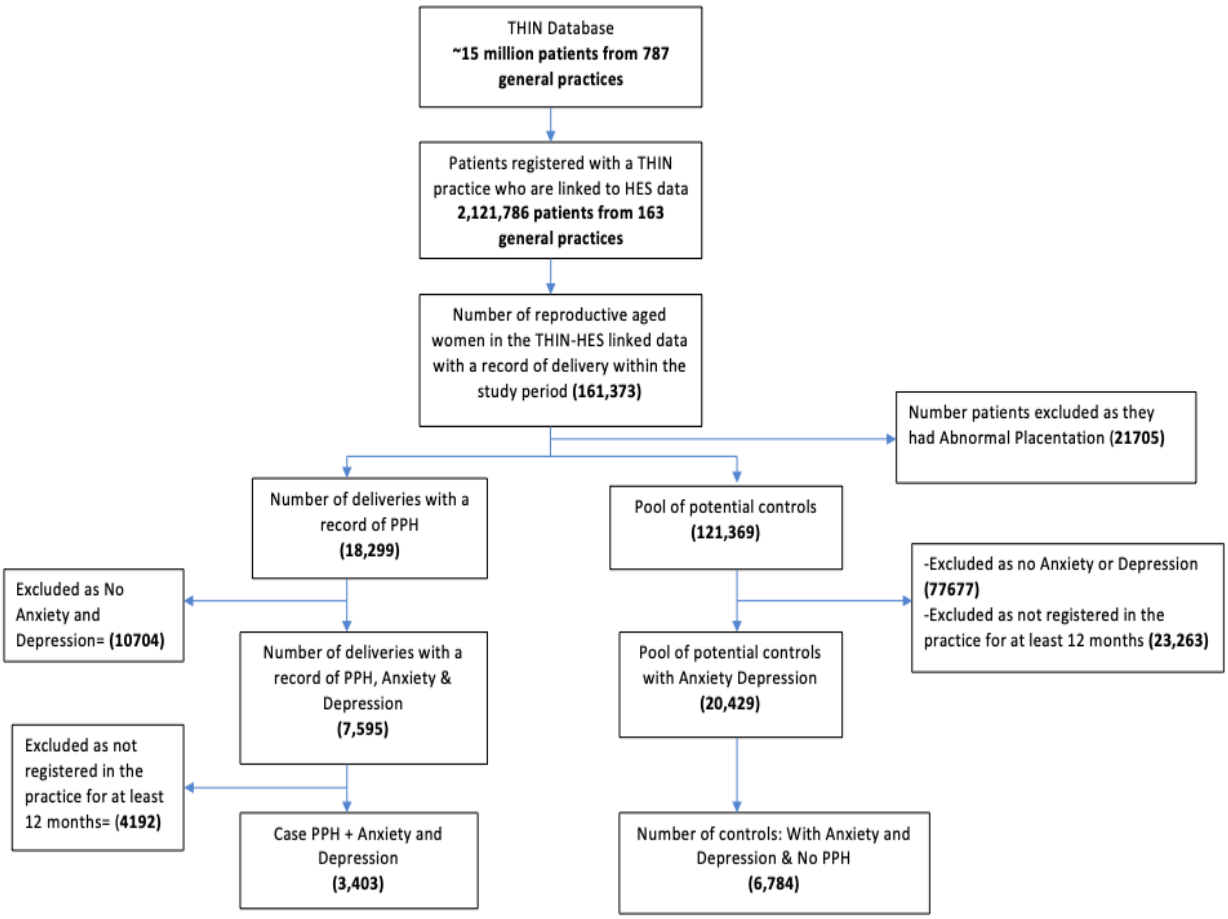

**Table 3**- Baseline characteristics of cases with postpartum haemorrhage (PPH) and controls without PPH matched by maternal age, BMI, parity, Townsend score, and delivery date within six months.

| Characteristics | Cases (*N*= 3,403)<br>*N* (%) | Controls (*N*= 6,784)<br>*N* (%) |
|---|---|---|
| **Age in years; Mean (*SD*)** | 31.2 (5.7) | 31.2 (5.6) |
| ***BMI categories*** | | |
| **Underweight (<18)** | 63 (1.9) | 166 (2.5) |
| **Normal weight (18-25)** | 1,559 (45.8) | 3,228 (47.6) |
| **Overweight (25-30)** | 763 (22.4) | 1,461 (21.5) |
| **Obese (>30)** | 676 (19.9) | 1,169 (17.2) |
| **Missing** | 342 (10.1) | 760 (11.2) |
| ***Townsend Deprivation quintile*** | | |
| **1 (most affluent)** | 762 (22.4) | 1,378 (20.3) |
| **2** | 613 (18.0) | 1,180 (17.4) |
| **3** | 723 (21.3) | 1,521 (22.4) |
| **4** | 704 (20.7) | 1,465 (21.6) |
| **5 (most deprived)** | 419 (12.3) | 838 (12.4) |
| **Missing** | 182 (5.4) | 402 (5.9) |
| ***Parity*** | | |
| **1** | 2,917 (85.7) | 5,706 (84.1) |
| **≥ 2** | 135 (4.0) | 221 (3.3) |
| **Missing** | 351 (10.3) | 857 (12.6) |
| ***Ethnicity status (HES)*** | | |
| **White** | 2,929 (86.1) | 5,852 (86.3) |
| **Mixed race** | 44 (1.3) | 73 (1.1) |

| | | |
|---|---|---|
| **Others** | 63 (1.9) | 130 (1.9) |
| **Black** | 63 (1.9) | 97 (1.4) |
| **South Asians** | 71 (2.1) | 158 (2.3) |
| **Missing** | 233 (6.9) | 474 (7.0) |
| ***Smoking status*** | | |
| **Non-smokers** | 1,649 (48.5) | 3,073 (45.3) |
| **Ex-smokers** | 871 (25.6) | 1,694 (25.0) |
| **Smokers** | 830 (24.4) | 1,928 (28.4) |
| **Missing** | 53 (1.6) | 89 (1.3) |
| ***Delivery method*** | | |
| **Caesarean** | 1,330 (39.1) | 2,648 (39.0) |
| **Spontaneous vaginal** | 1,316 (38.7) | 2,632 (38.8) |
| **Other delivery method** | 757 (22.5) | 1,504 (22.2) |
| ***Birthweight category (grams)*** | | |
| **ELBW (< 1000 g)** | 12 (0.4) | 14 (0.2) |
| **VLBW (1000-1500 g)** | 14 (0.4) | 40 (0.6) |
| **LBW (1500-2500 g)** | 144 (4.2) | 381 (5.6) |
| **NBW (2500-4000 g)** | 2,127(62.5) | 4,499 (66.3) |
| **HBW (4000-4500 g)** | 444 (13.1) | 533 (7.9) |
| **VHBW (>4500 g)** | 94 (2.8) | 108 (1.6) |
| **Missing** | 568 (16.7) | 1,209 (17.8) |
| **Endomyometritis** | 36 (1.1) | 57 (0.8) |
| **Uterine fibroids** | 24 (0.7) | 56 (0.8) |
| **Antepartum haemorrhage** | 25 (0.7) | 45 (0.7) |
| **PIH** | 3 (0.1) | 12 (0.2) |

| | | |
|---|---|---|
| **Preeclampsia** | 37 (1.1) | 84 (1.2) |
| **Gestational diabetes** | 84 (2.5) | 185 (2.7) |
| **Hypertension** | 62 (1.8) | 114 (1.7) |
| **Diabetes** | 44 (1.3) | 80 (1.2) |
| **Anaemia** | 355 (10.4) | 476 (7.0) |
| **Anxiety** | 2,018 (59.3) | 3,945 (58.2) |
| **Depression** | 2,420 (71.1) | 5,013 (73.9) |

**Footnotes**: BMI= Body mass index, ELBW= extremely low birth weight, HBW = high birth weight, HES= hospital episode statistics, LBW = low birthweight, NBW = normal birth weight, PIH = Pregnancy induced hypertension, SD= Standard deviation, VHBW= very high birth weight, VLBW= very low birth weight.

At three months and two months before delivery respectively, 244 (7.17%) and 220 (6.46%) of PPH cases were prescribed SSRI, and 509 (7.50%) and 446 (6.57%) of controls were prescribed SSRI.

After adjusting for potential confounders, prescribing of SSRI medication within the last three months and within the last two months prior to delivery was not associated with an increased risk of PPH: OR=0.97 (95% CI 0.82-1.14, *p*=0.69) and OR=0.99 (95% CI 0.84-1.17, *p*=0.94), respectively (see table 4). Covariates that increased the risk of PPH were: BMI >30 OR=1.48 (95% CI 1.09-2.02, *p*=0.012), antenatal anemia OR=1.59 (95% CI 1.37-1.84, p=0.001), birth weight over 4kg OR=1.80 (95% CI 1.51-1.99, *p*=0.001) and parity (2 or more babies) OR=1.32 (95% CI 1.05-1.66, *p*=0.02). The only covariate that was associated with reduced risk of PPH was active smoking OR=0.84 (95% CI 0.75-0.93, *p*=0.001).

**Table 4**- The crude and adjusted odds ratios for PPH among women exposed to SSRI medication 3 and 2 months prior to delivery compared to women unexposed to SSRI medication.

| | PPH Cases | Controls |
|---|---|---|
| **Total *n*** | 3,403 | 6,784 |
| **SSRI prescription within 3 months of delivery *N* (%)** | 244 (7.17%) | 509 (7.50%) |
| **Odds ratio (95%CI); *p*-value** | 0.95 (0.81-1.11); *p*=0.545 | |
| **Odds ratio ratio (95%CI) ; *p*-value^** | 0.97 (0.83-1.14); *p*=0.737 | |
| **Total *n*** | 3,403 | 6,784 |
| **SSRI prescription within 2 months of delivery *N* (%)** | 220 (6.46%) | 446 (6.57%) |
| **Odds ratio (95%CI); *p*-value** | 0.98 (0.83-1.16); *p*=0.833 | |
| **Adjusted Odds ratio (95%CI); p-value^** | 0.99 (0.84-1.18); *p*=0.944 | |

^adjusted for age category, BMI category, smoking status, ethnicity, Townsend deprivation quintile, baseline record of hypertensive disorders of pregnancy (pregnancy induced hypertension and pre-eclampsia), diabetes (pre-existing and gestational), antepartum haemorrhage, fibroid uterus, pre-delivery anaemia, endomyometritis, birthweight and delivery method.

## Discussion

This is the first UK population-based study investigating the risk of PPH following exposure to SSRI medication around the time of delivery; it is also the most comprehensive in terms of adjustment for covariates to date in the literature. In this large observational study of over 3,400 women with PPH and over 6,700 controls, SSRI prescribing prior to delivery was not associated with an increased risk of PPH.

## Strengths and limitations

Strengths of the study include a large sample size, using linked population wide primary and secondary care data and ensuring that the control group of women also had a similar proportion of depression and anxiety diagnosis present as the women who had PPH. The study made adjustments for many relevant confounding factors which was a limitation of previous studies (68).

Measurement of blood loss and definition of PPH is known to be a challenge with recognised underestimation of blood loss. This challenge is in part mitigated by the use of linked hospital data which provided access to the most complete routine data source available for case ascertainment (24). Severity of PPH is not recorded in HES data. It is likely that each delivery suffered from a similar underestimation of blood loss across the study population, there being no particular reason why SSRI prescription might predispose healthcare providers to overestimate blood loss at delivery. SSRIs are primarily prescribed in primary care and well recorded in THIN database, however it does not capture prescribing outside primary care (59). A prescription issued for medication is only an indication that the medication prescribed has been taken, but in this instance a reasonable and practical proxy.

## Comparison with previous studies

Several studies have suggested that SSRI use might increase the risk of bleeding following childbirth, but exposure time frames were not always clearly defined and potential important confounding factors, such as smoking and BMI were not adjusted for (62,68). The review by Bruning and colleagues included two studies and was inconclusive (60). A more recent review by Jiang and colleagues combined the results of three studies with a pooled OR of 1.19 (95% CI 1.02-1.37) for recent SSRIs use before delivery and two studies with OR of 1.24 (95% CI 1.02-1.37) for

current users and the risk of PPH (61). The heterogeneity of included studies was high.

The hypothesis that SSRI use might increase the risk of PPH due to the SSRI medication affecting the platelet function or myometrial contractility is recognized as biologically plausible. However, the pharmacokinetics and potential for subtherapeutic effects of SSRI on clotting during late pregnancy combined with the known complexity of hematological changes in pregnancy might account for the lack of effect seen (67). Equally, adjustments for more confounding factors and ensuring that the population was balanced in terms of background depression and anxiety might account for the results observed. Palmsten and colleagues in the most robust study to date researched a population in the USA that were low income and did not directly adjust for smoking and BMI (62). Our study population was drawn from all income levels and adjusted for Townsend social deprivation score. In addition, Palmsten's study only analysed data up to 2007 and had a much lower baseline risk of PPH (2.9%) than in our study. Our results might also differ from Palmsten's paper, because their estimates are based on comparison to the group with mood and anxiety disorders who were not exposed to any antidepressants, with adjustment for severity of mood or anxiety disorders.

Other risk factors identified within our study population are similar to those reported previously, namely obesity, giving birth to a baby weighing 4kg or more, increased parity, and antepartum anaemia (69). The finding that smoking is protective for PPH is in keeping with previous research and may be due to increased risk of poor uteroplacental blood flow in the smoking population and/or the hypercoagulation effects of smoking (41,52).

## Conclusion and implications for clinical practice

In this large UK-based study of women with history of anxiety or depression, SSRI prescribing in late pregnancy was not associated with an increase in odds of PPH. Future research in a prospective study would provide clarity on the dose, duration and timing of medication use in relation to delivery which is more challenging to define in database derived retrospective studies.

SSRI use in pregnancy is increasingly common as is PPH. While all drugs should be prescribed with caution in pregnancy, this study suggests that no excessive concern should be attached to the risk of bleeding following delivery in those taking SSRI medication. Women should be advised to continue to take SSRI medication in pregnancy if required and not stop due to worry about the risk of PPH.

## Ethics approval

The NHS South-East Multi-Centre Research Ethics Committee approved undertaking research using anonymized THIN data, provided an independent scientific review is undertaken. The study protocol (18THIN035) was reviewed and approved by the IQVIA Scientific Review Committee (SRC) and Independent Scientific Ethical Advisory Com

# Chapter 4 - Timing of Uterotonic medication administration: a secondary analysis of CHAMPION data

### *Preamble to Chapter 4*

In this thesis I have introduced four strategies to manage PPH; investigation of new risk factors, prevention with timing of medication, treatment drugs and long-term effects. I have addressed new risk factors for PPH in Chapters 2 and 3. I now move to address a new preventative strategy in Chapter 4, and describe a cohort study I carried out investigating the best time to administer prophylactic uterotonic medication to reduce blood loss following delivery.

### *Contributions*

Dr. Parry-Smith - conceived the idea, made substantial contribution to the design, acquisition, analysis and interpretation of the data, and wrote the manuscript.

Associate Professor Aurelio Tobias - contributed to the analysis and interpretation of data.

Dr. Ioannis Gallos - contributed to the design and interpretation of data.

Prof. Coomarasamy - made substantial contribution to the design, proofread the manuscript and provided substantial edits.

## Abstract

### *Introduction*

The best time to administer prophylactic uterotonic medication to a woman to reduce blood loss after delivery is unclear, though customary practice is to do so immediately following the birth of the baby. This cohort study explores the best time to administer uterotonic medication to reduce blood loss following delivery.

### *Methods*

A cohort study using the data derived from the UK sub-population of the WHO CHAMPION trial (ACTRN12614000870651). Descriptive statistics and a logistic regression model with blood loss as the dependent variable and timing of prophylactic uterotonic administration as the independent variable adjusted for potential confounders were carried out.

### *Results*

The total number of women in the study was 1,969, with a median age of 30 and median parity of 1. If the uterotonic drug was given within the first minute following birth the median blood loss was 235mL (range 0-2758 mL). The time at which blood loss was minimum was at 5 minutes with a median blood loss of 171mL (range 1-1475 mL). If timing of uterotonic administration was between 0-5 minutes, for each minute increase the blood loss decreased on average by 15.4mL. If timing of uterotonic administration was between 5-13 minutes, for each minute increase the blood loss increased on average by 16.5mL. Uterotonic administration between 0-5 minutes following delivery with adjustment (age, parity, birth weight, augmented labour, and instrumental), for each minute increase the blood loss decreased on average by 5.7mL. When the timing of the uterotonic administration was between 5-

13 minutes, following adjustment, for each minute increase the blood loss increased on average by 13.5mL.

### *Conclusion*

The consensus that currently exists around administration of uterotonic medication immediately following delivery should be revisited, as a short delay in administration is unlikely to be detrimental and may be beneficial. However, the effect of residual confounding means we cannot draw a firm inference about the observed association.

## Introduction

The CHAMPION trial was a phase three, randomized, double-blind, active controlled, multinational, multicentre, non-inferiority trial using room temperature stable (RTS) carbetocin for the prevention of postpartum haemorrhage during the third stage of labour in women delivering vaginally (WHO trial number A65870). The trial intervention was to evaluate the effectiveness of carbetocin (RTS) 100 µg administered intramuscularly (IM), compared to oxytocin 10 IU IM. The aims of the trial were two fold: to evaluate non-inferiority of the two uterotonic medications after vaginal delivery with blood loss of 500mL or more or the use of additional uterotonics as the composite endpoint at one hour and two hours after delivery. The second aim was to evaluate non-inferiority of the two medications in the prevention of severe PPH ≥1000 mL blood loss at one hour and up to two hours for those women continuing to bleed after the first hour.

Birmingham Women's Hospital was one of the 22 centres across 10 countries that recruited into the CHAMPION trial, and was the only UK site. The trial was conducted according to the published protocol by Widmer and colleagues and the primary study was published in the New England Journal of Medicine in August 2018 (33,70). I co-ordinated the day-to-day trial activity which included: recruitment, general trial management, serious and adverse event reporting, data collection, and liaison with the trial contract research organisation monitoring team. I also led the team processing the data for the local Birmingham trial site as a co-investigator under the guidance and mentorship of Professor Coomarasamy, the Birmingham site Principal Investigator, during the first year and a half of my Doctorate of Medicine studies.

Each site owns their locally collected trial data. The trial study team have given permission to use the local primary data to conduct analysis and investigate secondary questions, which are not part of the primary aims and objectives of the trial. This cohort study uses routinely collected trial data obtained during a randomised trial to investigate useful clinical questions.

A Cochrane review by Soltani and colleagues in 2010 included 1,671 women and addressed the timing of preventative uterotonic medication following childbirth (20). The uterotonic medication used was oxytocin; two trials used an intravenous oxytocin infusion and one used the intramuscular route. The Cochrane review concluded that there was no significant difference in clinically relevant outcomes between uterotonic use before and after placental delivery; on outcomes such as retained placenta, length of third stage, postpartum haemorrhage, blood transfusion and haemoglobin (20).

Since the 2010 Cochrane review a few studies have been published on timing of administration of the drug. A study by Orhan compared timing at two time points, delivery of the anterior shoulder and complete delivery of the baby (22). The study found that there was no significant difference in blood loss volume, haemorrhage over 600mL, haemoglobin and haematocrit (22).

Fidan et al. evaluated IV oxytocin at two time points: delivery of the anterior shoulder and at placental separation or delivery (21). The study did not record blood loss but instead focused on haemoglobin and haematocrit measurement. A significant difference in haemoglobin and haematocrit levels pre/post delivery was reported favouring the administration of oxytocin with the anterior shoulder; however the rate

of blood transfusion, use of further treatment uterotonics and retained placenta rates showed no difference (21).

The literature on active versus physiological/expectant management of the third stage of labour is more developed, as evidenced by the Cochrane review by Begley and colleagues (71). Active management comprises three separate interventions: administration of a uterotonic drug, delayed cord clamping, and controlled cord traction. The review favoured active management, but commented that the individual elements must be more carefully evaluated (71).

It can be agreed that using uterotonic medication following delivery is of benefit, especially as part of the active management of the third stage. However, the optimal time to administer the uterotonic medication remains a matter of contention.

### Hypothesis

The timing of uterotonic administration affects postpartum blood loss.

### Main objectives

To investigate the association between the time interval from the birth of the baby to the administration of the primary prophylactic uterotonic drug and:

- Maternal blood loss at both one hour and two hours;
- The number of women requiring manual removal of placenta.

## Methods

### Data collection

The participants are the UK sub-population of the WHO CHAMPION study who received the Investigational Medicinal Product (IMP) in accordance with the trial protocol with the exception of those who received the IMP >3 mins after birth of the baby were included (70). Women who had no data on the time of uterotonic

medication administration, missing blood loss data, or caesarean delivery were excluded. The database for analysis was derived from the cleaned and verified electronic case report forms extracted into Microsoft excel.

The timing of IMP administration was documented on the trial case report form; the data source was the electronic clinical record system - K2 Guardian™ (K2 Medical Systems Ltd. Plymouth UK). The K2 system provides full electronic capture of patient information in real time during childbirth at the bedside via a touchscreen. The K2 system uses a sequential series of questions to accurately document clinical data, which includes a mandatory question on uterotonic use and the time of administration (the software will not progress to allow completion of birth notes without this information being recorded). Only registered users- midwives or medical staff with appropriate K2 training can enter information in the K2 system and this data is verified by use of passwords or biometrics and checked with internal controls for consistency.

Blood loss was recorded and measured as set out in the trial protocol and accompanying manual of operations. The IMP was administered as soon as possible after the birth of the baby, and once the cord was clamped 1-3 minutes after delivery a plastic drape was placed under the woman's buttocks and blood loss measured for one, or two hours after delivery if bleeding continued beyond an hour. Figure 4 shows this sequence of events. In order to measure blood loss accurately scales with a digital record/sticker of the weight was attached to the paper CRF. All blood, clots and medium blood soaked gauze swabs were placed in the drape for measurement. The weight of the drape and blood loss was recorded as one measurement and conversion to blood volume in mls and average empty drape

weight taken into account for the final blood volumes reported. Manual removal of placenta was recorded in the CRF as were other relevant trial data.

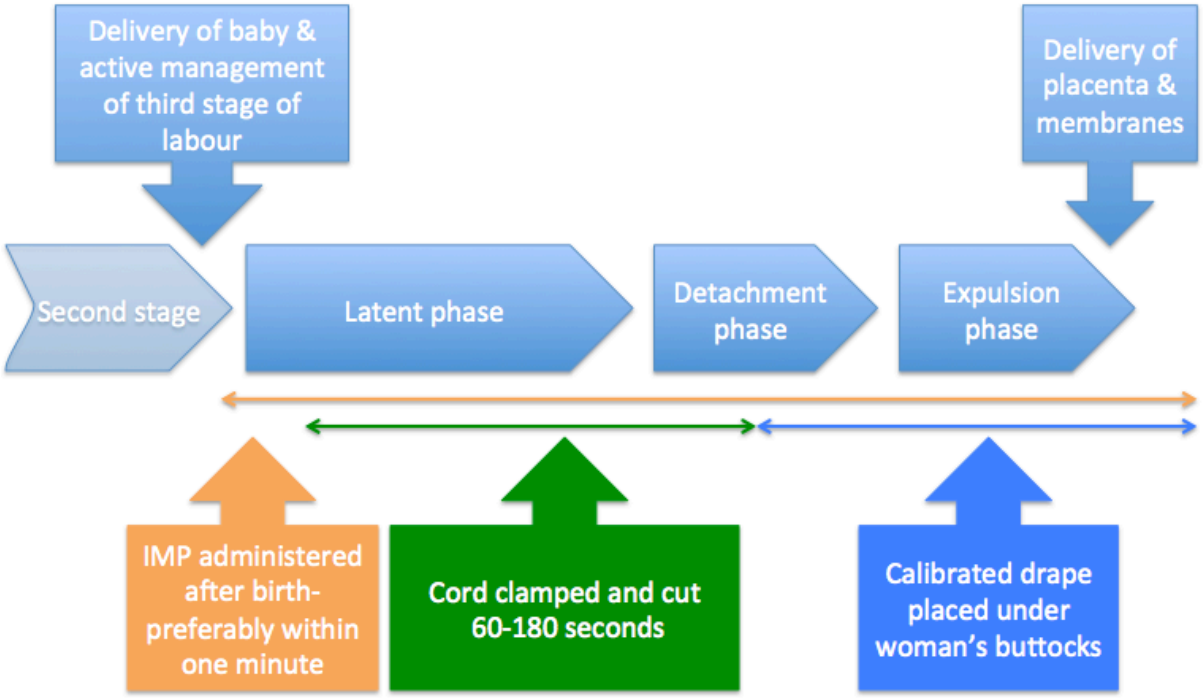


**Figure 4-** Schematic of labour and delivery phases

## Data analysis

I used descriptive statistics to report on the data collected and applied a logistic regression model with the blood loss as the dependent variable and timing of prophylactic uterotonic administration as the independent variable with adjustments for potential confounders such as age, parity, induction of labour, augmentation of labour, mode of birth and birth weight. The time in minutes when the prophylactic uterotonic medication was administered with minimum median blood loss was determined and termed the inflexion point. The inflexion point was used as the reference point to compare blood loss increase or decrease at other time points of

prophylactic uterotonic administration. The inflexion point provided a reference time and blood loss volume against which blood loss/gain per minute could be calculated. All statistical analyses were performed using STATA (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

## Results

The total number of participants eligible for inclusion in the database for analysis was 1,969 women.

### Maternal demographics

The median maternal age was 30 years (range 16-45 years), median parity was 1 (range 0-10), and 4.8% (*N*=94) women had previously had a PPH.

### Manual removal of Placenta

The number of women requiring manual removal of placenta (MROP) was 37 (1.9%).Of the women who immediately received uterotonic medication, 35 required MROP. Two further women required MROP having received uterotonic medication at four minutes and seven minutes respectively.

### Timing of uterotonic medication

The majority of women (1,856, 94%) received the IMP within the first 3 minutes of delivery. In the international study with 10 countries, 138 (0.47%) of 29,645 women received the IMP >3 mins after birth of the baby. The UK data accounts for 113 (82%) of those participants. The timing of uterotonic medication and blood loss from birth to one hour following delivery is reported in

Table 5 and from one hour to two hours follow delivery is reported in Table 6. The median blood loss when the IMP is given within the first minute following birth was 235mL (0-2758mL); the time at which blood loss was minimal as described by the

inflexion point in Figure 5, was at 5 minutes when the median blood loss was 171mL (1-1475mL). The median difference in blood loss between these two time points was 64mL. Figure 6 describes the adjusted regression model with adjustment for age from 16 years in increments of 5 years, parity categorized as nulliparous or multiparous, birth weight divided between birth weights less than or more than 4.5kg, augmented labour with oxytocin, and instrumental delivery. The inflection point for time with minimal blood loss (mL) was between 4-5 minutes.

Table 7 describes a crude and adjusted regression model. When timing of uterotonic administration was between 0-5 minutes, for each minute increase the blood loss decreased, on average 15.4mL. When the timing of uterotonic administration was between 5-13 minutes, for each minute increase the blood loss increased on average 16.5mL. After adjustment when timing of uterotonic administration was between 0-5 minutes, for each minute increase the blood loss decreased on average 5.7mL. When the timing of the uterotonic administration was between 5-13 minutes for each minute increase the blood loss increased on average 13.5mL.

**Table 5-** Blood loss recorded at one hour and time of uterotonic administration

| Time (min) | *N* | Median blood loss (mL) | Minimum blood loss (mL) | Maximum blood loss (mL) |
|---|---|---|---|---|
| **0-1** | 1595 | 235 | 0 | 2758 |
| **2-3** | 257 | 189 | 0 | 1570 |
| **4-5** | 74 | 171 | 1 | 1475 |
| **6-7** | 28 | 233 | 12 | 892 |
| **8-9** | 3 | 174 | 92 | 390 |

| | | | | |
|---|---|---|---|---|
| **10-11** | 5 | 235 | 39 | 292 |
| **12+** | 3 | 339 | 11 | 572 |

**Table 6-** Blood loss recorded in the second hour following delivery and time of uterotonic administration

| Time (min) | *N* | Median further blood loss (mL) | Minimum further blood loss (mL) | Maximum further blood loss (mL) |
|---|---|---|---|---|
| **0-1** | 42 | 67 | 1 | 1968 |
| **2-3** | 6 | 48 | 7 | 286 |
| **4-5** | 2 | 17 | 14 | 21 |
| **6+** | 2 | 72 | 20 | 124 |

Table 7- **Crude and adjusted model for time of uterotonic administration related to median total blood loss at 5 minute inflexion point.**

| | Uterotonic administration | Time 0-5 min | Time 6 min+ |
|---|---|---|---|
| **Crude blood volume gain/reduction from median total loss** | **Total *N*** | 1,930 | 39 |
| | **Blood loss per minute (mL/min)** | -15.4 | 16.5 |
| | **(95%CI); *p*-value** | (-26.1 – -4.7); 0.005 | (-12.9 – 46.0); 0.271 |
| **Adjusted* blood volume gain/reduction from median total loss** | **Total *N*** | 1,930 | 39 |
| | **Blood loss per minute (mL/min)** | -5.7 | 13.5 |
| | **(95%CI); *p*-value** | (-16.8 – 5.5); 0.32 | (-16.7 – 43.7); 0.38 |

*adjusted for age, parity, birth weight, augmented labour and instrumental delivery

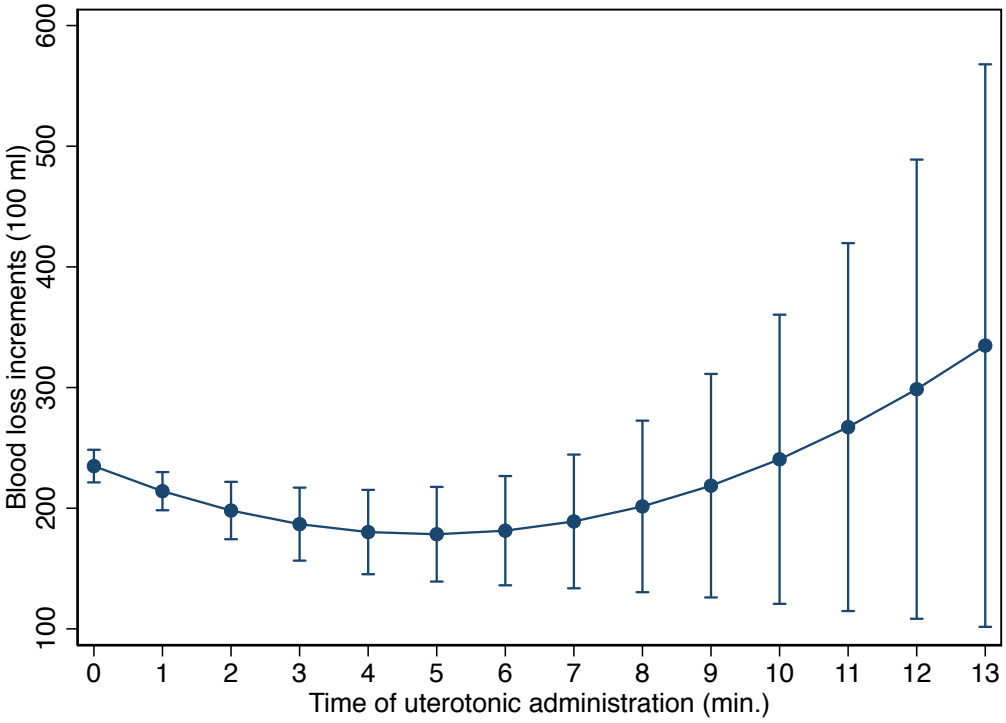


**Figure 5-** Crude regression model of blood loss (mL) and time (min.)

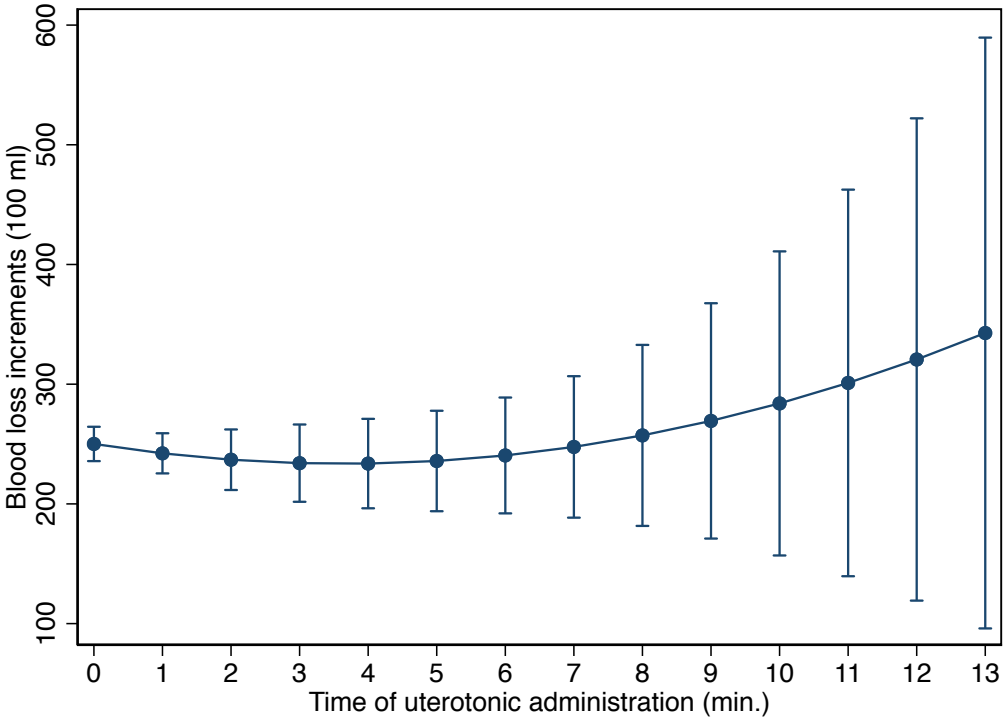


**Figure 6-**Adjusted regression model of blood loss (mL) and time (min.).

## Discussion

The investigation of the third stage of labour has focused on the prevention of bleeding, with comparatively little research on the physiological mechanism (72). In the last decade ultrasound studies in particular have increased and refined our understanding of the third stage (73–76). In one study which used a mixture of active and expectant management of the third stage the median duration was 8 minutes with a range of 2-39 minutes; 80% of women delivered within 12 minutes (75).

The third stage itself is divided into three parts; 1) latent, 2) contraction/detachment, and 3) expulsion (76). The latent phase occurs immediately following delivery while the uterus generates peristaltic contractions and thickens its wall away from the placental insertion site causing the surface area of the uterus to reduce shearing off the placenta and commencing the detachment phase; this process seems to happen in distinct regions of the uterus and finally leads to expulsion of the placenta (74–77).

Patwardhan and colleagues, using high quality ultrasound imaging found the median duration of the latent, detachment and expulsion phase was 163, 100, and 164 seconds respectively in a cohort of both active and expectant management patients (75). Krapp and colleagues in a study using active management of the third stage reported the following median durations for the latent, detachment and expulsion phases: 141, 50, and 80 seconds respectively (74). It is argued the latent phase is the main determinant of duration of the second stage and is independent of oxytocin administration (74,78).

The median duration of the latent phase of the third stage is likely to be at least 2 minutes in duration in either active or expectant management. The observation that the latent phase seems to be independent of oxytocin administration is plausible

given the postulated peristaltic and regional nature of the uterine contractions immediately after delivery. Indeed some investigators suggest that the uterus is contracting at the fundus and relaxing at the lower segment, allowing unobstructed delivery of the placenta (75). Furthermore there is some evidence to suggest that disruption of the regional pattern of uterine contraction is observed in those with a higher risk of postpartum haemorrhage (75).

The dynamic nature of the third stage of labour, and the uncertainty outlined above suggest that timing of preventative uterotonic medication needs further investigation. It is important to consider the risks of giving uterotonics too early and disrupting the regional contraction of the uterus in the latent phase or too late once the placenta has been expelled with a combination of contractions and controlled cord traction. The optimal time to administer a uterotonic medication might be at the junction between the latent and detachment phase at approximately 2 minutes or following detachment prior to expulsion at approximately 4 minutes.

The results of this study would suggest that delaying uterotonic drug administration by up to five minutes results in decreasing blood loss volume whereas administration after 5 minutes results in increasing blood loss. The findings of this study are supported by the biological mechanisms discussed above.

Trials conducted to date have used clear time-points to administer the uterotonic medication: delivery of the anterior shoulder, delivery of the entire baby, and delivery of the placenta. With an increased understanding of the physiology of the third stage and the results of this study; it is time to consider a more physiological timing of uterotonic medication. However the widespread use of ultrasound assessment of the components of the third stage of labour outside a research study would be onerous

to women and ethically unjustifiable as an adjunct to clinical practice until further research has been conducted.

## Summary of findings

The study provides a starting point for investigating the timing of uterotonic medication following delivery. The results in Figures 5 and 6 demonstrate that a biological gradient is evident in keeping with a plausible biological mechanism. There is a median difference of 64mL between administration of uterotonic medication within the first minute and within the fifth minute. Delaying uterotonic medication following delivery of the baby shows an association with reduced median blood loss by 15.4mL (crude) and 5.7mL (adjusted) per minute up to five minutes after birth; with an increase in blood loss of 16.5mL (crude) and 13.5mL (adjusted) from 6 minutes to 13 minutes.

## Strengths and weaknesses

This is the first large scale cohort study specifically addressing blood loss and uterotonic administration time in minutes rather than specific moments for administration such as crowning of the fetal head, delivery of the fetal shoulders or placenta. This study also benefits from a detailed trial protocol and careful measurement of blood loss combined with a close external monitoring and data integrity checks.

It is interesting to note that the Birmingham site had the majority of protocol deviations regarding timing of uterotonic medication for the whole trial (82%) while only contributing fewer than 7% of participants to the trial. This may suggest that Birmingham is unique in being slower to give uterotonic medication than other trial

sites. Perhaps in other sites two midwives routinely attended the delivery, one to deliver and another to administer the medication, which is not routine practice in Birmingham. An exploration of barriers to immediate uterotonic medication administration that seem to exist at the Birmingham site compared to other sites is beyond the remit of this study but might well indicate a risk of bias. It might be that in more complex births midwives were delayed in giving medication, or less experienced midwives tended to delay giving medication immediately, which might confound the blood loss observed. The fact that Birmingham's time of uterotonic medication is more variable than in other sites, might be attributed to the bedside electronic birth record system that is perhaps more robust than more traditional paper records. There may also be an element of recall bias and confirmation bias when documenting times of drug administration that are expected to be immediate.

Another source of bias might be that midwives promptly administer uterotonic medication after deliveries in those women they think are at higher risk of postpartum haemorrhage, and conversely less promptly to those women they deem at lower risk of bleeding excessively. Those with high-risk status could have offset any benefit from immediate uterotonic administration. Conversely any harm from delayed uterotonic administration could be offset by the low risk status of these women. The risk of residual confounding with a cohort study and secondary analysis is present and we cannot make a firm inference due to this.

By it's nature this type of secondary cohort study derived from a primary randomised control trial is only able to prompt hypothesis generation and associations at best, not least because the initial trial was not designed to answer the uterotonic timing question posed.

Finally the fact the analysis has been conducted un-blinded rather than by the two different medications used in the trial is a weakness. Given the longer half-life and sustained contractions caused by carbetocin it is reasonable to speculate that there may have been differences in blood loss, however the primary trial showed non-inferiority so this risk is reduced.

### Implications for clinical practice

There is the potential that the time of uterotonic medication administration could impact the volume of blood lost in a positive manner. This contradicts previous practice, which maintains that the earlier an uterotonic medication is administered the better, and is worthy of further investigation. In women where pregnancy is already complicated by anaemia, simply reducing blood loss by altering the timing of drug administration is an intriguing possibility.

## Conclusion

The Birmingham data suggests there could be a positive association between uterotonic timing with administration up to five minutes from birth and reduction in blood loss. The consensus that currently exists around administration of uterotonic medication immediately following delivery should be revisited, as a short delay is unlikely to be detrimental and may in fact be beneficial. Further research on the administration of uterotonic medication in keeping with the physiology of the third stage of labour is worth further investigation. However, the effect of residual confounding means we cannot draw a firm inference about the observed association.

## Ethics approval

Local ethical permission from Birmingham University has been granted for the secondary analysis Reference number ERN-17-0486. In addition The CHAMPION study ethics approval for the primary study made provision for secondary analysis.

# Chapter 5 - Cochrane Database of Systematic Reviews: Uterotonic agents for first- line treatment of postpartum haemorrhage

### *Preamble to Chapter 5*

In Chapters 1-4 of this thesis I have introduced strategies to reduce the risk of PPH considering risk factors and timing of prophylactic uterotonic medication. In Chapter 5 I describe which treatment uterotonic medication is best to use once a PPH has occurred. This chapter has been accepted for publication by the Cochrane collaboration and is under editorial review. The study manuscript is presented in the Cochrane Library format and referenced separately from the main body of the thesis.

### *Contributions*

Dr. Parry-Smith - drafted the protocol and study manuscript, screened trials, extracted data and performed pairwise statistical analyses. All other contributions are acknowledged in the manuscript.

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# Uterotonic agents for first-line treatment of postpartum haemorrhage

Editors: Cochrane Pregnancy and Childbirth Group

Contact Person: Argyro Papadopoulou (argypapadopoulou@gmail.com)

Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research
University of Birmingham
Edgbaston
Birmingham
B15 2TT
UK

William R Parry Smith [ 1 ]Argyro Papadopoulou [ 1 ]Eleanor Thomas [ 1 ]Aurelio Tobias [ 1 ]

Malcolm J Price [ 1 ]Shireen Meher [ 2 ]Zarko Alfirevic [ 3 ]Andrew D Weeks [ 3 ]

G Justus Hofmeyr [ 4 ]Ahmet Metin Gülmezoglu [ 5 ]Mariana Widmer [ 5 ]

Olufemi T Oladapo [ 6 ]Joshua P Vogel [ 7 ]Fernando Althabe [ 5 ]Arri Coomarasamy [ 1 ]

Ioannis D Gallos [ 1 ]

[1] WHO Collaborating Centre for Global Women's Health Research, Institute of Metabolism and Systems Research, School of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

[2] Birmingham Women's Hospital, Birmingham, UK

[3] Department of Women's and Children's Health, The University of Liverpool, Liverpool, UK

[4] Walter Sisulu University, University of Fort Hare, University of the Witwatersrand, Eastern Cape Department of Health, East London, South Africa

[5] 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

[6] UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Sexual and Reproductive Health and Research, World Health Organization, Geneva, Switzerland

[7] Maternal and Child Health, Burnet

Institute, Melbourne, Australia

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# Abstract

## Background

Postpartum haemorrhage (PPH), defined as a blood loss of more than 500 mL after birth, is the leading cause of maternal death worldwide. The World Health Organization (WHO) recommends that all women giving birth should receive a prophylactic uterotonic agent. Despite the routine administration of a uterotonic agent for PPH prevention, PPH remains a common complication causing one-quarter of all maternal deaths globally. When prevention fails and PPH occurs, further administration of uterotonic agents as 'first-line' treatment is recommended. However, there is uncertainty about which uterotonic agent is best for the 'first-line' treatment of PPH.

## Objectives

To identify the most effective uterotonic agent(s) with the least side effects for PPH treatment, and generate a ranking among all available agents according to their relative effectiveness and side-effect profile.

## Search methods

We searched the Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (5 May 2020), and the reference lists of all retrieved studies.

## Selection criteria

All randomised controlled trials or cluster-randomised trials comparing the effectiveness and safety of uterotonic agents with other uterotonic agents for the treatment of PPH were eligible for inclusion. Cross-over and quasi-randomised trials were excluded. Randomised trials published only as abstracts were eligible only if sufficient information could be retrieved.

## Data collection and analysis

At least two review authors independently assessed all trials for inclusion, extracted data and assessed each trial for risk of bias. Our primary outcomes were additional blood loss of more than 500 mL after recruitment to the trial until cessation of active bleeding and the composite outcome of maternal death or severe morbidity. Secondary outcomes included blood loss and related outcomes, morbidity outcomes, patient reported outcomes such as maternal sense of wellbeing, and side effects. We performed pairwise meta-analyses with inverse variance weighting to calculate the random-effects summary estimates. Indirect comparisons were performed, where possible, but due to the limited number of included studies, we were unable to conduct the planned network meta-analysis.

## Main results

Eight trials, involving 3838 women in 10 countries, were included in this review. All trials were conducted in hospital settings. Randomised women gave birth vaginally, except in one

trial, where women gave birth either vaginally or by caesarean section. Across the eight trials (16 trial arms) the following agents were used: four trial arms used misoprostol plus conventional uterotonics; four trial arms used conventional uterotonics alone; three trial arms used oxytocin; three trial arms used misoprostol; one trial arm used carbetocin; one trial arm used Syntometrine® (oxytocin and ergometrine) plus oxytocin.

Based on relative effects from pairwise meta-analysis of two trials (1787 participants) comparing misoprostol with oxytocin, low-certainty evidence suggests that misoprostol makes little or no difference to the additional blood loss of more than 500 mL (risk ratio (RR) 1.66, 95% confidence interval (CI) 0.69 to 4.02), the composite outcome of maternal mortality or severe morbidity (RR 1.98, 95% CI 0.36 to 10.72), the use of additional uterotonics (RR 1.30, 95% CI 0.57 to 2.94), and to the additional blood loss of more than 1000 mL (RR 2.57, 95% CI 1.00 to 6.64). However, misoprostol used as first-line treatment, increases the risk of women receiving a blood transfusion compared with oxytocin (RR 1.47, 95% CI 1.02 to 2.14, high-certainty).

According to relative effects from pairwise meta-analysis of four trials (1881 participants) comparing the combination of misoprostol plus conventional uterotonics with conventional uterotonics alone, we found that the combination is probably comparable to conventional uterotonics alone for the additional blood loss of more than 500 mL (RR 0.84, 95% CI 0.66 to 1.06, moderate-certainty), the composite outcome of maternal mortality or severe morbidity (RR 1.09, 95% CI 0.35 to 3.39, moderate-certainty), the use of additional uterotonics (RR 0.99, 95% CI 0.94 to 1.05, high-certainty), the additional blood loss of more than 1000 mL (RR 0.76, 95% CI 0.43 to 1.34, moderate-certainty), and for the risk of receiving a blood transfusion (RR 0.95, 95% CI 0.77 to 1.17, high-certainty).

For all outcomes the evidence on carbetocin versus oxytocin and misoprostol versus Syntometrine® plus oxytocin was of very low-certainty, and these effects remained unclear. An indirect comparison between carbetocin and misoprostol could be made, but the available evidence was also of very low-certainty.

In terms of side effects, misoprostol may make little difference to the incidence of fever (2 trials, 1787 participants, RR 3.43, 95% CI 0.65 to 18.18, low-certainty), and increases the risk for vomiting (2 trials, 1787 participants, RR 2.47, 95% CI 1.37 to 4.47, high-certainty) compared with oxytocin. Misoprostol plus conventional uterotonics increase the incidence of fever (4 trials, 1866 participants, RR 3.07, 95% CI 2.62 to 3.61, high-certainty), and vomiting (2 trials, 1482 participants, RR 1.85, 95% CI 1.16 to 2.95, high-certainty) compared with conventional uterotonics alone.

## Authors' conclusions

There is a lack of trial evidence for all uterotonic agents used as first-line treatment of PPH and no evidence for commonly used agents, such as injectable prostaglandins, ergometrine, and Syntometrine®. Misoprostol used as first-line treatment of PPH increases the risk of blood transfusion compared with oxytocin. Misoprostol in combination with conventional uterotonics is of comparable effectiveness to conventional uterotonics alone, but is associated with more side effects.

# Plain language summary

## Which drug is best for treating excessive blood loss after childbirth?

The aim of this Cochrane Review is to identify the most effective drug with the least side effects for treating excessive bleeding after childbirth. To do this, we used evidence from randomised controlled trials that compared one drug treatment to another drug treatment.

## What is the issue?

The most common reason why mothers die in childbirth is excessive bleeding, particularly in low- and lower-middle income countries. One of the main causes of excessive bleeding, or postpartum haemorrhage (PPH), is failure of the uterus to contract and close off blood supply to the placenta after the birth.
The World Health Organization (WHO) recommends giving drugs that increase uterine contractility (uterotonic drugs) immediately after the birth of the baby and as the placenta and its attached membranes are delivered to reduce blood loss. Some women still experience heavy bleeding that is described as PPH when a mother has lost 500 mL of blood or more after giving birth.

## Why is this important?

Giving uterotonic drugs is the main treatment when prevention fails and excessive bleeding occurs. Available uterotonic treatments include oxytocin, a manufactured oxytocin called carbetocin, ergometrine, misoprostol, injectable prostaglandins, and combination of these drugs. The drugs differ in their effectiveness and side-effects. It is important therefore to identify which drug is best for treating this life-threatening complication.

## What evidence did we find?

We searched for evidence in October 2017 and found eight studies involving 3838 women. The studies were conducted in hospitals across 10 countries. These were Argentina, Burkina Faso, Ecuador, Egypt, Gambia, Pakistan, South Africa, Thailand, Turkey, and Vietnam. Women gave birth vaginally except in one small study where they gave birth either vaginally or by caesarean section. Many but not all women had received uterotonic drugs to prevent excessive bleeding. The reason for excessive bleeding after birth was suspected to be failure of the uterus to contract effectively. In seven studies, the drugs used were misoprostol (as tablets dissolved under the tongue, given by mouth or rectally), oxytocin (by injection or slow infusion into a vein), Syntometrine® (ergometrine and oxytocin injected into muscle), or conventional uterotonics (oxytocin or a similar manufactured oxytocin; Syntometrine®; or ergometrine). One study compared carbetocin to oxytocin (both given by intravenous injection).
Comparing misoprostol with oxytocin (2 trials, 1787 women), misoprostol had a similar effect to oxytocin on further blood loss of more than 500 mL, a composite outcome of maternal death or severe ill-health, or the use of additional uterotonics (low-certainty evidence). Additional blood loss of more than 1000 mL tended to increase with misoprostol but without a clear increase. Misoprostol increased the risk of women receiving a blood transfusion compared with oxytocin (high-certainty evidence).
Misoprostol in combination with conventional uterotonic drugs (four trials, 1881 women) was comparable to conventional uterotonics alone when measuring further blood loss of more than 500 mL, additional blood loss of more than 1000 mL, the composite outcome of maternal death or severe ill-health (all moderate-certainty evidence), the use of additional uterotonics and the risk of receiving a blood transfusion (both high-certainty evidence).
Studies of carbetocin compared to oxytocin, and misoprostol compared to Syntometrine® plus additional oxytocin injected into a vein were of very low certainty, making any differences in the outcomes unclear. An indirect comparison of carbetocin and misoprostol was also of very low certainty.
Regarding side effects, misoprostol made little or no difference to the incidence of fever when compared with oxytocin but increased the risk of vomiting. The addition of misoprostol to conventional drugs increased the incidence of fever and vomiting when compared with conventional drugs alone.

## What does this mean?

We were not able to identify the most effective drug with the least side effects for treating excessive bleeding after childbirth as information was not available for all available drugs and for all possible comparisons.
Misoprostol increased the risk of women requiring a blood transfusion when compared with

oxytocin. Misoprostol in combination with conventional drugs was associated with a clear increase in side effects without being more effective.

---

**Summary of findings**

**Summary of findings 1**

## Additional blood loss of more than 500 mL

**Patient or population:** women in the third stage of labour with PPH
**Interventions:** multiple uterotonic agents (misoprostol, carbetocin, misoprostol plus conventional uterotonics)
**Comparison/Standard care (reference):** multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin, conventional uterotonics alone)
**Outcome:** additional blood loss of more than 500 mL after recruitment to cessation of active bleeding
**Setting:** hospital

| Uterotonic agent(s) | Direct evidence | | Indirect evidence | | NMA evidence | | Anticipated absolute effects for NMA estimate | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR (95% CI) | Certainty | RR (95% CI) | Certainty | RR (95% CI) | Certainty | Risk with standard care | Risk with intervention | Risk difference with intervention |
| **Misoprostol versus oxytocin** | 1.66 (0.69 to 4.02) | ⊕⊕⊖⊖ LOW[a] | Not reported by included studies | - | Not reported by included studies | - | 82 per 1000 (oxytocin) | 136 per 1000 (misoprostol) | 54 more per 1000 (from 25 fewer to 247 more) with misoprostol compared with oxytocin |
| **Misoprostol plus conventional uterotonics versus conventional uterotonics alone** | 0.84 (0.66 to 1.06) | ⊕⊕⊕⊖ MODERATE[b] | Not reported by included studies | - | Not reported by included studies | - | 211 per 1000 (conventional uterotonics alone) | 177 per 1000 (misoprostol plus conventional uterotonics) | 34 fewer per 1000 (from 72 fewer to 13 more) with misoprostol plus conventional uterotonics compared with conventional uterotonics alone |
| **Misoprostol versus Syntometrine® plus oxytocin** | Not reported by included studies | - | Not reported by included studies | - | Not reported by included studies | - | See comment* | See comment** | See comment*** |
| **Carbetocin versus oxytocin** | Not reported by included studies | - | Not reported by included studies | - | Not reported by included studies | - | See comment* | See comment** | See comment*** |
| **Carbetocin versus misoprostol** | Not reported by included studies | - | Not reported by included studies | - | Not reported by included studies | - | See comment* | See comment** | See comment*** |

*No included studies or there are no events in included studies to estimate the baseline risk.

**Absolute risk with intervention cannot be estimated in the absence of absolute risk with standard of care.

***Risk difference cannot be estimated in the absence of absolute risks with intervention and standard of care.
**CI:** Confidence interval; **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] Direct evidence downgraded -2 due to severe unexplained statistical heterogeneity and serious imprecision.

[b] Direct evidence downgraded -1 due to serious imprecision.

**Summary of findings 2**

## Composite of death or severe morbidity

**Patient or population:** women in the third stage of labour with PPH
**Interventions:** multiple uterotonic agents (misoprostol, carbetocin, misoprostol plus conventional uterotonics)
**Comparison/Standard care (reference):** multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin, conventional uterotonics alone)
**Outcome:** composite of death, hysterectomy, transfer to higher care, organ dysfunction, coagulopathy, shock
**Setting:** hospital

| Uterotonic agent(s) | Direct evidence | | Indirect evidence | | NMA evidence | | Anticipated absolute effects for NMA estimate | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR (95% CI) | Certainty | RR (95% CI) | Certainty | RR (95% CI) | Certainty | Risk with standard care | Risk with intervention | Risk difference with intervention |
| **Misoprostol versus oxytocin** | 1.98 (0.36 to 10.72) | ⊕⊕⊖⊖ LOW[a] | Not reported by included studies | - | Not reported by included studies | - | 2 per 1000 (oxytocin) | 4 per 1000 with (misoprostol) | 2 more per 1000 (from 1 fewer to 22 more) with misoprostol compared with oxytocin |
| **Misoprostol plus conventional uterotonics versus conventional uterotonics alone** | 1.09 (0.35 to 3.39) | ⊕⊕⊖⊖ MODERATE[c] | Not reported by included studies | - | Not reported by included studies | - | 14 per 1000 (conventional uterotonics alone) | 15 per 1000 (misoprostol plus conventional uterotonics) | 1 more per 1000 (from 9 fewer to 33 more) with misoprostol plus conventional uterotonics compared with conventional uterotonics alone |
| **Misoprostol versus Syntometrine® plus oxytocin** | 0.33 (0.01 to 7.89) | ⊕⊖⊖⊖ VERY LOW[b] | Not reported by included studies | - | Not reported by included studies | - | 31 per 1000 (Syntometrine® plus oxytocin) | 10 per 1000 (misoprostol) | 21 fewer per 1000 (from 31 fewer to 215 more) with misoprostol compared with Syntometrine® plus oxytocin |
| **Carbetocin versus oxytocin** | Not reported by included studies | - | Not reported by included studies | - | Not reported by included studies | - | See comment* | See comment** | See comment*** |
| **Carbetocin versus misoprostol** | Not reported by included studies | - | Not reported by included studies | - | Not reported by included studies | - | See comment* | See comment** | See comment*** |

*No included studies or there are no events in included studies to estimate the baseline risk.

**Absolute risk with intervention cannot be estimated in the absence of absolute risk with standard of care.

***Risk difference cannot be estimated in the absence of absolute risks with intervention and standard of care.
**CI:** Confidence interval; **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] Direct evidence downgraded -2 due to very serious imprecision.

[b] Direct evidence downgraded -3 due to multiple limitations in study design and very serious imprecision.

[c] Direct evidence downgraded -1 due to imprecision.

**Summary of findings 3**

## Use of additional uterotonics

**Patient or population:** women in the third stage of labour with PPH
**Interventions:** multiple uterotonic agents (misoprostol, carbetocin, misoprostol plus conventional uterotonics)
**Comparison/Standard care (reference):** multiple uterotonic agents (oxytocin, Syntometrine ® plus oxytocin, conventional uterotonics alone)
**Outcome:** use of additional uterotonics
**Setting:** hospital

| Uterotonic agent(s) | Direct evidence | | Indirect evidence | | NMA evidence | | Anticipated absolute effects for NMA estimate | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR (95% CI) | Certainty | RR (95% CI) | Certainty | RR (95% CI) | Certainty | Risk with standard care | Risk with intervention | Risk difference with intervention |
| **Misoprostol versus oxytocin** | 1.30 (0.57 to 2.94) | ⊕⊕⊖⊖ LOW[a] | Not reported by included studies | - | Not reported by included studies | - | 86 per 1000 (oxytocin) | 112 per 1000 (misoprostol) | 26 more per 1000 (from 37 fewer to 167 more) with misoprostol compared with oxytocin |
| **Misoprostol plus conventional uterotonics versus conventional uterotonics alone** | 0.99 (0.94 to 1.05) | ⊕⊕⊕⊕ HIGH | Not reported by included studies | - | Not reported by included studies | - | 322 per 1000 (conventional uterotonics alone) | 318 per 1000 (misoprostol plus conventional uterotonics) | 3 fewer per 1000 (from 19 fewer to 16 more) with misoprostol plus conventional uterotonics compared with conventional uterotonics alone |
| **Misoprostol versus Syntometrine® plus oxytocin** | 0.18 (0.04 to 0.76) | ⊕⊖⊖⊖ VERY LOW[b] | Not reported by included studies | - | Not reported by included studies | - | 344 per 1000 (Syntometrine® plus oxytocin) | 62 per 1000 (misoprostol) | 282 fewer per 1000 (from 330 fewer to 82 fewer) with misoprostol compared with Syntometrine® plus oxytocin |
| **Carbetocin versus oxytocin** | 0.48 (0.25 to 0.91) | ⊕⊖⊖⊖ VERY LOW[b] | Not reported by included studies | - | Not reported by included studies | - | 420 per 1000 (oxytocin) | 202 per 1000 (carbetocin) | 218 fewer per 1000 (from 315 fewer to 38 fewer) with carbetocin compared with oxytocin |
| **Carbetocin versus misoprostol** | Not reported by included studies | - | 0.37 (0.13 to 1.05) | ⊕⊖⊖⊖ VERY LOW[c] | Not reported by included studies | - | 113 per 1000 (misoprostol) | 42 per 1000 (carbetocin) | 71 fewer per 1000 (from 98 fewer to 6 more) with carbetocin compared with misoprostol |

**CI:** Confidence interval; **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] Direct evidence downgraded -2 due to severe unexplained statistical heterogeneity and serious imprecision.

[b] Direct evidence downgraded -3 due to multiple limitations in study design and serious imprecision.

[c] The lowest grading of the two direct comparisons corresponds to 'carbetocin versus oxytocin', which was of very low certainty.

**Summary of findings 4**

## Additional blood loss of more than 1000 mL

**Patient or population:** women in the third stage of labour with PPH
**Interventions:** multiple uterotonic agents (misoprostol, carbetocin, misoprostol plus conventional uterotonics)
**Comparison/Standard care (reference):** multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin, conventional uterotonics alone)
**Outcome:** additional blood loss of more than 1000 mL after recruitment to cessation of active bleeding
**Setting:** hospital

| Uterotonic agent(s) | Direct evidence | | Indirect evidence | | NMA evidence | | Anticipated absolute effects for NMA estimate | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR (95% CI) | Certainty | RR (95% CI) | Certainty | RR (95% CI) | Certainty | Risk with standard care | Risk with intervention | Risk difference with intervention |
| **Misoprostol versus oxytocin** | 2.57 (1.00 to 6.64) | ⊕⊕⊖⊖ LOW[a] | Not reported by included studies | - | Not reported by included studies | - | 7 per 1000 (oxytocin) | 17 per 1000 (misoprostol) | 11 more per 1000 (from 0 fewer to 38 more) with misoprostol compared with oxytocin |
| **Misoprostol plus conventional uterotonics versus conventional uterotonics alone** | 0.76 (0.43 to 1.34) | ⊕⊕⊕⊖ MODERATE[c] | Not reported by included studies | - | Not reported by included studies | - | 29 per 1000 (conventional uterotonics alone) | 22 per 1000 (misoprostol plus conventional uterotonics) | 7 fewer per 1000 (from 16 fewer to 10 more) with misoprostol plus conventional uterotonics compared with conventional uterotonics alone |
| **Misoprostol versus Syntometrine® plus oxytocin** | Not reported by included studies | - | Not reported by included studies | - | Not reported by included studies | - | See comment* | See comment** | See comment*** |
| **Carbetocin versus oxytocin** | 0.55 (0.22 to 1.36 | ⊕⊖⊖⊖ VERY LOW[b] | Not reported by included studies | - | Not reported by included studies | - | 220 per 1000 (oxytocin) | 121 per 1000 (carbetocin) | 99 fewer per 1000 (from 172 fewer to 79 more) with carbetocin compared with oxytocin |
| **Carbetocin versus misoprostol** | Not reported by included studies | - | 0.21 (0.06 to 0.80) | ⊕⊖⊖⊖ VERY LOW[d] | Not reported by included studies | - | 18 per 1000 (misoprostol) | 4 per 1000 (carbetocin) | 14 fewer per 1000 (from 17 fewer to 4 fewer) with carbetocin compared |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | with misoprostol |

*No included studies or there are no events in included studies to estimate the baseline risk.

**Absolute risk with intervention cannot be estimated in the absence of absolute risk with standard of care.

***Risk difference cannot be estimated in the absence of absolute risks with intervention and standard of care.
**CI:** Confidence interval; **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] Direct evidence downgraded -2 due to very serious imprecision.

[b] Direct evidence downgraded -3 due to multiple limitations in study design and very serious imprecision.

[c] Direct evidence downgraded -1 due to serious imprecision.

[d] The lowest grading of the two direct comparisons corresponds to 'carbetocin versus oxytocin', which was of very low certainty.

**Summary of findings 5**

## Blood transfusion or other blood products

**Patient or population:** women in the third stage of labour with PPH
**Interventions:** multiple uterotonic agents (misoprostol, carbetocin, misoprostol plus conventional uterotonics)
**Comparison/Standard care (reference):** multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin, conventional uterotonics alone)
**Outcome:** blood transfusion or other blood products
**Setting:** hospital

| Uterotonic agent(s) | Direct evidence | | Indirect evidence | | NMA evidence | | Anticipated absolute effects for NMA estimate | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR (95% CI) | Certainty | RR (95% CI) | Certainty | RR (95% CI) | Certainty | Risk with standard care | Risk with intervention | Risk difference with intervention |
| **Misoprostol versus oxytocin** | 1.47 (1.02 to 2.14) | ⊕⊕⊕⊕ HIGH | Not reported by included studies | - | Not reported by included studies | - | 49 per 1000 (oxytocin) | 73 per 1000 (misoprostol) | 23 more per 1000 (from 1 more to 56 more) with misoprostol compared with oxytocin |
| **Misoprostol plus conventional uterotonics versus conventional uterotonics alone** | 0.95 (0.77 to 1.17) | ⊕⊕⊕⊕ HIGH | Not reported by included studies | - | Not reported by included studies | - | 158 per 1000 (conventional uterotonics alone) | 150 per 1000 (misoprostol plus conventional uterotonics) | 8 fewer per 1000 (from 36 fewer to 27 more) with misoprostol plus conventional uterotonics compared with conventional uterotonics alone |
| **Misoprostol versus Syntometrine® plus oxytocin** | Not reported by included studies | - | Not reported by included studies | - | Not reported by included studies | - | See comment* | See comment** | See comment*** |
| **Carbetocin** | 0.67 | ⊕⊖⊖⊖ | Not reported | | Not reported | | | 121 per | 59 fewer per 1000 (from 133 fewer to 131 more) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **versus oxytocin** | (0.26 to 1.73) | VERY LOW[a] | by included studies | - | by included studies | - | 180 per 1000 (oxytocin) | 1000 (carbetocin) | with carbetocin compared with oxytocin |
| **Carbetocin versus misoprostol** | Not reported by included studies | - | 0.46 (0.16 to 1.26) | ⊕⊖⊖⊖ VERY LOW[b] | Not reported by included studies | - | 73 per 1000 (misoprostol) | 33 per 1000 (carbetocin) | 39 fewer per 1000 (from 61 fewer to 19 more) with carbetocin compared with misoprostol |

*No included studies or there are no events in included studies to estimate the baseline risk.

**Absolute risk with intervention cannot be estimated in the absence of absolute risk with standard of care.

***Risk difference cannot be estimated in the absence of absolute risks with intervention and standard of care.
**CI:** Confidence interval; **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] Direct evidence downgraded -3 due to multiple limitations in study design and very serious imprecision.

[b] The lowest grading of the two direct comparisons corresponds to 'carbetocin versus oxytocin', which was of very low certainty.

**Summary of findings 6**

## Side effects: fever

**Patient or population:** women in the third stage of labour with PPH
**Interventions:** multiple uterotonic agents (misoprostol, carbetocin, misoprostol plus conventional uterotonics)
**Comparison/Standard care (reference):** multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin, conventional uterotonics alone)
**Outcome:** fever
**Setting:** hospital

| Uterotonic agent(s) | Direct evidence | | Indirect evidence | | NMA evidence | | Anticipated absolute effects for NMA estimate | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR (95% CI) | Certainty | RR (95% CI) | Certainty | RR (95% CI) | Certainty | Risk with standard care | Risk with intervention | Risk difference with intervention |
| **Misoprostol versus oxytocin** | 3.43 (0.65 to 18.18) | ⊕⊕⊖⊖ LOW[a] | Not reported by included studies | - | Not reported by included studies | - | 96 per 1000 (oxytocin) | 331 per 1000 (misoprostol) | 234 more per 1000 (from 34 fewer to 1000 more) with misoprostol compared with oxytocin |
| **Misoprostol plus conventional uterotonics versus conventional uterotonics alone** | 3.07 (2.62 to 3.61) | ⊕⊕⊕⊕ HIGH | Not reported by included studies | - | Not reported by included studies | - | 151 per 1000 (conventional uterotonics alone) | 463 per 1000 (misoprostol plus conventional uterotonics) | 312 more per 1000 (from 244 more to 393 more) with misoprostol plus conventional uterotonics compared with |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | conventional uterotonics alone |
| **Misoprostol versus Syntometrine® plus oxytocin** | Not reported by included studies | - | Not reported by included studies | - | Not reported by included studies | - | See comment* | See comment** | See comment*** |
| **Carbetocin versus oxytocin** | Not reported by included studies | - | Not reported by included studies | - | Not reported by included studies | - | See comment* | See comment** | See comment*** |
| **Carbetocin versus misoprostol** | Not reported by included studies | - | Not reported by included studies | - | Not reported by included studies | - | See comment* | See comment** | See comment*** |

*No included studies or there are no events in included studies to estimate the baseline risk.

**Absolute risk with intervention cannot be estimated in the absence of absolute risk with standard of care.

***Risk difference cannot be estimated in the absence of absolute risks with intervention and standard of care.
**CI:** Confidence interval; **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] Direct evidence downgraded -2 due to severe unexplained statistical heterogeneity and serious imprecision.

**Summary of findings 7**

## Side effects: vomiting

**Patient or population:** women in the third stage of labour with PPH
**Interventions:** multiple uterotonic agents (misoprostol, carbetocin, misoprostol plus conventional uterotonics)
**Comparison/Standard care (reference):** multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin, conventional uterotonics alone)
**Outcome:** vomiting
**Setting:** hospital

| **Uterotonic agent(s)** | **Direct evidence** | | **Indirect evidence** | | **NMA evidence** | | **Anticipated absolute effects for NMA estimate** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **RR (95% CI)** | **Certainty** | **RR (95% CI)** | **Certainty** | **RR (95% CI)** | **Certainty** | **Risk with standard care** | **Risk with intervention** | **Risk difference with intervention** |
| **Misoprostol versus oxytocin** | 2.47 (1.37 to 4.47) | ⊕⊕⊕⊕ HIGH | Not reported by included studies | - | Not reported by included studies | - | 19 per 1000 (oxytocin) | 47 per 1000 (misoprostol) | 28 more per 1000 (from 7 more to 66 more) with misoprostol compared with oxytocin |
| **Misoprostol plus conventional uterotonics versus conventional uterotonics alone** | 1.85 (1.16 to 2.95) | ⊕⊕⊕⊕ HIGH | Not reported by included studies | - | Not reported by included studies | - | 35 per 1000 (conventional uterotonics alone) | 64 per 1000 (misoprostol plus conventional uterotonics | 30 more per 1000 (from 6 more to 68 more) with misoprostol plus conventional uterotonics compared with conventional uterotonics |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | alone |
| **Misoprostol versus Syntometrine® plus oxytocin** | Not reported by included studies | - | Not reported by included studies | - | Not reported by included studies | - | See comment* | See comment** | See comment*** |
| **Carbetocin versus oxytocin** | 3.00 (0.13 to 71.92) | ⊕⊖⊖⊖ VERY LOW[a] | Not reported by included studies | - | Not reported by included studies | - | 0 per 1000 (oxytocin) | 0 per 1000 (carbetocin) | 0 fewer per 1000 (from 0 fewer to 0 fewer) with carbetocin compared with oxytocin |
| **Carbetocin versus misoprostol** | Not reported by included studies | - | 1.21 (0.05 to 30.18) | ⊕⊖⊖⊖ VERY LOW[b] | Not reported by included studies | - | 48 per 1000 (misoprostol) | 58 per 1000 (carbetocin) | 10 more per 1000 (from 46 fewer to 1000 more) with carbetocin compared with misoprostol |

*No included studies or there are no events in included studies to estimate the baseline risk.

**Absolute risk with intervention cannot be estimated in the absence of absolute risk with standard of care.

***Risk difference cannot be estimated in the absence of absolute risks with intervention and standard of care.
**CI:** Confidence interval; **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] Direct evidence downgraded -3 due to multiple limitations in study design and very serious imprecision.

[b] The lowest grading of the two direct comparisons corresponds to 'carbetocin versus oxytocin', which was of very low certainty.

# Background

Postpartum haemorrhage (PPH), defined as a blood loss of more than 500 mL after birth, is the leading cause of maternal death worldwide, accounting for up to 27% of maternal deaths (Say 2014). Almost all maternal deaths (99%) due to PPH occur in low- and lower-middle income countries (Say 2014). When a mother dies from PPH, she often leaves behind a young family and her infant has less than a 20% chance of surviving past the first month (Say 2014). Even when death is avoided, it can result in major maternal morbidity, such as the need for surgery or hysterectomy and blood transfusions (Carroll 2016).

The most common cause of PPH is uterine atony (failure of the uterus to contract after birth). Therefore, the World Health Organization (WHO) recommends prophylactic administration of agents that increase uterine contractility (uterotonics) for all births (WHO 2018). Despite the administration of effective uterotonic agents for PPH prevention, PPH is still a very common complication, occurring in up to 15% of women giving birth (Gallos 2018). When prevention fails and PPH occurs, further administration of uterotonic agents as 'first-line' treatment is recommended (WHO 2012). There are several uterotonics available for treating PPH, including oxytocin, ergometrine, misoprostol, carbetocin, injectable prostaglandins, and combination agents. Each of these agents differs in terms of effectiveness and side-effects, which makes it difficult deciding which uterotonic agent is best for the 'first-line' treatment of PPH.

## Why it is important to do this review

A Cochrane Review evaluated the interventions used for treating PPH, including pairwise meta-analyses of randomised trials comparing different uterotonic agents (Mousa 2014). However, conventional pairwise meta-analyses can only generate effect estimates for those treatment interventions that have been compared in head-to-head trials. Therefore, in the absence of a single high-quality, randomised controlled trial comparing all uterotonic agents, uncertainty remains about which is the best for PPH treatment.

Where several competing treatment options exist, not all of which have been directly compared, a network meta-analysis may be better able to allow for more comparisons to be made and a more comprehensive synthesis of relative effects for all available uterotonic agents. A network meta-analysis, unlike conventional Cochrane Reviews, simultaneously pools all direct and indirect evidence into one single coherent analysis (Caldwell 2005; Caldwell 2010). Indirect evidence is obtained by inferring the relative effectiveness of two competing treatments through a common comparator, even when these two drugs have not been compared directly (Caldwell 2010). A network meta-analysis also calculates the probability for each competing agent to constitute the most effective agent with the least side effects, thereby allowing ranking of the available agents.

# Objectives

To identify the most effective uterotonic agent(s) with the least side effects for postpartum haemorrhage treatment, and generate a ranking among all available agents according to their relative effectiveness and side effect profile.

# Methods

## Criteria for considering studies for this review

### Types of studies

All randomised controlled trials or cluster-randomised trials comparing the effectiveness and side effects of uterotonic agents with other uterotonic agents for treating postpartum haemorrhage (PPH) were eligible for inclusion. Cross-over trials and quasi-randomised trials were excluded. The cross-over study design is inappropriate to investigate the effectiveness of PPH treatment, and quasi-randomisation rather than true randomisation brings an elevated risk of bias that we wish to eliminate for the purpose of this review. Randomised trials published only as abstracts were eligible only if sufficient information could be retrieved.

### Types of participants

This review included trials involving women with PPH after a vaginal or caesarean birth in hospital or community settings.

### Types of interventions

Trials were eligible for inclusion if they studied the systemic administration of uterotonic agents of any dosage, route or regimen for the treatment of primary PPH and compared them with any other uterotonic agent.

We classified the uterotonic agents into two distinct categories. The first category included single agents such as oxytocin, ergometrine (including also ergonovine, and methylergonovine), misoprostol, carbetocin and injectable prostaglandins (i.e. carboprost tromethamine or sulprostone). The second category included combination agents such as ergometrine plus oxytocin (either Syntometrine® as a fixed-combination drug containing 5 IU of oxytocin and 500 mcg of ergometrine, or any oxytocin dose and route when combined with any dose and route of ergometrine, ergonovine, or methylergonovine), and misoprostol plus oxytocin (any dose and route of oxytocin when combined with any dose and route of misoprostol).

We excluded all trials evaluating uterotonic agents not administered systemically (e.g. intrauterine administration) as well as those comparing exclusively different dosages, routes or regimens of the same uterotonic agent. Trials comparing other interventions including non-uterotonic drugs, such as tranexamic acid, or surgical procedures were also excluded.

For the purpose of this review, we assumed that any woman meeting our inclusion criteria is, in principle, equally likely to be randomised to any of the available uterotonic treatment options.

## Types of outcome measures

We estimated the relative effects and ranking of the competing uterotonic agents according to the following primary and secondary outcomes.

### Primary outcomes

- Additional blood loss of more than 500 mL after recruitment to the trial until cessation of active bleeding
- Composite outcome of maternal death or severe morbidity (e.g. hysterectomy, any organ dysfunction, transfer to higher level of care, coagulopathy, shock as defined by trialists)

### Secondary outcomes

- Maternal death
- Need for additional uterotonics
- Additional blood loss of more than 1000 mL after recruitment to the trial until cessation of active bleeding
- Additional surgical procedures (e.g. hysterectomy, balloon insertion, pack insertion, arterial ligation, embolization and compression sutures)
- Blood transfusion or transfusion of other blood products
- Mean additional blood loss (mL)
- Change in haemoglobin measurements before and after birth (g/L)
- Side effects: fever (> 38°C), hypothermia (< 36°C), nausea, vomiting, hypertension, headache, shivering, tachycardia, arrhythmia, diarrhoea, and abdominal pain
- Patient-reported outcomes: sense of well-being, acceptability and satisfaction of the intervention
- Breastfeeding on discharge

# Search methods for identification of studies

This Methods section is based on a standard template used by Cochrane Pregnancy and Childbirth and the recent protocol adaption for multiple interventions suggested by Chaimani and colleagues (Chaimani 2017).

## Electronic searches

We searched the Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (5 May 2020).

The Register is a database containing over 25,000 reports of controlled trials in the field of pregnancy and childbirth and it represents over 30 years of searching. For full current search 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.

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;
6. Weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above were reviewed. Based on the intervention described, each trial report was assigned a number that corresponded to a specific Pregnancy and Childbirth review topic (or topics), and was 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 or Ongoing studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (4 October 2017) (see: Appendix 1 for search methods used).

### Searching other resources

We retrieved additional relevant references cited in papers identified through the above search strategy. We also searched for the full texts of trials initially identified as abstracts. For randomised trials published only as abstracts, we sought information from primary authors to investigate whether these studies met our eligibility criteria before including them. We did not apply any language or date restrictions.

## Data collection and analysis

### Selection of studies

At least two review authors retrieved and independently assessed for inclusion all potential studies identified as a result of the search strategy (WRPS, AP, SM). We resolved any disagreements through discussion or, if required, through consultation with a third person (IDG).

We created a study flow diagram to map out the number of records identified, included and excluded (Figure 1).

### Data extraction and management

We designed an electronic form to extract data. For eligible studies, at least two review authors independently extracted the data using a blank electronic form (WRPS, AP, SM). We resolved discrepancies through discussion or, if required, we consulted a third person (IDG). We entered data into Review Manager software (RevMan 2014) and checked them for accuracy. When information was unclear, we attempted to contact the authors of the original reports to provide further details. We extracted the following data.

#### Outcome data

From each included trial we extracted: the number of participants, the number of fetuses (singleton or multiple gestations), exclusion criteria from the trial, the interventions being compared along with any co-interventions, and their respective primary and secondary outcomes. All relevant arm level data were extracted (e.g. number of events and number of patients for binary outcomes, and means and standard deviations per study arm for continuous outcomes).

### Data on potential effect modifiers

In addition, from each included trial we extracted the following study, intervention and population characteristics that could act as effect modifiers.

1. Gestational age
2. Parity
3. Mode of delivery (vaginal or caesarean birth)
4. Prior risk of PPH (as defined by trialists and categorised as low, high or mixed)
5. Uterotonic administration prior to enrolment
6. Dosage, regimen, and route of administration (sublingual, oral, rectal, intramuscular, intravenous bolus and/or infusion)
7. Study setting (community or hospital)
8. Co-interventions such as tranexamic acid and uterine massage
9. Randomisation unit

### Other data

From each included trial we extracted the following additional data.

1. Country or countries in which the study was performed
2. Year of publication and dates of recruitment
3. Type of publication (full text, abstract or unpublished data)
4. Trial registration reference

## Assessment of risk of bias in included studies

At least two review authors (WRPS, AP) independently assessed the risk of bias of each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), modified as appropriate to the context of this review, and described below. We resolved any disagreements by discussion or by involving a third assessor (IDG).

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

Studies were excluded if found to be at high risk for bias for random sequence generation (any non-random process, e.g. odd or even date of birth; hospital or clinic record number). We described for each included trial the method used to generate the allocation sequence and made an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator); or
- unclear risk of bias.

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

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

We assessed 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 (method unspecified).

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

We described for each included study 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 would be unlikely to affect the results.

We assessed 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 described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received.

We assessed 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 described for each included study 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 data were reported, or supplied by the trial authors, we re-included missing data in the analyses.

We assessed methods to handle incomplete outcome data as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups and not exceeding 10%);
- 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 (exclusions or attrition unreported).

### (5) Selective reporting (checking for reporting bias)

We described for each included study any inconsistency between the prespecified study protocol (if available), the study methods described in the study report, and the results listed in the study report.

We assessed the methods as:

- low risk of bias (where it is 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 prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; or failure to report results of a key outcome that would have been expected to have been included); or
- unclear risk of bias (prespecified study protocol unavailable).

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

We described 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 assessed 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 (unspecified source of funding).

Another source of bias that we assessed was the method of measuring blood loss.

We assessed the method described in each study and classified it as at:

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

### (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 for Systematic Reviews of Interventions* (Higgins 2011). For our primary outcomes, we combined quality items and judged trials as 'low risk of bias' if they were double-blind, had allocation concealment with little loss to follow-up (less than 10%). Trials were judged as 'intermediate risk of bias' if they demonstrated adequate allocation concealment, with assessor blinding and little loss to follow-up (less than 10%). Alternatively, trials were considered to be at 'high risk of bias'.

### Summary of findings

Each 'Summary of findings' table describes key features of the evidence relating to a single outcome, and there is one table for each of our most important outcomes in accordance with the GRADE approach. These include the outcome of additional blood loss of more than 500 mL, composite of death or severe morbidity, use of additional uterotonics, additional blood loss of more than 1000 mL, blood transfusion or other blood products, fever, and vomiting. We used the GRADE working group's approach (Brignardello-Petersen 2018; Puhan 2014) for rating the certainty of the analysis effect estimates for all the comparisons and all outcomes.

We assessed the certainty of the direct evidence, and rated the evidence using the standard GRADE approach based on assessment of study design limitations, inconsistency, imprecision, indirectness and publication bias (Higgins 2011). On the network diagram for all the comparisons and all outcomes we display the GRADE assessment of the direct evidence. We also rated the certainty of the indirect evidence, where available, based on the lower of the certainty ratings of the two comparisons with the common comparator. For example, we were able to compare carbetocin with misoprostol indirectly with the common comparator being oxytocin. Carbetocin was compared to oxytocin and misoprostol was compared to oxytocin, but there was no direct evidence comparing carbetocin with misoprostol. The certainty rating for this indirect comparison was the lower of the two comparisons (carbetocin versus oxytocin and misoprostol versus oxytocin) with the common comparator of oxytocin.

The quality of evidence for each outcome was rated as ‘high', ‘moderate', ‘low’ or ‘very low' in accordance with the GRADE approach: 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; and 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.

## Measures of treatment effect

### Relative treatment effects

We summarised the relative treatment effects of dichotomous outcomes with risk ratios (RRs) and for continuous outcomes as mean difference (MD) with 95% confidence intervals (CIs). If different scales had been used we used standardised mean differences (SMDs)

with 95% CIs (Dias 2013).

### Relative treatment ranking

We were not able to estimate the cumulative probabilities of each uterotonic agent being at each possible rank and obtain a treatment hierarchy.

## Unit of analysis issues

There were no cluster-randomised or multi-arm trials included in this review.

## Dealing with missing data

For included studies we noted the levels of attrition (see also 'Incomplete outcome data' in Assessment of risk of bias in included studies).

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention.

We used the number randomised minus any participants whose outcomes were known to be missing as the denominator for each outcome in each trial.

## Assessment of clinical and methodological heterogeneity within treatment comparisons

To evaluate the presence of clinical heterogeneity, we described the study population characteristics across all included trials. We assessed the presence of clinical heterogeneity by comparing these characteristics.

## Assessment of intransitivity across treatment comparisons

We considered that the assumption of transitivity for the indirect evidence is likely to hold given that: the common treatment used to compare different uterotonics indirectly is likely to be similar in different trials (e.g. oxytocin is administered in a similar way in studies of oxytocin versus misoprostol as it is in studies of oxytocin versus carbetocin); and pairwise comparisons are unlikely to differ in respect of the distribution of effect modifiers (e.g. all trial designs and characteristics are similar).

## Assessment of reporting biases

We were not able to assess for reporting bias in view of the limited number of included trials.

## Data synthesis

### Methods for direct treatment comparisons

We performed standard pairwise meta-analyses using a random-effects model for every treatment comparison with at least two trials.

### Methods for indirect treatment comparisons

We used the method described by Butcher to produce indirect comparisons for the most relevant agents and outcomes (carbetocin versus misoprostol via oxytocin) (Bucher 1997). The indirect comparisons were estimated using Excel as described by Tobias (Tobias 2014).

### Assessment of statistical heterogeneity

In standard pairwise meta-analyses we estimated the heterogeneity for each comparison. We assessed statistically the presence of heterogeneity within each pairwise comparison using the $I^2$ statistic and its 95% CI that measures the percentage of variability that cannot be attributed to random error. The certainty of the evidence was downgraded for inconsistency where $I^2 \geq 60\%$.

### Subgroup analysis

Subgroup analysis was not performed due to the limited number of included trials.

### Sensitivity analysis

Sensitivity analysis was not performed in view of the limited number of included trials.

# Results

## Description of studies

### Results of the search

The results of the search strategy are summarised in the PRISMA (Preferred reporting Items for Systematic Reviews and Meta-Analysis) flow diagram (Figure 1).

Our search strategy retrieved in total 427 records. from which 396 were screened and excluded as they were not within the scope of this review. From the 31 records remaining, we examined the full text and decided to include in the final analysis eight trials from 17 records (for details see Characteristics of included studies). Six records were excluded because they did not meet the inclusion criteria (for details see Characteristics of excluded studies), seven were listed as ongoing (for details see Characteristics of ongoing studies) and one is awaiting classification (for details see Characteristics of studies awaiting classification).

We have contacted the authors of two of the included trials for additional data and clarifications. We have also contacted the authors of six of the ongoing trials which are reported to have finished recruitment to obtain data, but no additional information was made available to us.

[May 2020 updated search - addtional 4 trial reports ro assess - additional 38 screened out]

### Included studies

This review includes eight two-arm randomised trials, published between 2001 and 2016, involving 3838 women. All studies were reported in English and were conducted in hospital settings across 10 countries: Argentina, Burkina Faso, Ecuador, Egypt, Gambia, Pakistan, South Africa, Thailand, Turkey, and Vietnam. The included trials included a median of 480 participants (interquartile range (IQR) 61 to 1422).

Randomised women gave birth vaginally (3774 women), except in one trial, where women gave birth either vaginally or by caesarean section (64 women). In all included studies women were judged to be at mixed risk for postpartum haemorrhage (PPH) (including women both low and high risk for PPH).

Across all eight trials (16 trial arms) the following agents were used:

- four trial arms (25%) used misoprostol plus conventional uterotonics*;
- four trial arms (25%) used conventional uterotonics alone*;
- three trial arms (18.75%) used oxytocin;
- three trial arms (18.75%) used misoprostol;
- one trial arm (6.25%) used carbetocin;
- one trial arm (6.25%) used Syntometrine® (oxytocin and ergometrine) plus oxytocin.

*Conventional uterotonics used in the included studies: Hofmeyr 2004: oxytocin administered by an intravenous infusion, and/or Syntometrine®; Walraven 2004: oxytocics not further specified; Widmer 2010: (in most cases) 10 IU of oxytocin administered intramuscularly or by a slow intravenous injection; Zuberi 2008: 10 IU of oxytocin administered intravenously or 5 IU of oxytocin plus 400 mcg of ergometrine administered either intramuscularly or intravenously.

See Characteristics of included studies for details.

### Excluded studies

We excluded six trials (for detail see Characteristics of excluded studies). Three of the excluded studies investigated ineligible interventions, whilst the remaining three studies had ineligible designs.

## Risk of bias in included studies

We present summaries of the methodological quality of the included studies for each domain assessed across all studies (Figure 2) and for each included study (Figure 3).

### Allocation

No trials were excluded due to sequence generation concerns. Seven trials (87.5%) used an adequate method to generate the random sequence and were judged to be at low risk of bias. Only one trial (12.5%) did not provide enough evidence to judge the method of random sequence generation and it was judged to have an unclear risk of bias. All trials reported adequate methods for allocation concealment and were judged to be at low risk of bias.

### Blinding

In total, five out of the eight included trials (62.5%) reported adequate methods for blinding both participants and personnel to treatment allocation and were judged to be at a low risk of bias. Three trials (37.5%) did not provide enough information to assess the blinding of participants and personnel and the risk of bias was judged to be unclear. All trials, except one, reported adequate methods for blinding the assessment of the primary outcomes and were judged to be at a low risk of detection bias.

### Incomplete outcome data

All trials were judged to be at a low risk of attrition bias, since missing data were balanced across study arms and did not exceed 10%.

### Selective reporting

Only three out of the eight included trials (37.5%) pre-specified all outcomes in publicly available protocols and were judged to be at a low risk of bias. Three trials (37.5%) reported all outcomes as specified in their published protocols, but the protocols were registered retrospectively. These trials were judged to be at an unclear risk of bias. For the remaining two trials (25%), the protocol was unavailable for verification and they were also judged to be at unclear risk of bias.

### Other potential sources of bias

Six trials (75%) used objective methods for measuring blood loss such as weighing sponges, measurements in drapes or volumetric assessment and were judged to be at low risk of bias. Two trials (25%) were judged to be at high risk of bias for measuring blood loss, since investigators used subjective methods such as visual estimation.

Seven trials (87.5%) were judged to be at a low risk of bias regarding funding or potential conflicts of interest. There was one trial (12.5%) that did not provide enough information to assess the source of funding or potential conflicts of interest, and the risk of bias was judged to be unclear.

## Effects of interventions

Please note that all of the analyses presented in the Data and analyses section relate to the 'direct evidence' and were used to grade the evidence. The analyses for the only indirect comparison of carbetocin versus misoprostol are described narratively and included in the summary of findings tables, where available. For each outcome we present the network

diagrams displaying the available comparisons and the grading of the direct evidence.

## Primary outcomes

### Additional blood loss of more than 500 mL

The network diagram for additional blood loss of more than 500 mL is presented in Figure 4. There were two available comparisons for this outcome. In the first one, misoprostol was compared with oxytocin (2 trials, 1787 women) and in the second one, misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (4 trials, 1873 women). Based on the relative effects from the pairwise analysis, misoprostol compared with oxytocin may make little or no difference to this outcome (risk ratio (RR) 1.66, 95% confidence interval (CI) 0.69 to 4.02, low-certainty, Summary of findings table 1). For the second comparison, we found that adding misoprostol to treatment with conventional uterotonics probably also makes little or no difference to conventional uterotonics alone (RR 0.84, 95% CI 0.66 to 1.06, moderate-certainty, Summary of findings table 1). The included studies provided no data on this outcome for misoprostol versus Syntometrine® plus oxytocin and carbetocin versus oxytocin.

### Composite of death or severe morbidity

The network diagram for the composite outcome of death or major morbidity is presented in Figure 5. There were four available comparisons for this outcome. Misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (4 trials, 1881 participants), misoprostol was compared with Syntometrine® plus oxytocin (1 trial, 64 women), and carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, misoprostol may make little or no difference to this outcome compared with oxytocin (1 trial, 809 women, RR 1.98, 95% CI 0.36 to 10.72, low-certainty, Summary of findings table 2). Additionally, we found that misoprostol plus conventional uterotonics and conventional uterotonics alone probably have comparable effects (RR 1.09, 95% CI 0.35 to 3.39, moderate-certainty, Summary of findings table 2). Given that the certainty of the evidence was very low for misoprostol versus Syntometrine® plus oxytocin, these effects remained unclear (Summary of findings table 2). The relative effects from the comparison of carbetocin versus oxytocin were not estimable as the one trial involving this comparison had no events.

## Secondary outcomes

### Death

The network diagram for death is presented in Figure 6. There were three available comparisons for this outcome. Misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (4 trials, 1881 women), and carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, misoprostol may make little or no difference to this outcome compared with oxytocin (1 trial, 809 women, RR 0.99, 95% CI 0.06 to 15.74, low-certainty, Analysis 1.3). The effects for misoprostol plus conventional uterotonics compared with conventional uterotonics were uncertain. There were five deaths, all in misoprostol arm (822 women). However, due to the small number of events, the wide confidence intervals, and the indirectness from one of the studies, the evidence was judged to be of very low certainty (Analysis 2.3). Data were not available for the comparison between misoprostol and Syntometrine® plus oxytocin. The relative effects from the comparison of carbetocin versus oxytocin were not estimable as the one trial involving this comparison had no events.

### Use of additional uterotonics

The network diagram for the use of additional uterotonics is presented in Figure 7. There were four available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (4 trials, 1866 women), misoprostol was compared with

Syntometrine® plus oxytocin (1 trial, 64 women), and carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, misoprostol may make little or no difference to the use of additional uterotonics compared with oxytocin (RR 1.30, 95% CI 0.57 to 2.94, low-certainty, Summary of findings table 3). Misoprostol administered together with conventional uterotonics makes little or no difference to this outcome when compared to conventional uterotonics alone (RR 0.99, 95% CI 0.94 to 1.05, high-certainty, Summary of findings table 3). The effects for both misoprostol compared with Syntometrine® plus oxytocin and carbetocin compared with oxytocin were uncertain (Summary of findings table 3). The evidence from the indirect comparison of carbetocin versus misoprostol was of very low certainty (Summary of findings table 3).

### Additional blood loss of more than 1000 mL

The network diagram for additional blood loss of more than 1000 mL is presented in Figure 8. There were three available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (4 trials, 1873 women), and carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, misoprostol may make little or no difference to additional blood loss of more than 1000 mL (RR 2.57, 95% CI 1.00, to 6.64, low-certainty, Summary of findings table 4). Misoprostol plus conventional uterotonics probably makes little or no difference to this outcome when compared with conventional uterotonics alone (3 trials, 1814 women, RR 0.76, 95% CI 0.43 to 1.34, moderate-certainty, Summary of findings table 4). Included studies provided no data for the comparison of misoprostol and Syntometrine® plus oxytocin for this outcome. The evidence on carbetocin was found to be of very low certainty (Summary of findings table 4). An Indirect comparison for carbetocin with misoprostol was possible for this outcome, but the resulting evidence was of very low certainty (Summary of findings table 4).

### Additional surgical procedures (e.g. hysterectomy, balloon insertion, pack insertion, arterial ligation, embolization, and compression sutures)

The network diagram for the additional surgical procedures is presented in Figure 9. There were four available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (4 trials, 1881 women), misoprostol was compared with Syntometrine® plus oxytocin (1 trial, 64 women), and carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, misoprostol may make little or no difference to this outcome compared with oxytocin (1 trial, 809 women, RR 1.10, 95% CI 0.45 to 2.67, low-certainty, Analysis 1.6). For the same outcome, misoprostol plus conventional uterotonics and conventional uterotonics alone may have comparable effects (RR 0.65, 95% CI 0.21 to 2.00, low-certainty, Analysis 2.6). The evidence for both carbetocin versus oxytocin and misoprostol versus Syntometrine® plus oxytocin was of very low-certainty (Analysis 4.6, Analysis 3.6). The evidence from the indirect comparison of carbetocin versus misoprostol was of very low certainty.

### Blood transfusion or other blood products

The network diagram for blood transfusion or other blood products is presented in Figure 10. There were three available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (4 trials, 1877 women), and carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, the need for blood transfusion is increased amongst women receiving misoprostol, when compared to those treated with oxytocin (RR 1.47, 95% CI 1.02 to 2.14, high-certainty, Summary of findings table 5). In absolute terms, about 73 per 1000 women given misoprostol for a vaginal birth would need a blood transfusion, compared with 49 given oxytocin. Misoprostol plus conventional uterotonics make little or no difference to this outcome, when compared with conventional uterotonics alone (RR 0.95, 95% CI 0.77 to 1.17, high-certainty, Summary of findings table 5). For the same outcome, no data were available for the comparison between misoprostol and Syntometrine® plus oxytocin. The evidence on carbetocin and from the indirect comparison of carbetocin versus misoprostol

were of very low certainty (Summary of findings table 5).

### Mean additional blood loss (mL)

The network diagram for mean blood loss (mL) is presented in Figure 11. There were three available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (4 trials, 1873 women), and carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, blood loss is on average increased among women receiving misoprostol compared with oxytocin (mean difference (MD) 42.85 mL higher, 95% CI 16.79 mL higher to 68.90 mL higher, high-certainty, Analysis 1.8). There is probably little or no difference between misoprostol plus conventional uterotonics and conventional uterotonics alone for this outcome (MD 14.59 mL lower, 95% CI 38.47 mL lower to 9.30 mL higher, moderate-certainty, Analysis 2.8). Included studies provided no data for the comparison between misoprostol and Syntometrine® plus oxytocin. The evidence on carbetocin versus oxytocin (Analysis 4.8) and from the indirect comparison of carbetocin versus misoprostol were of very low certainty.

### Change in haemoglobin (g/L)

The network diagram for change in haemoglobin (g/L) is presented in Figure 12. There were two available comparisons for this outcome. In the first one, misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (1 trial, 61 women), and in the second, carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, misoprostol plus conventional uterotonics may have comparable effects with conventional uterotonics alone (MD 2.00 g/L lower, 95% CI 8.29 mL lower to 4.29 mL higher, low-certainty, Analysis 2.9). The evidence on carbetocin was of very low certainty (Analysis 4.9). Included studies provided no data for the comparison between misoprostol and oxytocin, and misoprostol versus Syntometrine® plus oxytocin.

### Side effects: fever (temperature above 38°C)

The network diagram for blood transfusion or other blood products is presented in Figure 13. There were two available comparisons for this outcome. In the first one, misoprostol was compared with oxytocin (2 trials, 1787 women), and in the second, misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (4 trials, 1866 women). Based on the relative effects from the pairwise analysis, misoprostol may make little or no difference to the risk for fever when compared with oxytocin (RR 3.43, 95% CI 0.65 to 18.18, low-certainty, Summary of findings table 6). Misoprostol plus conventional uterotonics increase the risk for fever compared with conventional uterotonics alone (RR 3.07, 95% CI 2.62 to 3.61, high-certainty, Summary of findings table 6). These results suggest that about 463 per 1000 women given misoprostol plus conventional uterotonics for a vaginal delivery experience fever, compared with 151 given conventional uterotonics alone. For the same side effect no data were available for misoprostol versus Syntometrine® plus oxytocin and carbetocin versus oxytocin.

### Side effects: hypothermia (temperature below 36°C)

Not reported.

### Side effects: nausea

The network diagram for nausea is presented in Figure 14. There were three available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (3 trials, 1642 women), and carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, misoprostol probably makes little or no difference to women's experience of nausea compared with oxytocin (RR 0.99, 95% CI 0.70 to 1.39, moderate-certainty, Analysis 1.12). Additionally, misoprostol plus conventional uterotonics probably make little or no difference to the occurrence of nausea compared with conventional uterotonics alone (RR 1.19, 95% CI 0.84 to 1.68, moderate-certainty, Analysis 2.12). The evidence on carbetocin (Analysis 4.12) and

from the indirect comparison of carbetocin versus misoprostol were of very low certainty. There were no data available for the comparison between misoprostol and Syntometrine® plus oxytocin.

### Side effects: vomiting

The network diagram for vomiting is presented in Figure 15. There were three available comparisons for this outcome. Misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (2 trials, 1482 participants), and carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, misoprostol increases the risk of vomiting compared with oxytocin (RR 2.47, 95% CI 1.37 to 4.47, high-certainty, Summary of findings table 7). This means that approximately 47 per 1000 women given misoprostol for a vaginal birth will experience vomiting, compared with 19 given oxytocin. Additionally, misoprostol plus conventional uterotonics increase women's experience of vomiting when compared with conventional uterotonics alone (RR 1.85, 95% CI 1.16 to 2.95, high-certainty, Summary of findings table 7). In absolute terms, about 64 per 1000 women given both misoprostol and conventional uterotonics for a vaginal birth experience vomiting, compared with 35 given conventional uterotonics alone. The evidence on carbetocin was found to be of very low certainty (Summary of findings table 7). No data were available for misoprostol versus Syntometrine® plus oxytocin for this side effect. The evidence from the indirect comparison of carbetocin versus misoprostol was of very low certainty (Summary of findings table 7).

### Side effects: hypertension

Not reported.

### Side effects: headache

The network diagram for headache is presented in Figure 16. There were three available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (3 trials, 1642 women), and carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, misoprostol may make little or no difference to the incidence of headache compared with oxytocin (RR 1.05, 95% CI 0.22 to 4.99, low-certainty, Analysis 1.15). Misoprostol plus conventional uterotonics probably have a similar likelihood to conventional uterotonics alone of causing headache (RR 1.12, 95% CI 0.65 to 1.93, moderate-certainty, Analysis 2.15). There were no data available for the comparison between misoprostol and Syntometrine® plus oxytocin. The evidence on carbetocin (Analysis 4.15) and from the indirect comparison of carbetocin versus misoprostol were of very low certainty.

### Side effects: shivering

The network diagram for shivering is presented in Figure 17. There were three available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (4 trials, 1876 women), and carbetocin was compared with oxytocin (1 trial, 100 women). Based on the relative effects from the pairwise analysis, misoprostol is more likely to cause shivering than oxytocin (RR 2.70, 95% CI 2.28 to 3.19, high-certainty, Analysis 1.16). This means that about 427 per 1000 women given misoprostol for a vaginal delivery will experience shivering, compared with 158 given oxytocin. Additionally, misoprostol plus conventional uterotonics are more likely to cause shivering compared with conventional uterotonics alone (RR 2.25, 95% CI 1.77 to 2.86, high-certainty, Analysis 2.16). Based on these results 693 per 1000 women given both misoprostol and conventional uterotonics for a vaginal birth will experience shivering, compared to 308 given conventional uterotonics alone. The included studies provided no data for misoprostol versus Syntometrine® plus oxytocin. The evidence on carbetocin (Analysis 4.16) and from the indirect comparison of carbetocin versus misoprostol were of very low certainty.

### Side effects: tachycardia

The network diagram for vomiting is presented in Figure 18. Carbetocin versus oxytocin was the only available comparison for this side effect (1 trial, 100 women). The evidence on this direct comparison were of very low-certainty (Analysis 4.17).

### Side effects: arrhythmia

Not reported.

### Side effects: diarrhoea

The network diagram for diarrhoea is presented in Figure 19. There were two available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women), and misoprostol plus conventional uterotonics were compared with conventional uterotonics alone (2 trials, 1482 women). Based on the relative effects from the pairwise analysis, misoprostol may make little or no difference to the incidence of diarrhoea compared with oxytocin (RR 1.39, 95% CI 0.44 to 4.39, low-certainty, Analysis 1.19). According to the second available comparison, misoprostol plus conventional uterotonics also may make little or no difference to the number of women suffering diarrhoea compared with conventional uterotonics alone (RR 1.22, 95% CI 0.37 to 3.99, low-certainty, Analysis 2.19). Data were not available for misoprostol versus Syntometrine® plus oxytocin and carbetocin versus oxytocin.

### Side effects: abdominal pain

Not reported.

### Participants reporting a sense of wellbeing

Not reported.

### Participants reporting acceptability of the intervention

Not reported.

### Participants reporting satisfaction with the intervention

Not reported.

### Number of participants breastfeeding on discharge

Not reported.

# Discussion

## Summary of main results

In summary, we reviewed eight trials, involving 3838 women in 10 countries. All trials were conducted in hospital settings and randomised women usually gave birth vaginally. The following agents were used in the trial: oxytocin; misoprostol; misoprostol plus conventional uterotonics; conventional uterotonics alone; Syntometrine® (oxytocin and ergometrine) plus oxytocin; and carbetocin. It was not possible to perform a network meta-analysis and rank the available uterotonic agents, because of the limited number of trials. Only one indirect comparison was possible of carbetocin versus misoprostol with the common comparator being oxytocin.

We found that misoprostol makes little or no difference to the additional blood loss of more than 500 mL, the composite outcome of maternal mortality or severe morbidity, the use of additional uterotonics, and to the additional blood loss of more than 1000 mL compared with oxytocin. However, misoprostol used as first-line treatment, increases the risk of women receiving a blood transfusion compared with oxytocin.

The combination of misoprostol plus conventional uterotonics is probably comparable to conventional uterotonics alone for the additional blood loss of more than 500 mL, the composite outcome of maternal mortality or severe morbidity, the use of additional uterotonics, the additional blood loss of more than 1000 mL, and for the risk of receiving a

blood transfusion.

For all outcomes the evidence on misoprostol versus Syntometrine® plus oxytocin and carbetocin versus oxytocin was of very low-certainty, meaning these effects remain unclear. An indirect comparison between carbetocin and misoprostol could be made, but the available evidence was also of very low-certainty.

In terms of side effects, misoprostol may make little difference to the incidence of fever, but increases the risk for vomiting, compared with oxytocin. Misoprostol plus conventional uterotonics increase the incidence of fever, and vomiting compared with conventional uterotonics alone.

## Overall completeness and applicability of evidence

This review was set out to find the most effective uterotonic agent with the least side effects for the first-line treatment of postpartum haemorrhage (PPH). Eight trials met the inclusion criteria and reported results for our primary and secondary outcomes with the exception that no trials provided data on hypothermia, hypertension, arrhythmia, abdominal pain, maternal sense of wellbeing, acceptability of the intervention, maternal satisfaction, and breastfeeding outcomes. The majority of trials recruited women experiencing PPH after a singleton term vaginal birth in low-resource hospital settings. Women with significant co-morbidities were largely excluded from all trials. The most frequent intervention reported was misoprostol plus conventional uterotonics compared with conventional uterotonics alone. The local standard of care varied from trial to trial, though, all trials included readily available standard uterotonic agents, reflecting widespread practice. The dosage and route of administration for each agent also varied by trial (Characteristics of included studies). Subgroup, sensitivity analysis, and the planned network meta-analysis were not performed given the paucity of trials. However, further trials are yet to report, which should allow for a more complete set of available comparisons in the future. See Characteristics of ongoing studies.

## Quality of the evidence

Although there is no single established approach for assessing the certainty of evidence generated by both direct and indirect comparisons, we applied the appraising method proposed by the GRADE Working Group. Our confidence in the effect estimates of this review ranged from very low to high with the majority of the available being of low certainty. See Summary of findings table 1; Summary of findings table 2; Summary of findings table 3; Summary of findings table 4; Summary of findings table 5; Summary of findings table 7; Summary of findings table 6. For the primary outcome of additional blood loss of more than 500 mL, we have limited to moderate confidence of where the true effect estimates might lie. For our composite outcome of maternal death and severe maternal morbidity the certainty of the evidence varied from very low to moderate. Overall, only some of the comparisons involving misoprostol (i.e. misoprostol versus oxytocin, and misoprostol plus conventional uterotonics versus conventional uterotonics alone) generated evidence of high certainty. In all cases, the evidence from the direct comparison between carbetocin and oxytocin was of very low certainty. The single trial that provided data on the comparison of misoprostol and Syntometrine® plus oxytocin also generated evidence of very low certainty. For our indirect comparison of carbetocin and misoprostol, the evidence was of very low certainty in all cases.

## Potential biases in the review process

Two review authors have been involved in two of the included trials, but did not participate in any decisions regarding these studies. For the purpose of this review, tasks, such as assessment for inclusion/exclusion, trial quality, and data extraction, were carried out by other members of the team who were not directly involved in these two protocols.

Significant heterogeneity was observed in some of the analyses involving misoprostol and oxytocin. This could be attributed to the differences noted in the management of third stage of labour in two of the included studies. However, given that these were the only trials

providing data for the direct comparison of misoprostol with oxytocin, we were unable to perform a subgroup analysis and assess for effect modifiers.

Two out of the eight included trials (25%, Figure 3) were judged to be at high risk of bias regarding the methods of blood loss assessment. Since these trials constituted the only available evidence for two of our direct comparisons (carbetocin versus oxytocin, and misoprostol versus Syntometrine® plus oxytocin), it was not possible to perform a subgroup analysis and evaluate the method of blood loss assessment as a possible confounding factor.

## Agreements and disagreements with other studies or reviews

Our results agree with the existing Cochrane Review (Mousa 2014).

# Authors' conclusions

### Implications for practice

Misoprostol used as first-line treatment of postpartum haemorrhage (PPH) increases the risk of blood transfusion compared with oxytocin and is also associated with more side effects. Misoprostol in combination with conventional uterotonics is of comparable effectiveness to conventional uterotonics alone, but again is associated with more side effects. Misoprostol use is widespread for treating PPH, but agents with more favourable side effect profiles are available.

### Implications for research

There is considerable uncertainty over which is the best uterotonic agent to use for the first-line treatment of PPH. There is lack of evidence on the effectiveness of commonly used drugs, such as injectable prostaglandins (i.e. carboprost and sulprostone) and Syntometrine®, but even the available evidence for most of the other uterotonic agents is generally of low certainty. Interestingly, only trials from low- and middle-income countries have been published results so far. Meanwhile, there is no consensus over the best route and dose that maximises the effectiveness of each uterotonic agent, and different treatment regimens are widely used. These variations in clinical practice could imply that some women, although excessively bleeding after childbirth, do not receive appropriate treatment interventions. Therefore, further research should be conducted in this area, and new evidence-based guidelines should be shaped to ensure a positive childbirth experience.

# Data and analyses

**Comparison 1**

### Misoprostol versus oxytocin

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 Additional blood loss of more than 500 mL | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 1.66 [0.69, 4.02] |
| 1.2 Composite of maternal death or severe morbidity | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 1.98 [0.36, 10.72] |
| 1.3 Death | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 0.99 [0.06, 15.74] |
| | | | Risk Ratio (IV, | |

| | | | | |
|---|---|---|---|---|
| 1.4 Additional uterotonics | 2 | 1787 | Random, 95% CI) | 1.30 [0.57, 2.94] |
| 1.5 Additional blood loss of more than 1000 mL | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 2.57 [1.00, 6.64] |
| 1.6 Additional surgical procedures | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 1.10 [0.45, 2.67] |
| 1.7 Blood transfusion or other blood products | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 1.47 [1.02, 2.14] |
| 1.8 Mean additional blood loss | 2 | 1787 | Mean Difference (IV, Random, 95% CI) | 42.85 [16.79, 68.90] |
| 1.9 Change in haemoglobin | 0 | 0 | Mean Difference (IV, Random, 95% CI) | Not estimable |
| 1.10 Fever | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 3.43 [0.65, 18.18] |
| 1.11 Hypothermia | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 1.12 Nausea | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 0.99 [0.70, 1.39] |
| 1.13 Vomiting | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 2.47 [1.37, 4.47] |
| 1.14 Hypertension | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 1.15 Headache | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 1.05 [0.22, 4.99] |
| 1.16 Shivering | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 2.70 [2.28, 3.19] |
| 1.17 Tachycardia | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 1.18 Arrhythmia | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 1.19 Diarrhoea | 2 | 1787 | Risk Ratio (IV, Random, 95% CI) | 1.39 [0.44, 4.39] |
| 1.20 Abdominal pain | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |

| | | | | |
|---|---|---|---|---|
| 1.21 Maternal sense of wellbeing | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 1.22 Acceptability of intervention | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 1.23 Maternal satisfaction | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 1.24 Breastfeeding on discharge | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |

**Comparison 2**

## Misoprostol plus conventional uterotonics versus conventional uterotonics alone

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 Additional blood loss of more than 500 mL | 4 | 1873 | Risk Ratio (IV, Random, 95% CI) | 0.84 [0.66, 1.06] |
| 2.2 Composite of maternal death or severe morbidity | 4 | 1881 | Risk Ratio (IV, Random, 95% CI) | 1.09 [0.35, 3.39] |
| 2.3 Death | 4 | 1881 | Risk Ratio (IV, Random, 95% CI) | 6.10 [0.73, 50.59] |
| 2.4 Additional uterotonics | 4 | 1866 | Risk Ratio (IV, Random, 95% CI) | 0.99 [0.94, 1.05] |
| 2.5 Additional blood loss of more than 1000 mL | 4 | 1873 | Risk Ratio (IV, Random, 95% CI) | 0.76 [0.43, 1.34] |
| 2.6 Additional surgical procedures | 4 | 1881 | Risk Ratio (IV, Random, 95% CI) | 0.65 [0.21, 2.00] |
| 2.7 Blood transfusion or other blood products | 4 | 1877 | Risk Ratio (IV, Random, 95% CI) | 0.95 [0.77, 1.17] |
| 2.8 Mean additional blood loss | 4 | 1873 | Mean Difference (IV, Random, 95% CI) | -14.59 [-38.47, 9.30] |
| 2.9 Change in haemoglobin | 1 | 61 | Mean Difference (IV, Random, 95% CI) | -2.00 [-8.29, 4.29] |
| 2.10 Fever | 4 | 1866 | Risk Ratio (IV, Random, 95% CI) | 3.07 [2.62, 3.61] |
| 2.11 Hypothermia | 0 | 0 | Risk Ratio (IV, | Not estimable |

| | | | | |
|---|---|---|---|---|
| | | | Random, 95% CI) | |
| 2.12 Nausea | 3 | 1642 | Risk Ratio (IV, Random, 95% CI) | 1.19 [0.84, 1.68] |
| 2.13 Vomiting | 2 | 1482 | Risk Ratio (IV, Random, 95% CI) | 1.85 [1.16, 2.95] |
| 2.14 Hypertension | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 2.15 Headache | 3 | 1642 | Risk Ratio (IV, Random, 95% CI) | 1.12 [0.65, 1.93] |
| 2.16 Shivering | 4 | 1876 | Risk Ratio (IV, Random, 95% CI) | 2.25 [1.77, 2.86] |
| 2.17 Tachycardia | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 2.18 Arrhythmia | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 2.19 Diarrhoea | 2 | 1482 | Risk Ratio (IV, Random, 95% CI) | 1.22 [0.37, 3.99] |
| 2.20 Abdominal pain | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 2.21 Maternal sense of wellbeing | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 2.22 Acceptability of intervention | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 2.23 Maternal satisfaction | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 2.24 Breastfeeding on discharge | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |

**Comparison 3**

## Misoprostol versus Syntometrine® plus oxytocin

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.1 Additional blood loss of more than 500 mL | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.2 Composite of maternal death or severe morbidity | 1 | 64 | Risk Ratio (IV, Random, | 0.33 [0.01, 7.89] |

| | | | | |
|---|---|---|---|---|
| | | | 95% CI) | |
| 3.3 Death | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.4 Additional uterotonics | 1 | 64 | Risk Ratio (IV, Random, 95% CI) | 0.18 [0.04, 0.76] |
| 3.5 Additional blood loss of more than 1000 mL | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.6 Additional surgical procedures | 1 | 64 | Risk Ratio (IV, Random, 95% CI) | 0.67 [0.12, 3.73] |
| 3.7 Blood transfusion or other blood products | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.8 Mean additional blood loss | 0 | 0 | Mean Difference (IV, Random, 95% CI) | Not estimable |
| 3.9 Change in haemoglobin | 0 | 0 | Mean Difference (IV, Random, 95% CI) | Not estimable |
| 3.10 Fever | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.11 Hypothermia | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.12 Nausea | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.13 Vomiting | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.14 Hypertension | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.15 Headache | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.16 Shivering | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.17 Tachycardia | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.18 Arrhythmia | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| | | | Risk Ratio (IV, | |

| | | | | |
|---|---|---|---|---|
| 3.19 Diarrhoea | 0 | 0 | Random, 95% CI) | Not estimable |
| 3.20 Abdominal pain | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.21 Maternal sense of wellbeing | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.22 Acceptability of intervention | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.23 Maternal satisfaction | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 3.24 Breastfeeding on discharge | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |

**Comparison 4**

## Carbetocin versus oxytocin

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.1 Additional blood loss of more than 500 mL | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.2 Composite of maternal death or severe morbidity | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.3 Death | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.4 Additional uterotonics | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.5 Additional blood loss of more than 1000 mL | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.6 Additional surgical procedures | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.7 Blood transfusion or other blood products | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.8 Mean additional blood loss | 0 | 0 | Mean Difference (IV, Random, 95% CI) | Not estimable |
| 4.9 Change in haemoglobin | 0 | 0 | Mean Difference (IV, Random, 95% CI) | Not estimable |

| | | | | |
|---|---|---|---|---|
| 4.10 Fever | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.11 Hypothermia | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.12 Nausea | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.13 Vomiting | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.14 Hypertension | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.15 Headache | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.16 Shivering | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.17 Tachycardia | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.18 Arrhythmia | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.19 Diarrhoea | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.20 Abdominal pain | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.21 Maternal sense of wellbeing | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.22 Acceptability of intervention | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.23 Maternal satisfaction | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |
| 4.24 Breastfeeding on discharge | 0 | 0 | Risk Ratio (IV, Random, 95% CI) | Not estimable |

# History

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Review first published: Issue 8, 2020

# Contributions of authors

Ioannis D Gallos (IDG) and Arri Commarasamy (AC) conceived the idea for this study. William R Parry-Smith (WRPS) drafted the protocol. WRPS, Argyro Papadopoulou (AP) screened trials, extracted data and performed pairwise statistical analyses. IDG and AP graded the evidence. Shireen Meher (SM) screened trials and extracted data. Malcolm J Price (MJP), Mariana Widmer (MW), Aurelio Tobias (AT), Zarko Alfirevic (ZA), Andrew Weeks (AW), G Justus Hofmeyr (GJH), A Metin Gülmezoglu (AMG), IDG and AC designed the analysis. AT and MJP provided statistical advice and input. IDG, AP, WRPS, ET, MW, MJP, AT, SM, AW, GJH, Olufemi T Oladapo (OTO), Joshua Vogel (JV), Fernando Althabe (FA) AC edited and revised the review.

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As part of the prepublication 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 Cochrane Pregnancy and Childbirth's international panel of consumers and the Group's Statistical Adviser.

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# Declarations of interest

William R Parry-Smith (WRPS) is an Executive Board member of AmmaLife (UK registered charity 1120236), and a member of The UK Membership Board of The Royal College of Obstetricians and Gynaecologists (UK registered charity 213280). He was also a Trustee of Baby Lifeline (UK registered charity 1006457) until April 2019. He does not receive payment for these roles but has received payment from these organisations for travel for activities not related to this review. He has also received payment from the Liverpool School of Tropical Medicine for an invited lecture on cervical cancer and women's health. AmmaLife contributed to this review by funding literature/library costs.

Argyro Papadopoulou (AP): none known.

Eleanor Thomas (ET): none known.

Aurelio Tobias (AT): none known.

Malcolm J Price (MJP): none known.

Shireen Meher (SM): none known.

Zarko Alfirevic (ZA): has been an external adviser for Gynuity related to the charity's work on PPH.

Andrew Weeks (AW): voluntarily runs the not-for-profit misoprostol.org website that provides information about the optimal doses of misoprostol, including for the treatment of PPH. He also has two large clinical trial grants (from NIHR) on PPH treatment. These studies could

potentially be eligible for inclusion in subsequent updates of this review, but he will not participate in decisions regarding these trials. He is also a consultant to Gynuity Health projects (unpaid) and to Azanta A/S and Monash University (both pay consultancy fees to his institution (University of Liverpool). He is also the inventor of the PPH Butterfly device and one of the inventors of the LifeStart neonatal resuscitation trolley. He may in future receive personal payments in connection to the PPH Butterfly for which the University of Liverpool holds the patent.

G Justus Hofmeyr (GJH): is an author of trials included in the review. GJH did not participate in decisions regarding these trials.

A Metin Gülmezoglu (AMG): none known.

Mariana Widmer (MW): is an author of trials included in the review. MW did not participate in decisions regarding these trials.

Olufemi T Oladapo (OTO): none known.

Joshua Vogel (JV): none known.

Fernando Althabe (FA): none known.

Arri Coomarasamy (AC): is the founder of Ammalife (UK registered charity 1120236), and remains an active member of the Executive Board of this organisation. He does not receive any payment for this relationship.

Ioannis D Gallos (IDG): none known.

# 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
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- University of the Witwatersrand and Walter Sisulu University, South Africa
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- JN Medical College Belgaum, India
  The authors of this review are employed by the institutions indicated by their respective affiliations except where otherwise stated.
- University of Liverpool, UK
  The authors of this review are employed by the institutions indicated by their respective affiliations except where otherwise stated.

## External sources

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# Differences between protocol and review

We were not able to produce a network meta-analysis as there were too few trials comparing the available uterotonic agents to produce a connected network. We were not able to proceed with the network methods outlined in the protocol, specifically it was impossible to produce a meaningful hierarchy of first-line uterotonic agents for the treatment

of PPH.

### Methods for direct treatment comparison

We used RevMan 5.3 to estimate all direct treatment comparisons rather than in STATA as suggested in the protocol.

### Methods for indirect treatment comparison

We used the method described by Butcher to produce indirect comparisons for the most relevant agents and outcomes-carbetocin versus misoprostol via oxytocin (Bucher 1997). The indirect comparisons were estimated using Excel as described by our co-author Aurelio Tobias (Tobias 2014).

# Characteristics of studies

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

**Blum 2010**

| ***Study characteristics*** | | |
|---|---|---|
| Methods | 2-arm active-controlled double-blind double-dummy randomised controlled trial | |
| Participants | 809 women were randomised in a hospital setting in Burkina Faso, Egypt, Turkey and Vietnam between August, 2005, and January, 2008. The population comprised women giving birth vaginally, at mixed risk for PPH. They had received prophylactic oxytocin intravenously or intramuscularly during the third stage of labour and had diagnosed with PPH due to suspected uterine atony, either by clinical judgement or blood loss reaching 700 mL in the calibrated drape during the first hour after delivery. Women were not eligible for the trial if their PPH was suspected to have another cause other than uterine atony, oxytocin was not received during the third stage of labour or if they underwent a caesarean section. | |
| Interventions | Misoprostol 800 mcg (4 tablets of 200 mcg) administered sublingually versus oxytocin 40 IU administered by an intravenous infusion. | |
| Outcomes | The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death or severe morbidity; death; additional uterotonics; additional blood loss of more than 1000 mL; additional surgical procedures, blood transfusion or other blood products; mean additional blood loss; fever; nausea; vomiting; headache; shivering; diarrhoea. | |
| Notes | Contact with study authors for additional information: no. Additional data from authors: no. | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | A computer-generated random allocation sequence in blocks of ten was derived by Gynuity Health Projects, New York, NY, USA, and was not revealed until data collection and cleaning were completed. |
| Allocation concealment (selection bias) | Low risk | Sealed and numbered opaque boxes contained the treatment allocation and were opened in strict numeric sequence. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Both providers and women were blinded to treatment assignment. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Assessors were blinded to treatment allocations. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Data were collected completely from all randomised study participants. |

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | The study report matches the study protocol that was registered prospectively (NCT00116350). |
| Method to measure blood loss for all outcomes | Low risk | Investigators appraised blood loss by a polyurethane receptacle with calibrated funnel (Brass-V Drapes, Excellent Fixable Drapes, Madurai, Tamil Nadu, India), placed under the woman's buttocks after delivery of the baby. |
| Funding and conflicts of interest | Low risk | This research was funded by the Bill & Melinda Gates Foundation and no conflicts of interest were identified. |

### Hofmeyr 2004

| ***Study characteristics*** | | |
|---|---|---|
| Methods | 2-arm active-controlled double-blind randomised trial | |
| Participants | 244 women were randomised in a hospital setting in South Africa between January, 2002, and December, 2003. The population comprised women giving birth vaginally, at mixed risk for PPH. They received prophylactic oxytocin 10 IU or Syntometrine® 1 ampoule without specifying the route of administration during the third stage of labour. The women included in the trial were bleeding more than expected at least 10 minutes after giving birth due to uterine atony, and additional uterotonic therapy was required. Exclusion criteria were not specified. | |
| Interventions | Misoprostol 1000 mcg administered through multiple routes (1 tablet of 200 mcg orally, 2 tablets of 200 mcg sublingually, and 2 tablets of 200 mcg rectally) plus conventional uterotonics versus conventional uterotonics alone. | |
| Outcomes | The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death or severe morbidity; death; additional uterotonics; additional blood loss of more than 1000 mL; additional surgical procedures; blood transfusion or other blood products; mean additional blood loss; fever (≥ 38.5$^{0}$C); shivering. | |
| Notes | Contact with study authors for additional information: yes. Additional data from authors: no. | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | A computer-generated random sequence was used. |
| Allocation concealment (selection bias) | Low risk | Treatment packs were prepared independently and numbered consecutively. The treatment sequence was kept sealed and the code was broken only after complete entry and checking of all trial data. |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Study participants and care givers were blinded to treatment allocation. |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Assessors were blinded to treatment allocations. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Although 244 women were enrolled in the trial, the pack numbers on the data sheets were incomplete for 6 women. The group allocation of these women was therefore unknown and they could not be included in the analysis. More missing data per outcome, but not exceeding 10%. |
| Selective reporting (reporting bias) | Unclear risk | The study report matches the study protocol that was registered retrospectively (ISRCTN72263357). |
| Method to | | A low-profile plastic ‘fracture bedpan was placed under women's buttocks. Any |

| | | |
|---|---|---|
| measure blood loss for all outcomes | Low risk | small swabs soaked in blood were dropped into the bedpan. After 1 hour, the blood collected in the bedpan was measured in a graduated measuring jug. |
| Funding and conflicts of interest | Low risk | This research was funded by the University of the Witwatersrand (South Africa) and no conflicts of interest were identified. |

## Lokugamage 2001

| ***Study characteristics*** | | |
|---|---|---|
| Methods | 2-arm active-controlled double-dummy randomised trial | |
| Participants | 64 women were randomised in a hospital setting in South Africa. The population comprised women giving birth either vaginally or by caesarean section, at mixed risk for PPH. It was not specified if a uterotonic was given in the third stage for prevention of PPH. The women included in the trial had an estimated blood loss greater than 500 mL with visible signs of continued heavy vaginal bleeding and whose uterus was poorly contracted within 24 hours of birth. Women were not eligible for the trial if they were hypertensive at the time of potential recruitment, had cardiac abnormalities, ongoing severe asthma, connective tissue disorders, any contra-indications to prostaglandin therapy or haemorrhage due to obvious genital tract trauma. | |
| Interventions | Misoprostol 800 mcg (4 tablets of 200 mcg) administered rectally versus Syntometrine® (ergometrine 500 mcg plus oxytocin 5 IU) administered intramuscularly plus oxytocin 10 IU administered by an intravenous infusion. | |
| Outcomes | The study recorded the following outcomes: composite of maternal death or severe morbidity; additional uterotonics; additional surgical procedures. | |
| Notes | Contact with study authors for additional information: no. Additional data from authors: no. | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Randomisation was performed by generating random numbers via STATA, a statistical software package. |
| Allocation concealment (selection bias) | Low risk | The randomly selected group allocations were placed in sealed sequentially-numbered envelopes. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Obstetricians were aware of the study allocation but not midwifes. It is unclear if this was an effective method of blinding for the care-giving team. It is also unclear if study participants were blinded, but it can be assumed they were blinded, in view of the use of a double-dummy in the trial. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Midwives mainly measured the bleeding and assessed uterine contraction, and were blinded to treatment allocations. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1 patient was recruited to the misoprostol arm, but was excluded from the analysis because the haemorrhage was due to uterine rupture. |
| Selective reporting (reporting bias) | Unclear risk | The protocol of the study was unavailable for verification. For some of the outcomes only the 'P' values of statistical significance were reported. |
| Method to measure blood loss for all outcomes | High risk | Investigators appraised blood loss by visual estimation of attending physicians. |
| Funding and conflicts of | Low risk | This study was funded by the University College London and the University of Natal. No conflicts of interest were identified. |

| | | |
|---|---|---|
| interest | | |

### Walraven 2004

| ***Study characteristics*** | | |
|---|---|---|
| Methods | 2-arm active-controlled randomised trial | |
| Participants | 160 women were randomised in a hospital setting in Gambia between November, 2002, and October, 2003. The population comprised women giving birth vaginally, at mixed risk for PPH, who had received prophylactic oxytocin 10 IU or Syntometrine ® 1 ampoule without specifying the route of administration during the third stage of labour. The women included in the trial had blood loss greater than 500 mL within the first hour postpartum, due to suspected uterine atony. Women were not eligible for the trial if they had a caesarean section, their blood loss was less than 500 mL in the first hour after delivery, the delivery occurred at less than 28 weeks of gestation, inadequate uterine contraction was not thought to be a possible causative factor for the PPH or if they were not consenting. | |
| Interventions | Misoprostol 600 mcg administered through multiple routes (1 tablet of 200 mcg orally, and 2 tablets of 200 mcg sublingually) plus conventional uterotonics versus conventional uterotonics alone. | |
| Outcomes | The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death or severe morbidity; death; additional uterotonics; additional blood loss of more than 1000 mL; additional surgical procedures; blood transfusion or other blood products; mean additional blood loss; fever; nausea; headache; shivering. | |
| Notes | Contact with study authors for additional information: no. Additional data from authors: no. | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Method of sequence generation was not reported. |
| Allocation concealment (selection bias) | Low risk | They were enrolled by opening the next in a series of randomised treatment packs in opaque envelopes containing either misoprostol or placebo tablets. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | The tablets were similar in size and colour but not in shape. Efforts to obtain identical placebo tablets were unsuccessful. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | The randomisation code was broken only after entry and checking of data. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There were no withdrawals after enrolment, and all outcomes were analysed according to the allocated study group. |
| Selective reporting (reporting bias) | Unclear risk | The protocol of the study was unavailable for verification. |
| Method to measure blood loss for all outcomes | Low risk | The blood collected in the bedpan was then transferred to a measuring jar. The measuring jar and all gauzes and pads used were put in a standard plastic bag and the total difference between the dry and wet weights was calculated. |
| Funding and conflicts of interest | Unclear risk | Funding sources were not reported. No other conflicts of interest were identified. |

## Widmer 2010

| *Study characteristics* | | |
|---|---|---|
| Methods | 2-arm active-controlled double-blind randomised trial | |
| Participants | 1422 women were randomised in a hospital setting in Argentina, Egypt, South Africa, Thailand, and Vietnam between July, 2005, and August, 2008. The population comprised women giving birth vaginally, at mixed risk of PPH, who had received prophylactic oxytocin 10 IU or ergometrine or prostaglandins without specifying the dose or route of administration during the third stage of labour. The women included in the trial had clinically diagnosed PPH that was suspected to be due to uterine atony, and needed additional uterotonics. Women were not eligible for the trial if: delivery was by caesarean section; misoprostol could not be given sublingually; any severe allergic or bleeding disorders (e.g. haemophilia) were recorded; temperature was higher than 38.5°C; the delivery was defined as a miscarriage according to local gestational age limits; or the placenta was not delivered. | |
| Interventions | Misoprostol 600 mcg (3 tablets of 200 mcg) administered sublingually plus conventional uterotonics versus conventional uterotonics alone administered intravenously. | |
| Outcomes | The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death or severe morbidity; death; additional uterotonics; additional blood loss of more than 1000 mL; blood transfusion or other blood products; mean additional blood loss; fever; nausea; vomiting; headache; shivering; diarrhoea. | |
| Notes | Contact with study authors for additional information: yes. Additional data from authors: yes. | |
| *Risk of bias* | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | A computer-generated randomisation sequence was derived centrally by Gynuity Health Projects, New York, NY, USA, stratified by country with varying blocks of 6 and 8. |
| Allocation concealment (selection bias) | Low risk | To conceal allocation, treatment boxes were sealed and numbered sequentially according to the randomisation sequence, and distributed in the order that women were judged to be eligible and were enrolled in the study. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Treatment boxes were identical in appearance for both groups, and placebo tablets were identical in shape, colour, weight, feel, and taste to misoprostol tablets. Both providers and participants were masked to treatment allocation. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Assessors were blinded to treatment allocations. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 5 women were lost to follow up (blood loss not recorded) and 3 did not receive the intervention. |
| Selective reporting (reporting bias) | Unclear risk | The study report matches the study protocol that was registered retrospectively (ISRCTN34455240). |
| Method to measure blood loss for all outcomes | Low risk | Blood collection started immediately after the study drug was given. A fresh, non-absorbent sheet was placed under the buttocks of the woman. A low-profile plastic fracture bedpan was positioned below the woman's perineum to collect all subsequent blood lost for 90 minutes. The blood in the bedpan plus any spilled blood from the non-absorbent sheet or blood-soaked gauze swabs, or both, was transferred to a jar and the volume was measured. At the centre in Egypt, blood was collected into a calibrated plastic sheet that was placed below the woman immediately after she took the study drug, and the volume was measured accordingly. Measures of blood loss were recorded at 60 minutes and 90 minutes after randomisation. |
| Funding and conflicts of | Low risk | This research was funded by the Bill & Melinda Gates Foundation through a grant to Family Care International and Gynuity Health Projects. Additional funds were provided by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, |

| | | |
|---|---|---|
| interest | | Development and Research Training in Human Reproduction. No conflicts of interest were identified. |

### Winikoff 2010

| ***Study characteristics*** | | |
|---|---|---|
| Methods | 2-arm active-controlled double-blind double-dummy randomised trial | |
| Participants | 978 women were randomised in a hospital setting in Ecuador, Egypt and Vietnam between August, 2005, and January, 2008. The population comprised women giving birth vaginally, at mixed risk for PPH, who were not exposed to prophylactic oxytocin during third stage of labour. The women included in the trial had blood loss that exceeded 700 mL due to suspected uterine atony. Women were not eligible for the trial if they had a known allergy to prostaglandins, received any uterotonic agent in labour, underwent caesarean section, delivered outside the study site or their postpartum bleeding was not suspected to be due to atonic uterus. | |
| Interventions | Misoprostol 800 mcg (4 tablets of 200 mcg) administered sublingually versus oxytocin 40 IU administered by an intravenous infusion. | |
| Outcomes | The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death or severe morbidity; death; additional uterotonics; additional blood loss of more than 1000 mL; additional surgical procedures; blood transfusion or other blood products; mean additional blood loss; fever; nausea; vomiting; headache; shivering; diarrhoea. | |
| Notes | Contact with study authors for additional information: no. Additional data from authors: no. | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | A computer-generated random allocation sequence in blocks of ten was maintained by Gynuity Health Projects, New York, NY, USA. |
| Allocation concealment (selection bias) | Low risk | The random allocation sequence was concealed from study staff who enrolled and allocated treatments. Study staff immediately administered the next sequentially numbered allocated treatment packet, which contained 1 active treatment and matching placebo. |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Providers and women were blinded to treatment assignment. |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Assessors were blinded to treatment allocations. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Data were collected completely from all randomised study participants. |
| Selective reporting (reporting bias) | Low risk | The study report matches the study protocol that was registered prospectively (NCT00116350). |
| Method to measure blood loss for all outcomes | Low risk | Immediately after delivery the blood collection drape was placed beneath the woman’s buttocks. Study staff measured postpartum blood loss by use of a polyurethane receptacle with a calibrated funnel. |
| Funding and conflicts of interest | Low risk | This research was funded by the Bill & Melinda Gates Foundation and no conflicts of interest were identified. |

### Zuberi 2008

| ***Study characteristics*** | | |
|---|---|---|
| Methods | 2-arm active-controlled double-blind randomised trial | |
| Participants | 61 women were randomised in a hospital setting in Pakistan between December, 2005, and April, 2007. The population comprised women giving birth vaginally, at mixed risk for PPH. They received prophylactic oxytocin 10 IU by an intravenous bolus or oxytocin 5 IU plus ergometrine 400 mcg administered intramuscularly or intravenously during the third stage of labour. The women included in the trial received the standard additional injectable oxytocics for treatment of PPH, due to suspected uterine atony and blood loss exceeding 500 mL. Women were not eligible for the trial if they underwent caesarean section, their gestational age was less than 28 weeks at time of delivery, they were not consenting or if their blood loss was less than 500 mL. | |
| Interventions | Misoprostol 600 mcg (3 tablets of 200 mcg) administered sublingually plus conventional uterotonics versus conventional uterotonics alone. | |
| Outcomes | The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death severe morbidity; death; additional uterotonics; additional blood loss of more than 1000 mL; additional surgical procedures; blood transfusion or other blood products; mean additional blood loss; change in haemoglobin measurements before and after birth; fever; nausea; vomiting; headache; shivering; diarrhoea. | |
| Notes | Contact with study authors for additional information: no. Additional data from authors: no. | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | The sample was randomised in blocks of 10, stratified by site, using a computer-generated random sequence provided by Gynuity Health Projects, New York, NY, USA, where the code was kept. |
| Allocation concealment (selection bias) | Low risk | A member of study team gave each woman the pills in the next randomised study envelope. The randomisation code was concealed until all data were entered and cleaned. |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | All women, providers and investigators were blinded to the treatment assignments. |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Assessors were blinded to treatment allocations. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 2 women in the misoprostol arm were excluded from the analysis of measured postpartum blood loss, because of incomplete measurements. |
| Selective reporting (reporting bias) | Low risk | The study report matches the study protocol that was registered prospectively (NCT00116480). |
| Method to measure blood loss for all outcomes | Low risk | The blood collected on the bedpan and perineal pan was transferred to a calibrated jug for measurement. All used gauzes and pads were counted and placed in a plastic bag which was then weighed. |
| Funding and conflicts of interest | Low risk | This research was funded by the Bill & Melinda Gates Foundation through a grant to Gynuity Health Projects and Family Care International. The Foundation had no role in the actual planning, writing or submission of this paper. |

[8] PPH: postpartum haemorrhage

# Characteristics of excluded studies [ordered by study ID]

| Study | Reason for exclusion |
|---|---|
| Chatterjee 2016 | Not eligible study design. |
| IRCT2012122411862N1 | Not eligible intervention. |
| Maged 2016 | |
| Raghavan 2016 | Not eligible study design. |
| Sahhaf 2014 | Not eligible intervention. |
| Suhrabi 2016 | Not eligible intervention. |
| Takagi 1976 | Not eligible study design. |

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

### Abbas 2019

| | |
|---|---|
| Methods | COMMUNITY SETTING UNETHICAL STUDY. WOMEN WITH DIAGNOSED PPH RECEIVED EITHER MISOPROSTOL OR PLACEBO. SUCH A COMPARISON WAS NOT PREVIOUSLY INCLUDED. i don't see the point of using this study. we can refer to it in discussion |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

### EUCTR2018-001829-11-GB 2019 UPDATED SEARCH

| | |
|---|---|
| Methods | NEED TO MOVE TO ONGOING |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

### NCT01116050

| | |
|---|---|
| Methods | Randomised controlled trial. |
| Participants | Not recorded. |
| Interventions | Misoprostol 1000 mcg administered rectally versus placebo |
| Outcomes | The study recorded the following outcomes: additional blood loss of more than 500 mL after recruitment to cessation of active bleeding; composite of death or severe morbidity; additional uterotonics; additional blood loss of more than 1000 mL after recruitment to cessation of active bleeding. |
| Notes | Awaiting full text publication. |

# Characteristics of ongoing studies [ordered by study ID]

### ISRCTN16416766

| | |
|---|---|
| Study name | COPE. Carboprost vs Oxytocin as the First Line Treatment of Primary Postpartum Haemorrhage; A phase IV, double-blind, double-dummy, randomised controlled trial. |
| Methods | Double-blind, double-dummy, randomised controlled trial. |
| Participants | Inclusion criteria: women aged 16 years or older with a requirement for medical treatment of primary PPH.<br><br>Exclusion criteria: women who have hypersensitivity to carboprost or oxytocin, have known cardiac or pulmonary disease, have previously been treated as part of the trial, have already received a treatment uterotonic drug or have a stillbirth, have opted out of participation. |
| Interventions | Carboprost 250 mcg administered intramuscularly plus placebo 1 mL administered intravenously versus oxytocin 10 IU administered intravenously plus placebo 1 mL administered intramuscularly. |
| | Primary outcome measure:<br>Blood transfusion - any RBC blood transfusion or cell salvage of ≥ 300 mL commenced any time |

| | |
|---|---|
| Outcomes | between randomisation and 48 hours after randomisation (or hospital discharge if earlier than 48 hrs), measured using medical notes.<br><br>Secondary outcome measures:<br>1. Volume of blood transfusion from randomisation up to 48 hours (or hospital discharge if earlier), measured using medical notes;<br>2. Use of a further uterotonic drug from randomisation up to 24 hours after randomisation, measured using medical notes;<br>3. Composite outcome of any organ dysfunction based on WHO near-miss approach for maternal health (2) from randomisation up to hospital discharge (or 4 weeks whichever is earlier);<br>4. Hysterectomy from randomisation up to hospital discharge (or 4 weeks whichever is earlier), measured using medical notes;<br>5. Blood loss in mL commencing in the first 24 hours from randomisation, up to cessation of active bleeding, measured using medical notes;<br>6. Blood loss ≥ 1000 mL, measured using medical notes;<br>7. Haemoglobin closest to 24 hours after randomisation, measured using medical notes;<br>8. Shock within 24 hours of randomisation, measured using medical notes;<br>9. Maternal death within 4 weeks of the birth where PPH was a contributing factor (it does not need to be the primary cause), measured using medical notes;<br>10. Non-pharmacological approach to treat or investigate bleeding from randomisation up to hospital discharge, measured using medical notes;<br>11. Manual removal of placenta post-randomisation up to hospital discharge, measured using medical notes;<br>12. Any adverse reactions of the intervention for the mother (i.e. hypotension occurring within 2 minutes of Investigational Medicinal Product (IMP) administration, and all other adverse reactions occurring within 2 hours of administration), measured using medical notes;<br>13. 'Skin-to-skin' care with baby within the first hour after birth, measured using medical notes;<br>14. Separation from new-born in first hour after birth, measured using medical notes;<br>15. Breastfeeding, measured at 24 hours, 48 hours (or hospital discharge if sooner) and 4 weeks;<br>16. Woman's experience, measured using Childbirth Experience Questionnaire (CEQ) at 4 weeks;<br>17. Resource use, measured using EQ-5D-5L, resource use questionnaire and hospital episode statistics at 24 hours and 4 weeks. |
| Starting date | September 2018 |
| Contact information | Mr Alex Astor<br>Address Research Support Office<br>2nd Floor Block D Waterhouse Building<br>3 Brownlow Street<br>Liverpool<br>L69 3GL<br>United Kingdom<br>+44 (0)1517948739<br>sponsor@liverpool.ac.uk |
| Notes | Study team not contacted. |

**NCT01485562**

| | |
|---|---|
| Study name | Treatment of postpartum haemorrhage (PPH) using misoprostol in home births. |
| Methods | A double-blind individual randomised controlled study of misoprostol versus placebo for treatment in home births in the Chitral district, in the Khyber Pakhtunkhwa province in Pakistan. The purpose of the study is to assess the overall clinical and programmatic effectiveness of Traditional Birth Attendants (TBAs) administering 800 mcg sublingual misoprostol to treat PPH at the community level. |
| Participants | Inclusion criteria: pregnant women who deliver at home. |
| Interventions | Misoprostol 800 mcg (4 tablets of 200 mcg) administered sublingually versus placebo (4 tablets) administered sublingually. |
| Outcomes | Primary outcome: haemoglobin concentration of greater than or equal to 2 g/dL from pre- to post-delivery.<br><br>Secondary outcomes: number of participants who experience side effects; number of women who experience side effects and the severity of side effects, as rated on a scale; additional care provided; number of women who received additional interventions; number of women who received care by a skilled provider, and the type of care provided; number of women who found misoprostol treatment to be acceptable, as rated on a scale; number of women who experience severe adverse events, defined as uterine rupture, hysterectomy, hospitalisation, maternal deaths, and neonatal deaths. |
| Starting date | May 2012 |

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| Contact information | Zafar Khan Aga Khan Health Services |
| Notes | Study team contacted for results with no response. |

**NCT01508429**

| | |
|---|---|
| Study name | Misoprostol for the treatment of postpartum haemorrhage (PPH) following self-administration of misoprostol prophylaxis in home deliveries |
| Methods | A double-blind individual randomised controlled study. |
| Participants | Inclusion criteria: pregnant women who are likely to deliver at home. |
| Interventions | Standard of care plus 800 mcg misoprostol (4 tablets of 200 mcg) versus standard of care plus placebo (4 tablets). |
| Outcomes | Primary outcome: haemoglobin of greater than or equal to 2 g/dL from pre- to post-delivery. Secondary outcomes: side effects, including perceived severity, and additional care provided; any serious adverse outcomes, including uterine rupture, hysterectomy, hospitalisation, maternal deaths, and neonatal deaths; additional interventions, including additional interventions and additional care provided to the woman, referrals, and transfers; acceptability and management of side effects, and acceptability of interventions. |
| Starting date | July 2012 |
| Contact information | Shafiq Mirzazada, Aga Khan Services |
| Notes | Study team contacted for results with no response. |

**NCT01600612**

| | |
|---|---|
| Study name | Oxytocin, carbetocin and misoprostol for treatment of postpartum haemorrhage: a multicentric randomised trial |
| Methods | A multicentric randomised trial. |
| Participants | Inclusion criteria: women with atonic PPH who delivered vaginally.<br>Exclusion criteria: women who deliver by caesarean section, with retained placenta, with traumatic PPH, associated coagulopathy, and those who refuse to participate in the study. |
| Interventions | Oxytocin 30 IU administered intravenously versus misoprostol 600 mcg administered sublingually versus carbetocin 100 mcg administered intravenously. |
| Outcomes | Primary outcome: cessation of bleeding.<br>Secondary outcomes: time needed to control bleeding (minutes); amount of blood loss till control of bleeding (mL), changes in haemoglobin levels (gm) before and after treatment; changes in hematocrit values (%) before and after treatment; use of additional uterotonics; the rate of complications (%); the necessity for surgical intervention; and the cost of each medication. |
| Starting date | September 2012 |
| Contact information | Salah M Rasheed. Sohag University Egypt. |
| Notes | Study team contacted for results with no response. |

**NCT01619072**

| | |
|---|---|
| Study name | A randomised controlled community study of the effectiveness of misoprostol for PPH treatment at the community level (home births attended by Primary Care Unit staff) in Etay El Barood and Kafr El Dawar Districts (El Beheira Governorate), Egypt |
| Methods | Randomised controlled community-based trial. |
| Participants | Inclusion criteria: women having a vaginal delivery and willing and able to give informed consent aged 18-45 years.<br>Exclusion criteria: women too advanced in active labour, allergic to misoprostol, having hypertensive disorders, with multiple gestation, previous caesarean section, suspected stillbirth, antepartum haemorrhage, and previous complications in the third trimester. |
| Interventions | Standard of care plus misoprostol 800 mcg administered sublingually or standard of care plus placebo. |
| Outcomes | Primary outcome: change in haemoglobin measurement of > 2 g/dL pre- to post-delivery. |
| Starting date | November 2012 |
| Contact information | Mohamed Cherine Ramadan. El Galaa Teaching Hospital. |

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| Notes | Study team contacted for results with no response. |

### NCT02306733

| | |
|---|---|
| Study name | Ergometrine versus oxytocin in the management of atonic post-partum haemorrhage (PPH) in women delivered vaginally: a randomised controlled trial. |
| Methods | Randomised controlled trial. |
| Participants | Inclusion criteria: women experiencing PPH, due to uterine atony, signing informed consents.<br>Exclusion criteria: gestational age < 37 weeks, hypertension, cardiac disease or pre-eclampsia. |
| Interventions | Ergometrine 400 mcg administered intravenously versus oxytocin 10 IU (Syntocinon® Novartis, Switzerland) administered intravenously. |
| Outcomes | Primary outcome: the need for additional uterotonics.<br>Secondary outcome: the development of major PPH. |
| Starting date | November 2014 |
| Contact information | AbdelGany MA Hassan, Cairo University Hospitals, Egypt. |
| Notes | Study team contacted for results, write up and data analysis is ongoing. |

### NCT02410759

| | |
|---|---|
| Study name | Carbetocin versus oxytocin in the management of atonic post partum haemorrhage (PPH) in women delivered vaginally: a randomised controlled trial. |
| Methods | Randomised controlled trial. |
| Participants | Inclusion criteria: women aged 20 to 40 years with atonic PPH who delivered vaginally.<br>Exclusion criteria: women with preterm delivery, hypertension, pre-eclampsia, cardiac, renal, liver diease, epilepsy and known hypersensitivity to carbetocin. |
| Interventions | Carbetocin 100 mcg administered intramuscularly or ergometrine 500 mcg administered intramuscularly. |
| Outcomes | Primary outcome: the need for additional uterotonics.<br>Secondary outcome: the development of major PPH. |
| Starting date | April 2015 |
| Contact information | AbdelGany MA Hassan, Cairo University Hospitals, Egypt. |
| Notes | Study team contacted for results, write up and data analysis is ongoing. |

### NCT03584854 UPDATED SEARCH

| | |
|---|---|
| Study name | Second-line uterotonics in postpartum hemorrhage: a randomized clinical trial |
| Methods | Randomised controlled trial. |
| Participants | Inclusion criteria: women aged 18 to 50 years with atonic PPH who delivered by non-emergent caesarean section.<br>Exclusion criteria: women delivering at <24 weeks, any hypertensive disorders, cardiac diease, asthma, refusal of transfused blood products, coagulation disorders, known hypersensitivity to ergometrine or carboprost. |
| Interventions | Carboprost 250 mcg administered intramuscularly (followed by ergometrine if needed) or ergometrine 200 mcg administered intramuscularly (followed by carboprost if needed). |
| Outcomes | Primary outcome: uterine tone at 10 minutes after drug administration<br>Secondary outcomes: uterine tone at 5 minutes after drug administration, need for additional uterotonics, need for blood transfusion, additional surgical or radiologic interventions to control the bleeding, amount of blood loss, change in haematocrit, length of hospital stay, maternal morbidity related to PPH (e.g. cardiovascular event, intubation, ICU admission, hypovolemic shock, adverse study drug reaction). |
| Starting date | March 2019 |
| Contact information | Naida M Cole, MDBrigham and Women's Hospital, 75 Francis Street, Boston MA 02115 |
| Notes | Active not recruiting |

### NCT03870503 UPDATED SEARCH

| | |
|---|---|
| | Carbetocin versus oxytocin plus sublingual misoprostol in the management of atonic post- |

| | |
|---|---|
| Study name | partum hemorrhage (PPH) after vaginal delivery: a randomized controlled trial |
| Methods | Randomised controlled trial. |
| Participants | Inclusion criteria: women aged 20 to 40 years with atonic PPH who delivered vaginally.<br>Exclusion criteria: women with preterm delivery, hypertension, pre-eclampsia, cardiac, renal, liver diease, epilepsy and known hypersensitivity to carbetocin or oxytocin. |
| Interventions | Oxytocin 20 IU administered by an intravenous infusion or oxytocin 20 IU administered by an intravenous infusion plus misoprostol 400 mcg administered sublingually or carbetocin 100 mcg administered by an intravenous bolus injection. |
| Outcomes | Primary outcome: the amount of blood loss.<br>Secondary outcome: the development of major PPH, the need for blood transfusion. |
| Starting date | April 2019 |
| Contact information | Hany F Allam, MD, Aswan University Hospital, Aswan, Egypt, 81528 |
| Notes | Recruting |

[9] PPH: postpartum haemorrhage

# Appendices

## Appendix 1. Search terms for ClinicalTrials.gov and ICTRP

### The WHO International Clinical Trials Registry Platform (ICTRP)

We ran each line separately
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

Third stage AND labo(u)r AND carboprost

Third stage AND labo(u)r AND syntometrine
uterotonic* AND oxytocin
uterotonic* AND misoprostol
uterotonic* AND carbetocin
uterotonic* AND ergometrine

uterotonic* AND syntometrine

uterotonic* AND carboprost
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

h(a)emorrhage AND postpartum AND syntometrine

h(a)emorrhage AND postpartum AND carboprost

### ClinicalTrials.gov

Advanced search

Intervention studies

Condition = postpartum hemorrhage (taken from their index terms).

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[CTG: NCT00116350]


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Blum J , Winikoff B , Raghavan S , Dabash R , Ramadan MC , Dilbaz B , et al. Treatment of postpartum hemorrhage with sublingual misoprostol versus oxytocin: results from a randomized non-inferiority trial among women receiving prophylactic oxytocin. International Journal of Gynecology & Obstetrics 2009;107(Suppl 2):S22-S23. [NCT00116350]

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[ISRCTN: ISRCTN72263357]


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[CTG: NCT01462422]


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# Figures and tables

**Figure 1**

Study flow diagram.

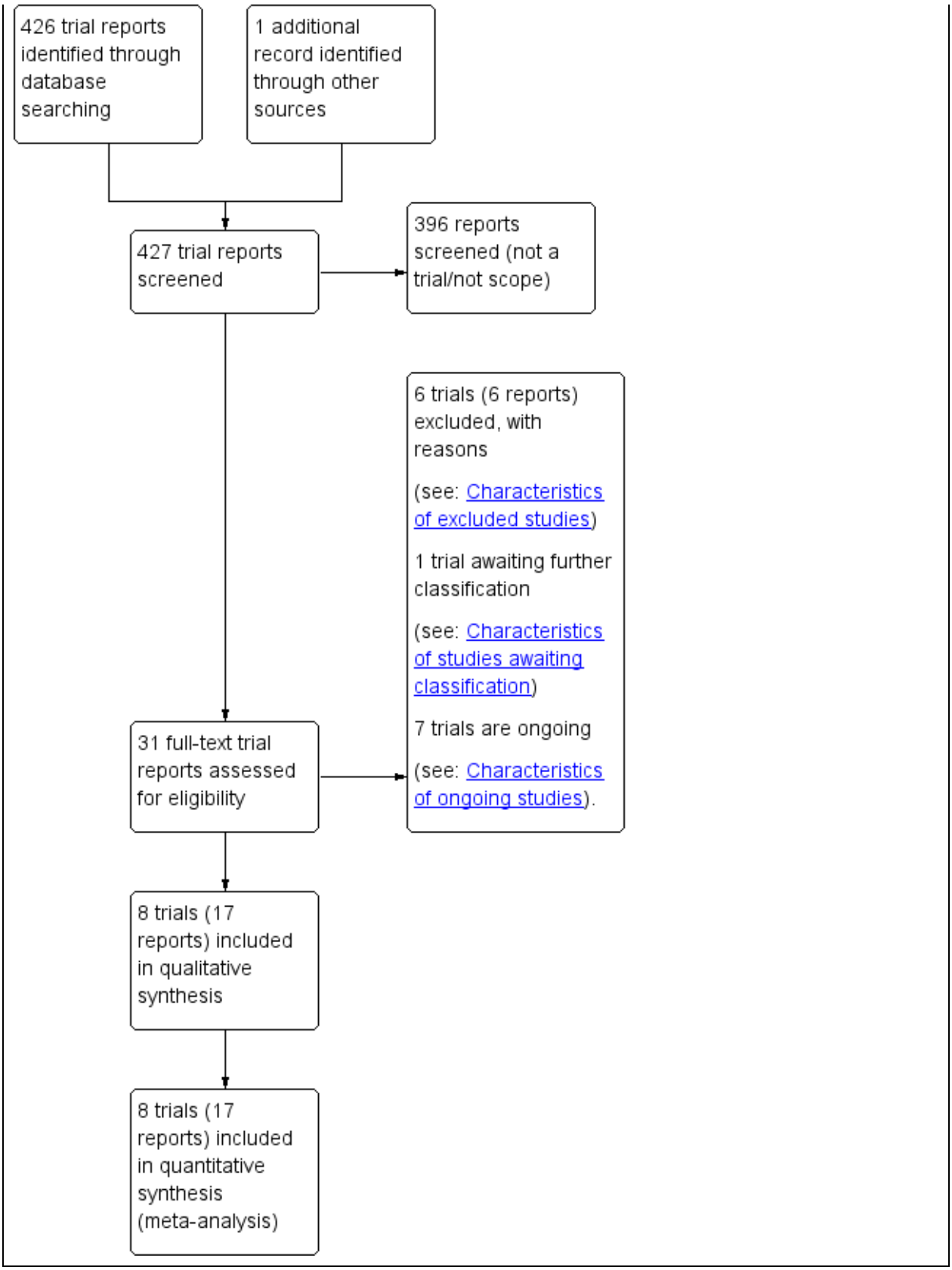



**Figure 2**

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

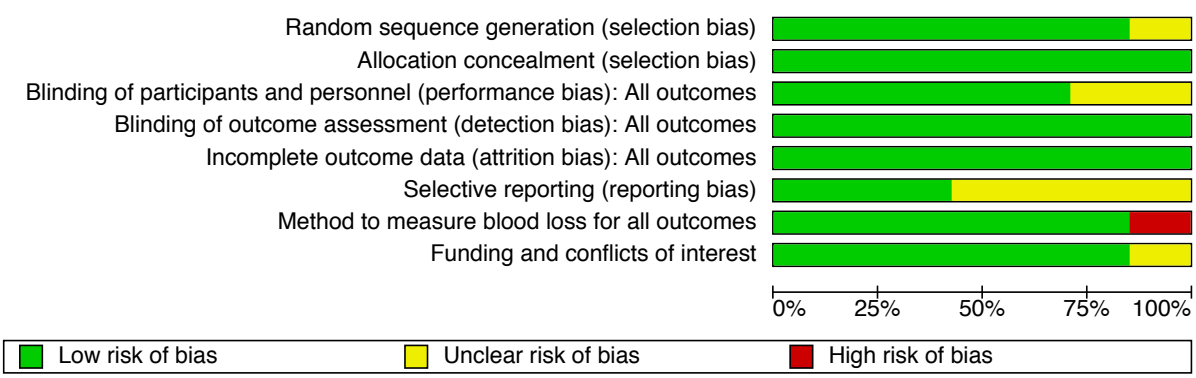



**Figure 3**

Risk of bias summary: Review authors' judgements about each risk of bias item, for each included study.

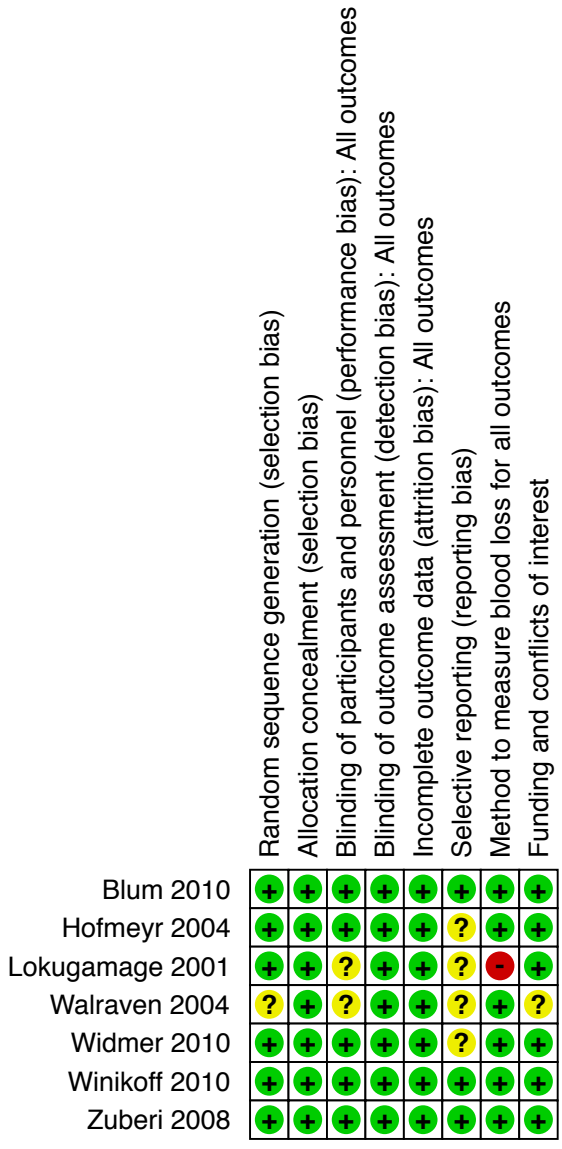



**Figure 4**

Network Diagram for additional blood loss of more than 500 mL after recruitment to the trial and until cessation of active bleeding. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is light green for moderate-certainty evidence and orange for low-

certainty evidence.

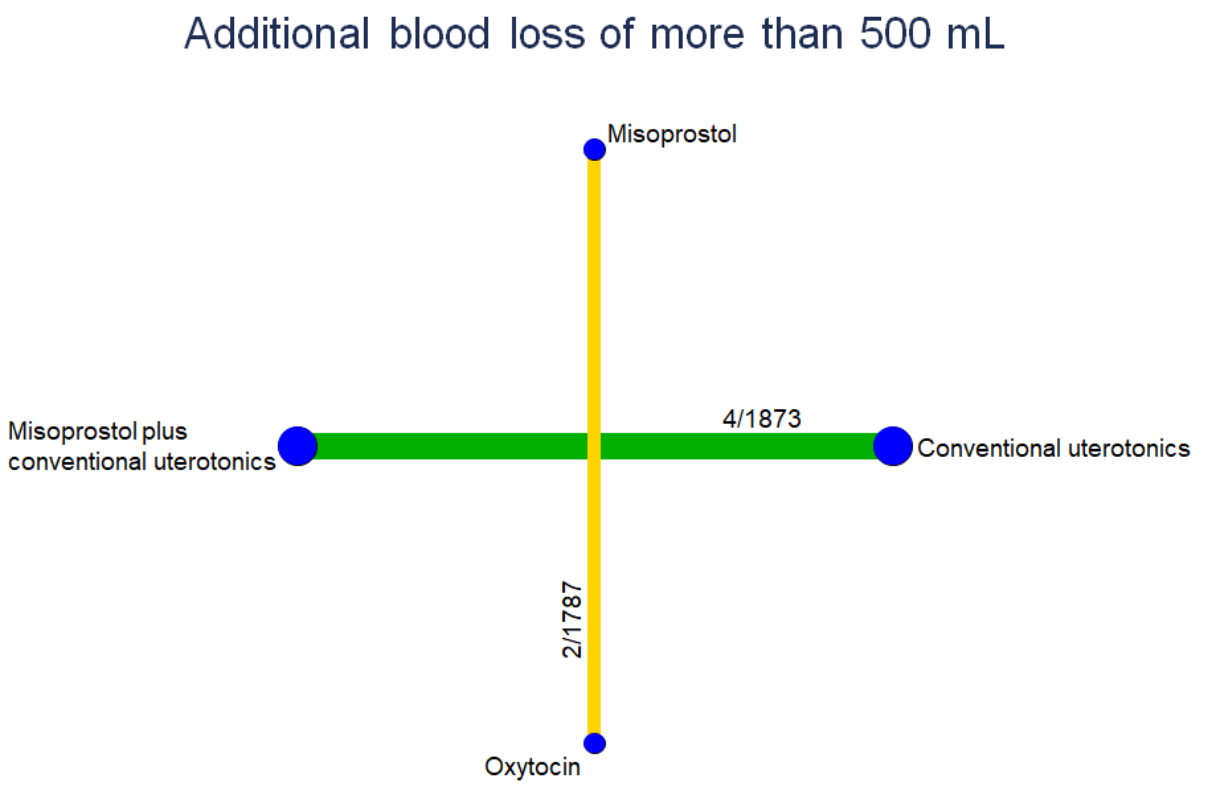



**Figure 5**

Network Diagram for the composite outcome of maternal mortality and serious morbidity (e.g. hysterectomy, any organ dysfunction, transfer to higher level of care, coagulopathy, shock as defined by trialists). The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is light green for moderate-certainty evidence, orange for low-certainty evidence, and red for very low-certainty evidence. The certainty of the evidence for the comparison of carbetocin versus oxytocin could not be assessed, because of a single trial with no events for this comparison, and is displayed in black.

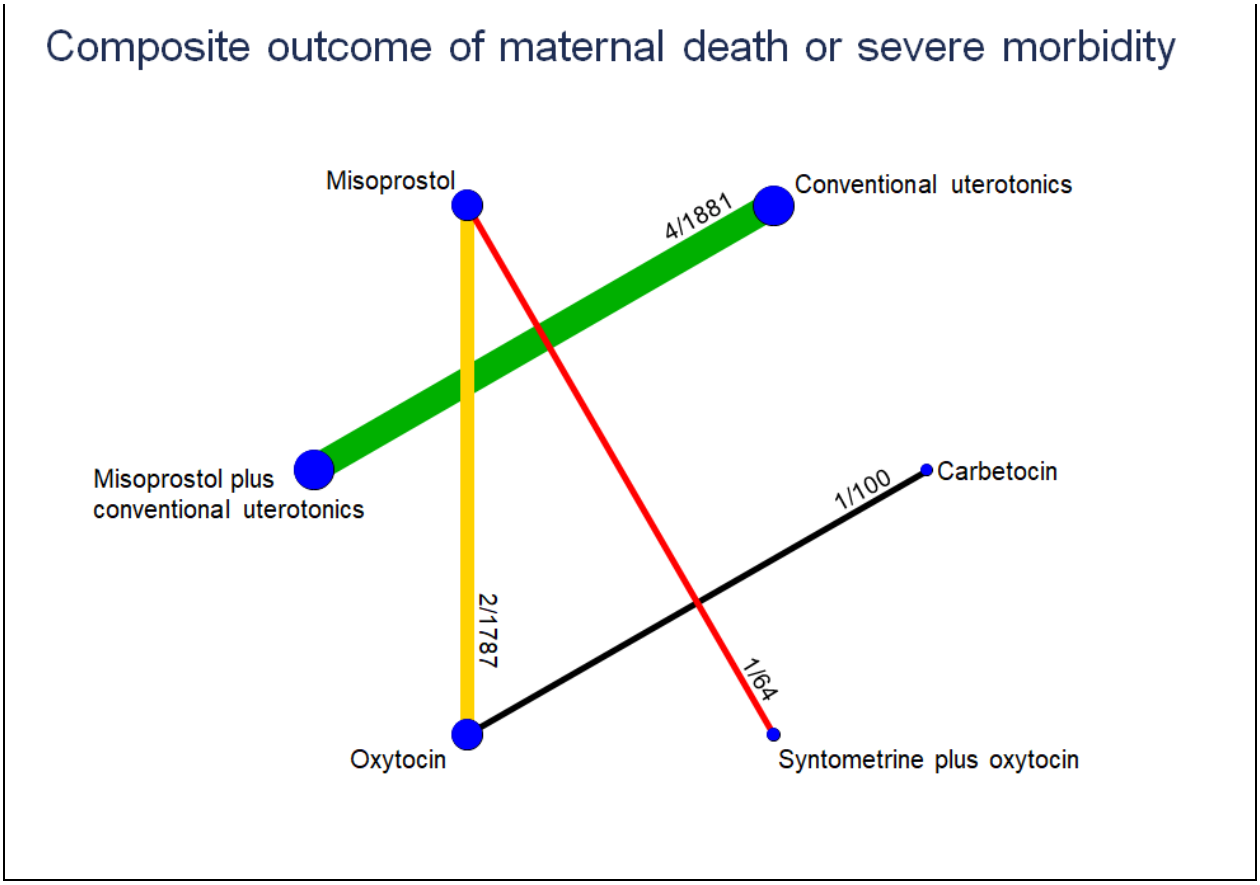



**Figure 6**

Network Diagram for death. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is orange for low-certainty evidence, and red for very low-certainty evidence. The certainty of the evidence for the comparison of carbetocin versus oxytocin could not be assessed, because of a single trial with no events for this comparison, and is displayed in black.

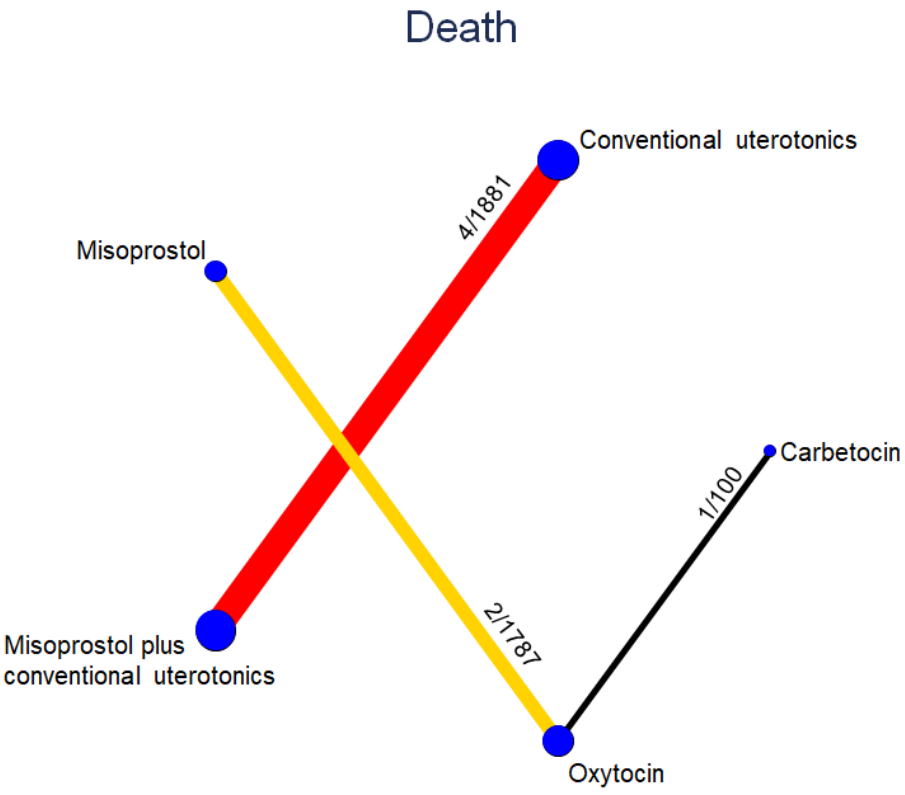


**Figure 7**

Network Diagram for the use of additional uterotonics. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is dark green for high-certainty evidence, orange for low-certainty evidence, and red for very low-certainty evidence.

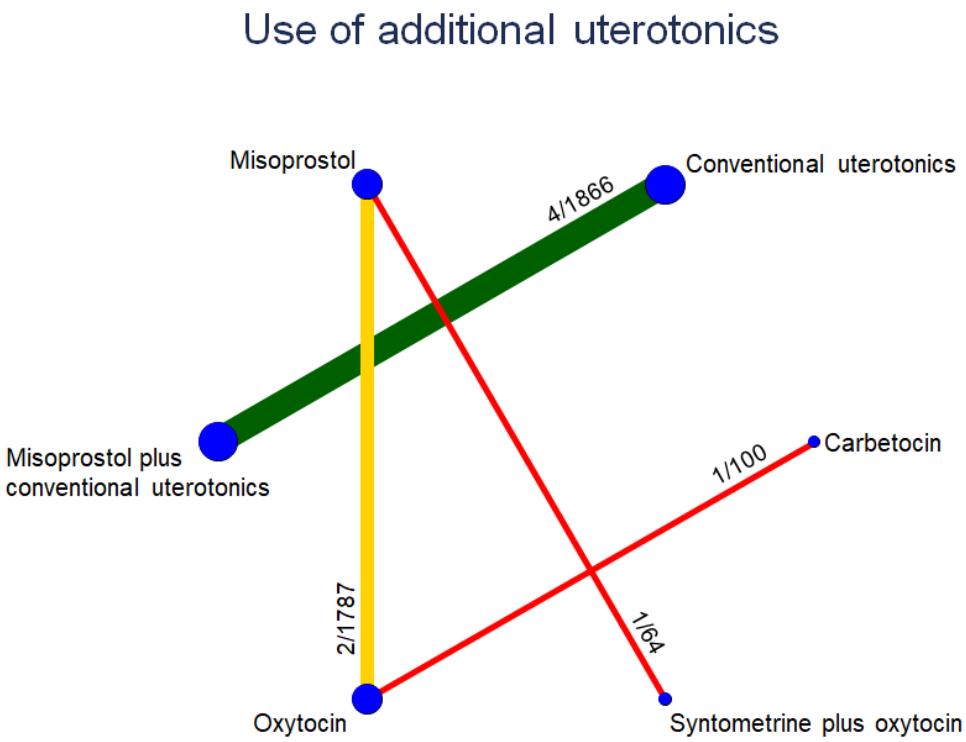



**Figure 8**

Network Diagram for additional blood loss of more than 1000 mL after recruitment to cessation of active bleeding. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is light green for moderate-certainty evidence, orange for low-certainty evidence, and red for very low-certainty evidence.

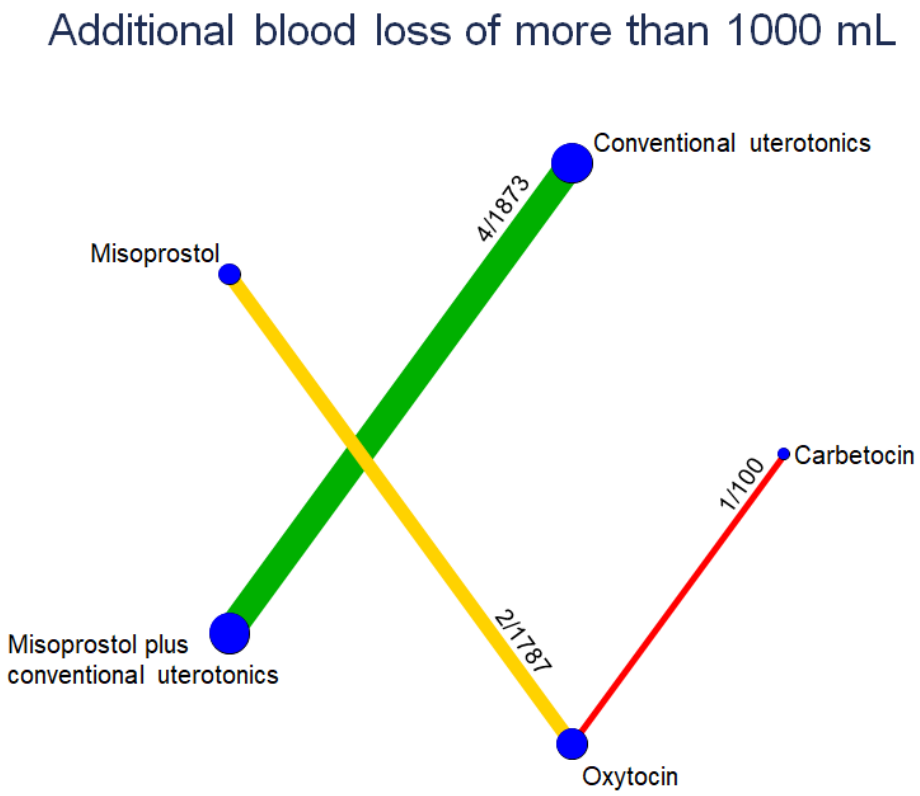



**Figure 9**

Network Diagram for additional surgical procedures. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is orange for low-certainty evidence and red for very low-certainty evidence.

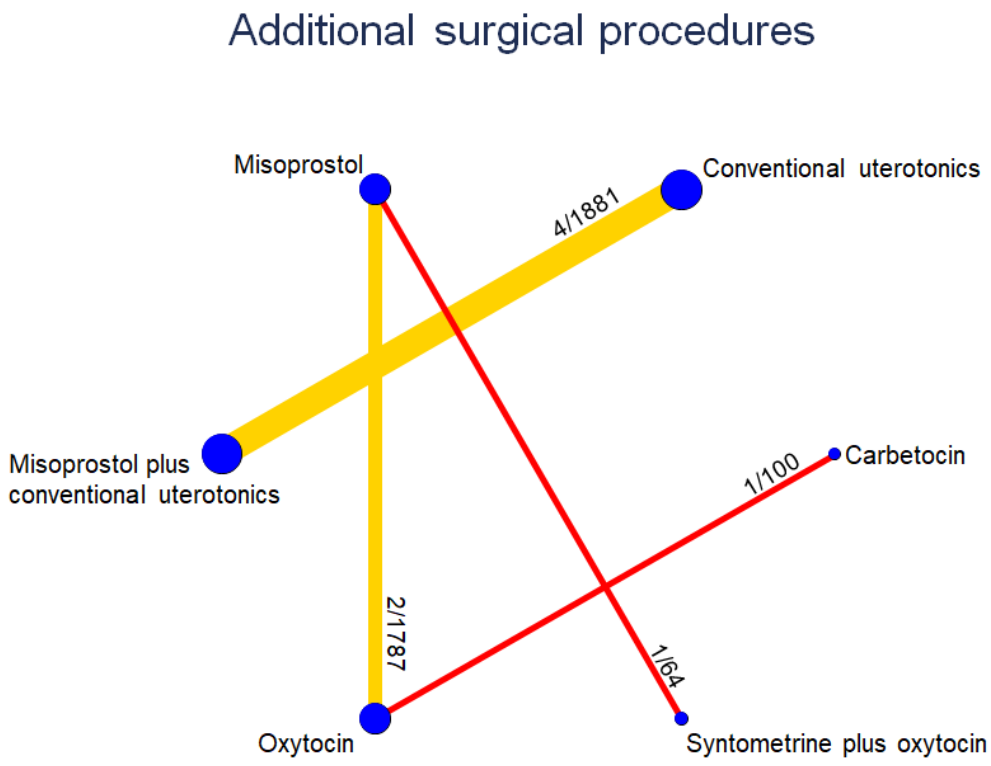



**Figure 10**

Network Diagram for blood transfusion or other blood products. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is dark green for high-certainty evidence, and red for very low-certainty evidence.

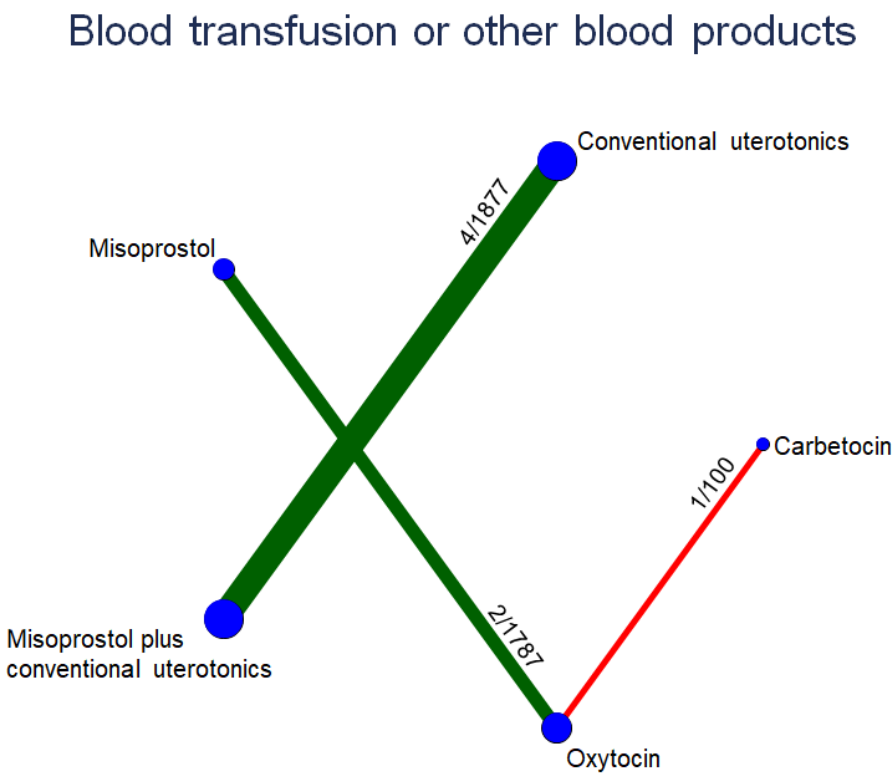



**Figure 11**

Network Diagram for blood transfusion or other blood products. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is dark green for high-certainty evidence, light green for moderate-certainty evidence, and red for very low-certainty evidence.

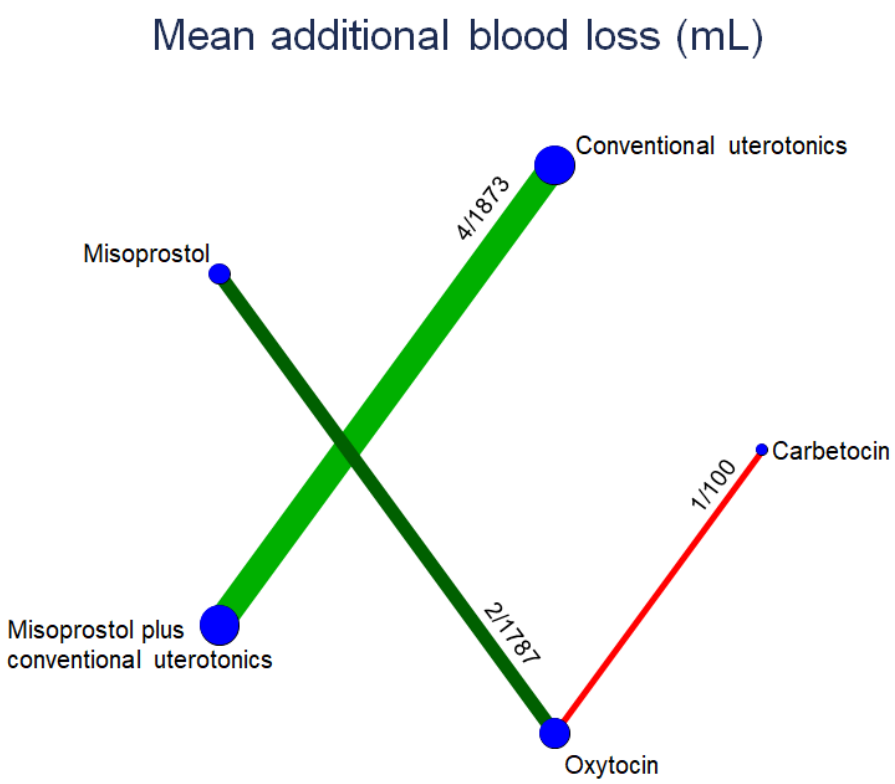



**Figure 12**

Network Diagram for change in haemoglobin (g/L). The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is orange for low-certainty evidence, and red for very low-certainty evidence.

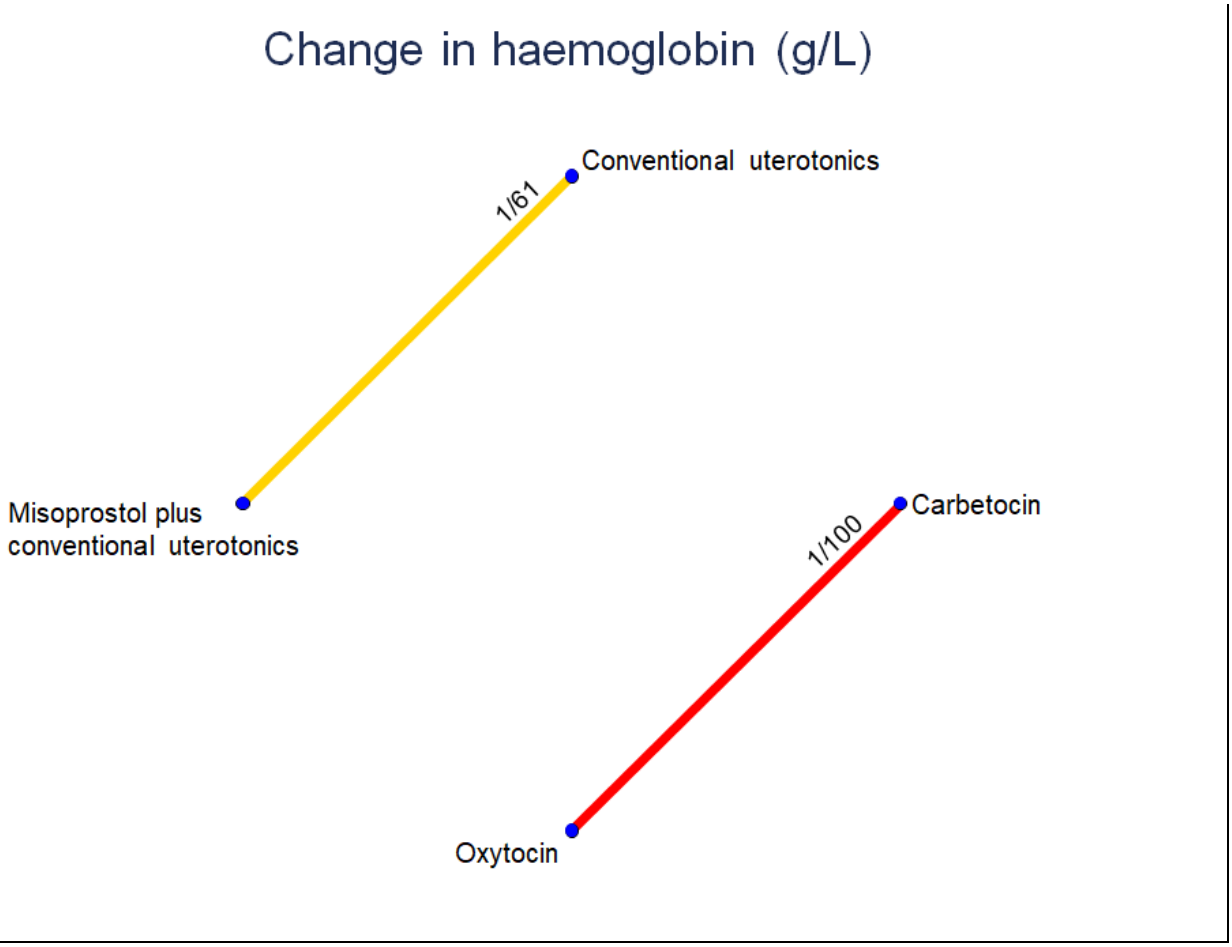



**Figure 13**

Network Diagram for fever (temperature above 38$^{o}$C). The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is dark green for high-certainty evidence, and orange for low-certainty evidence.

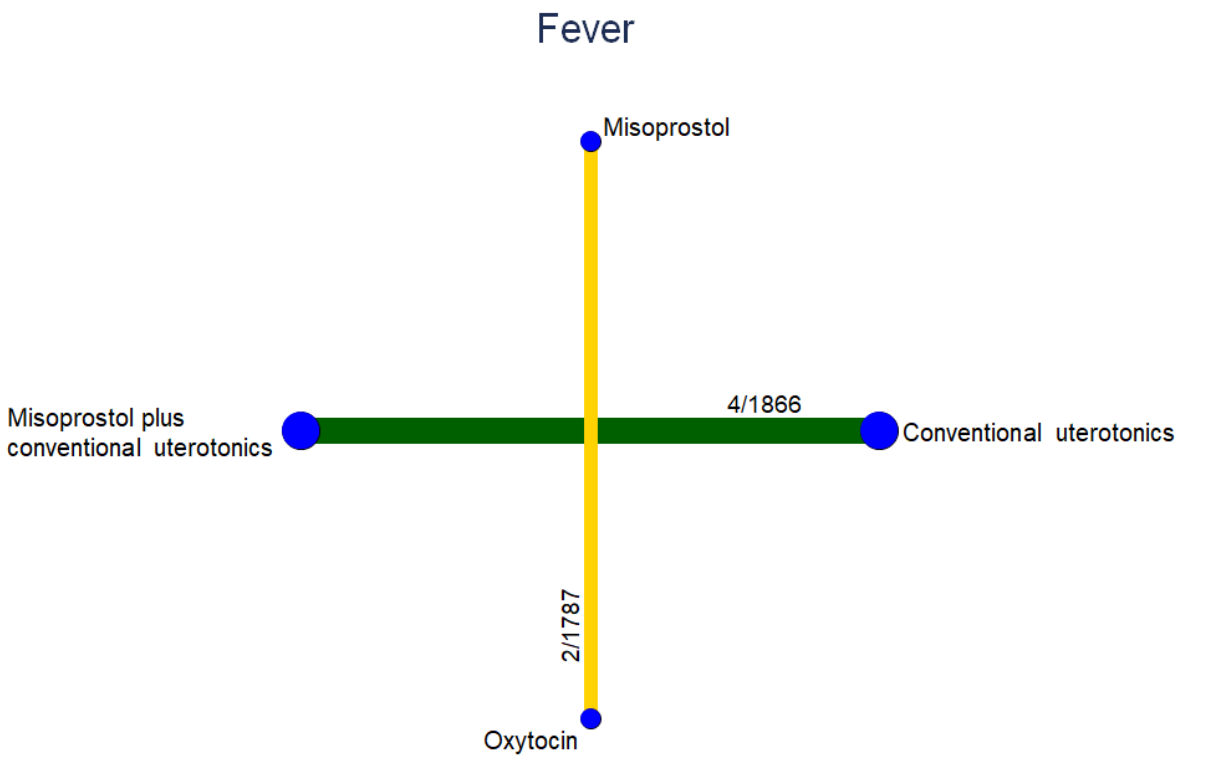



**Figure 14**

Network Diagram for nausea. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is light green for moderate-certainty evidence, and red for very low-certainty evidence.

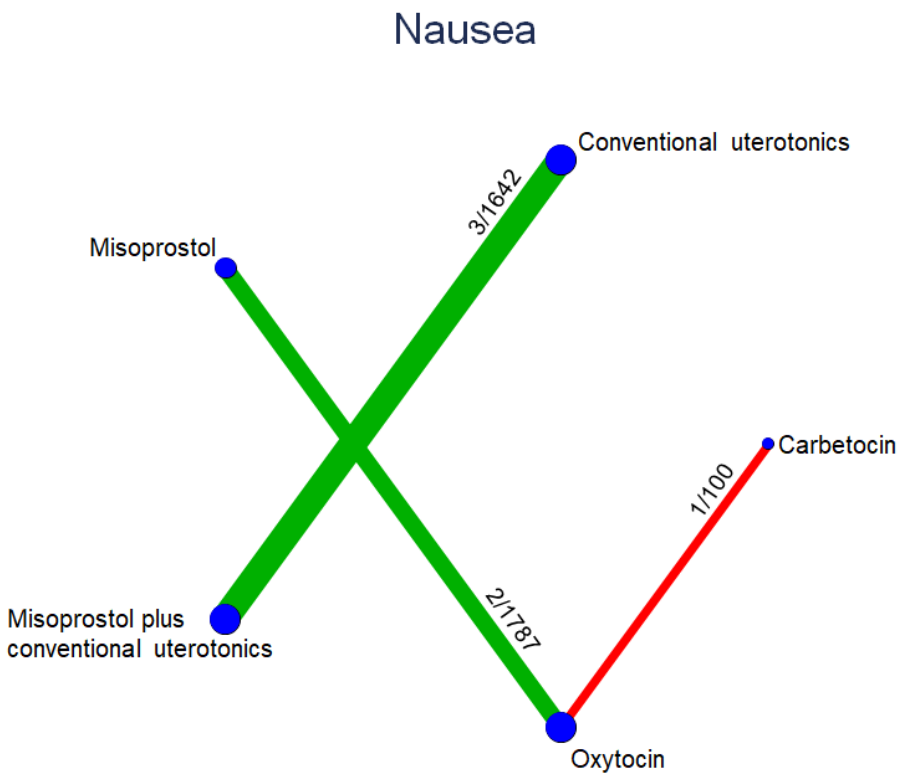


**Figure 15**

Network Diagram for vomiting. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is dark green for high-certainty evidence, and red for very low-certainty evidence.

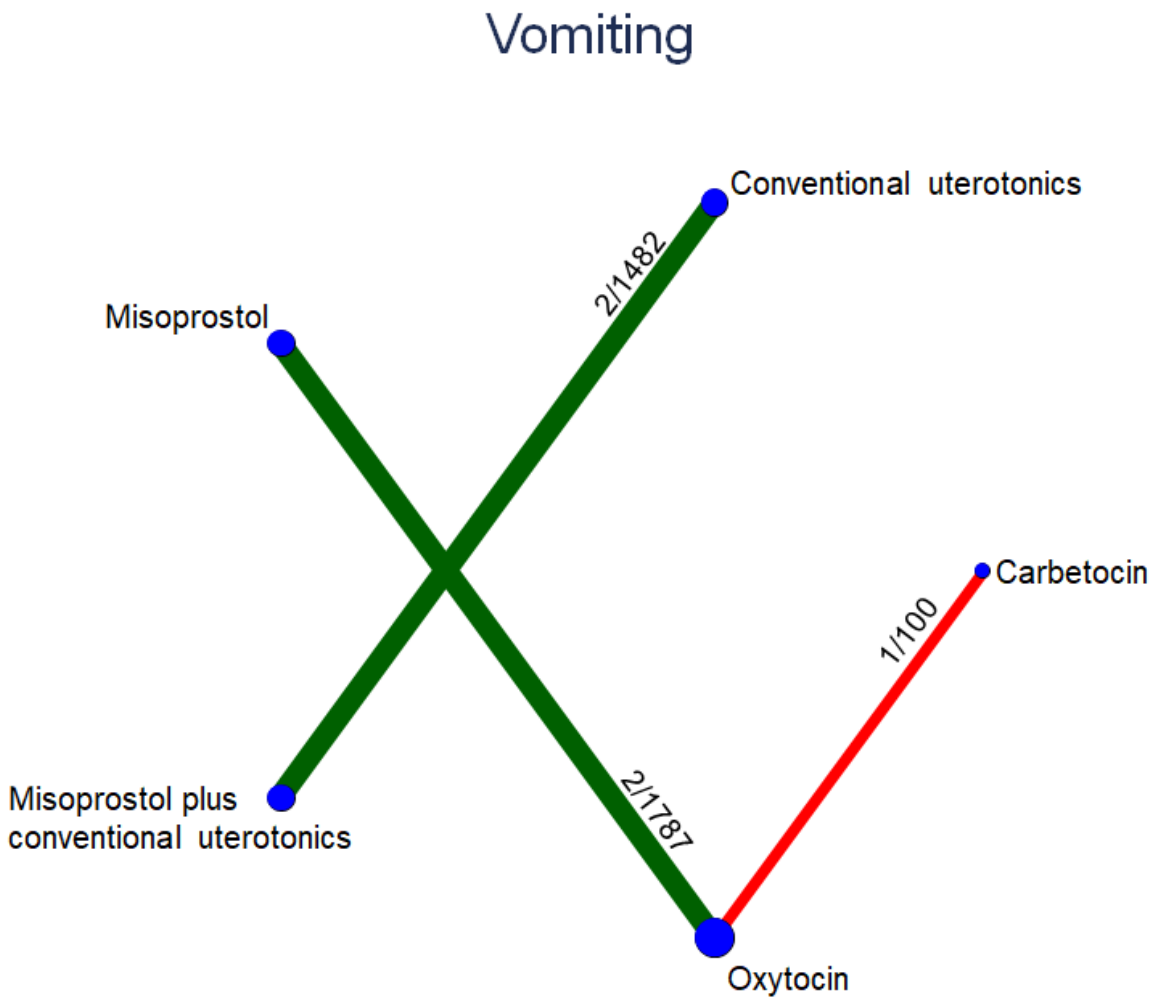



**Figure 16**

Network Diagram for headache. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is light green for moderate-certainty evidence, orange for low-certainty evidence, and red for very low-certainty evidence.

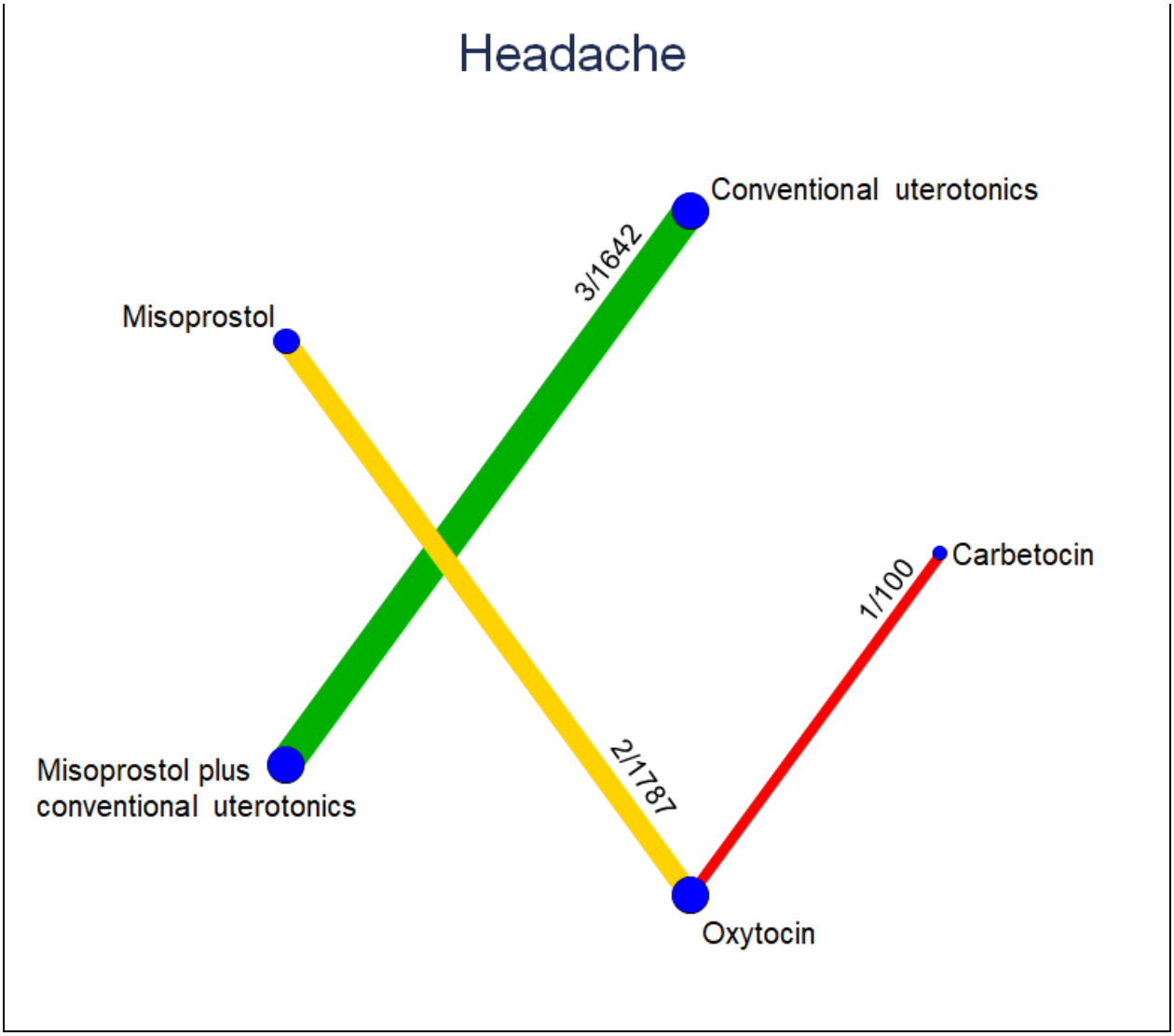



**Figure 17**

Network Diagram for shivering. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is dark green for high-certainty evidence, and red for very low-certainty evidence.

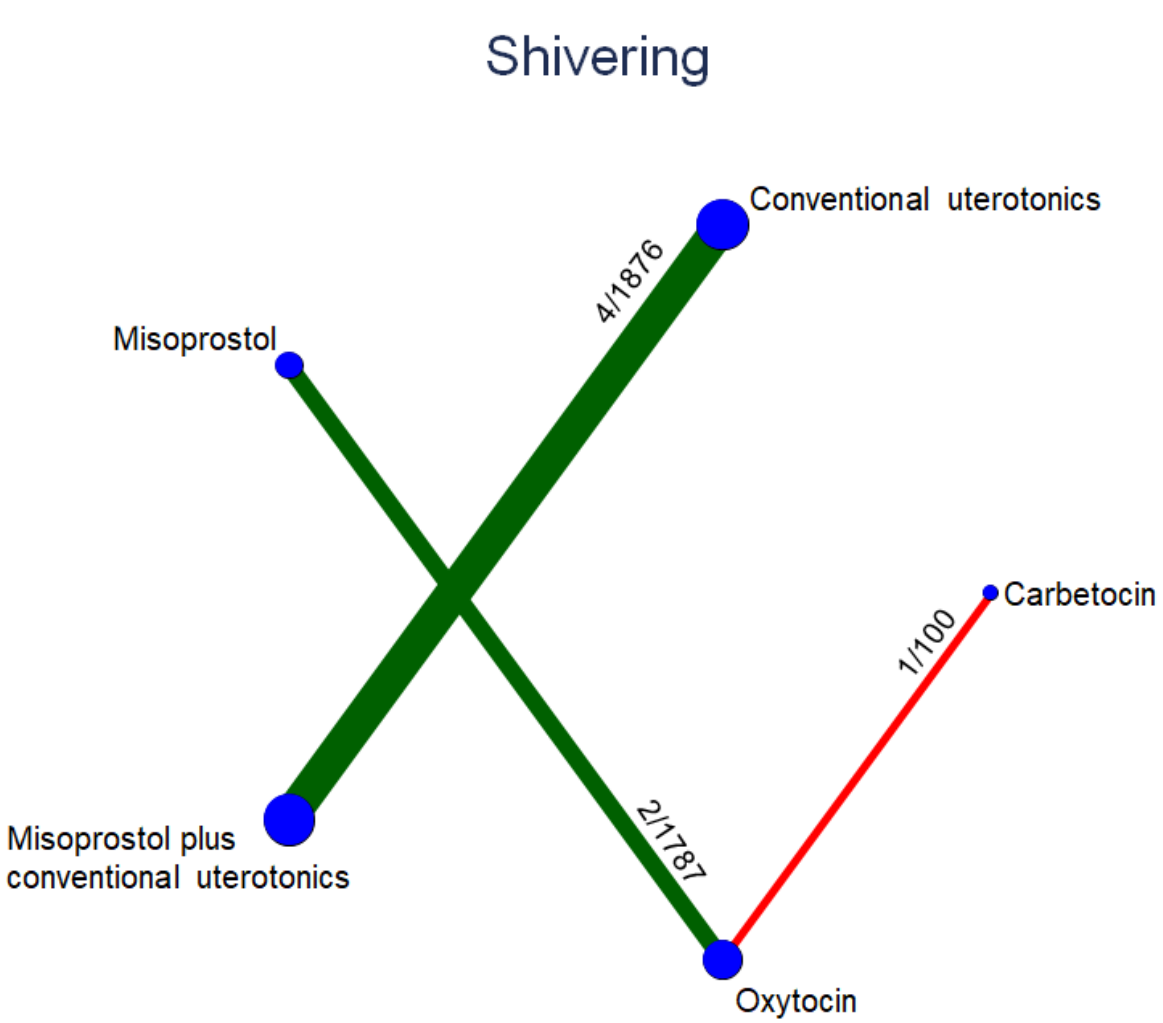



**Figure 18**

Network Diagram for tachycardia. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is red for very low-certainty evidence.

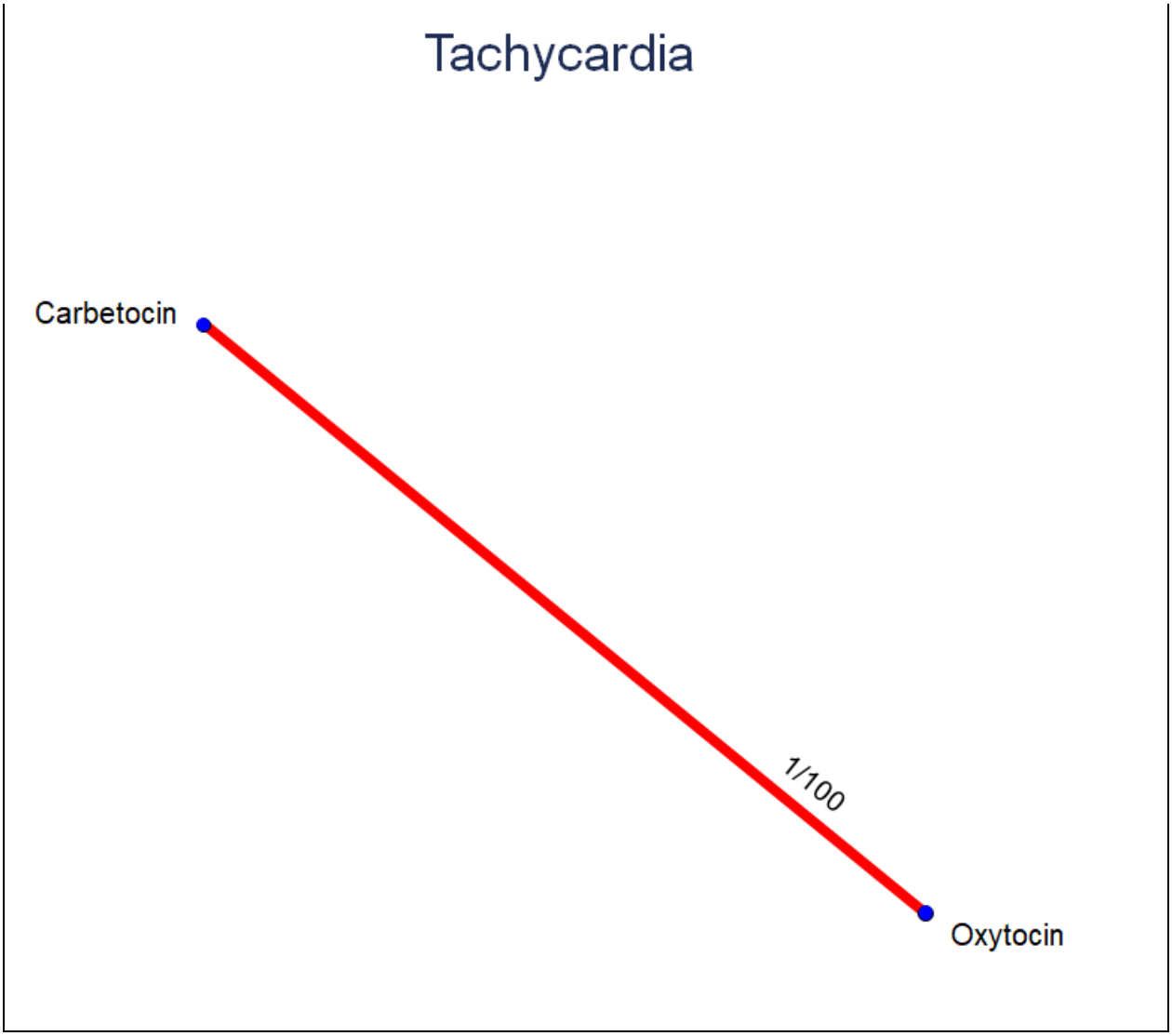
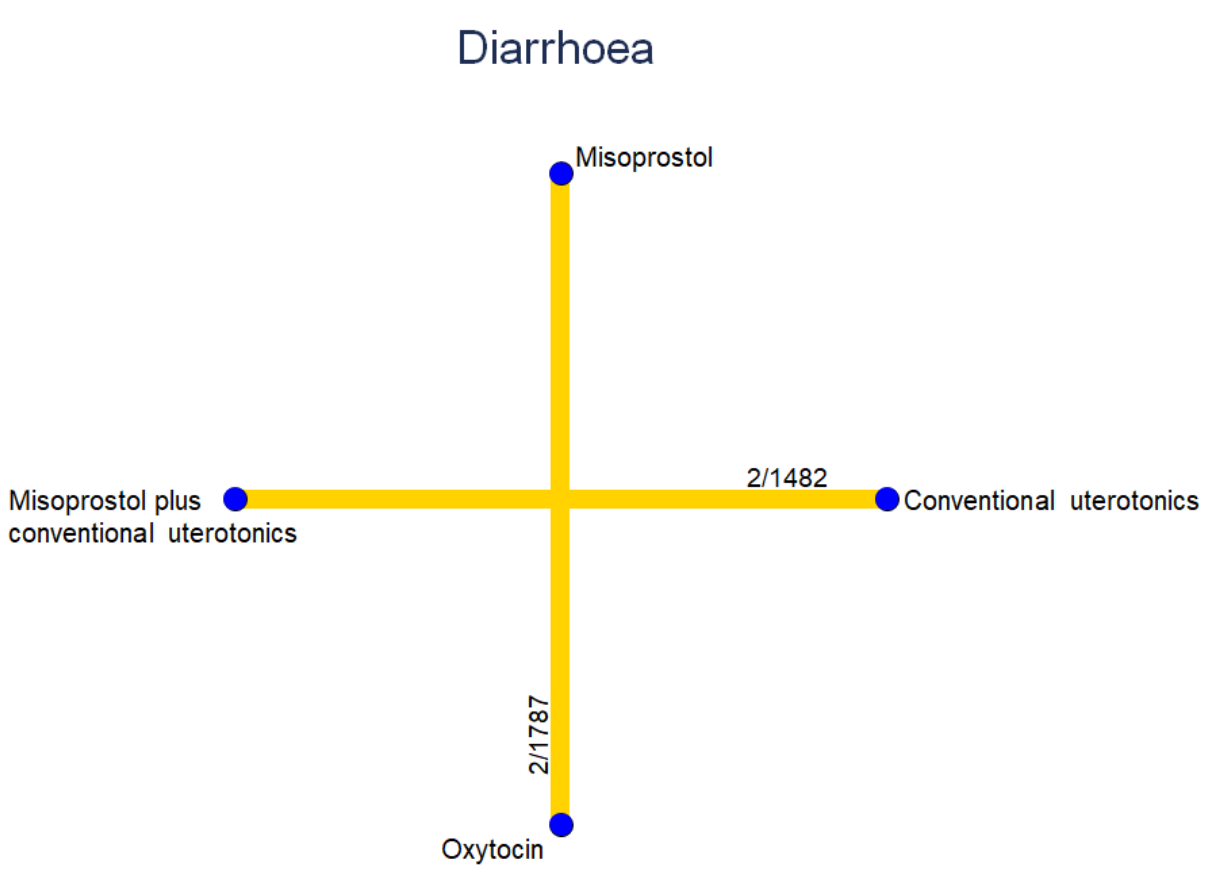



**Figure 19**

Network Diagram for diarrhoea. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is orange for low-certainty evidence.

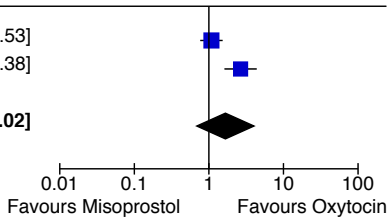



**Analysis 1.1**

Comparison 1: Misoprostol versus oxytocin, Outcome 1: Additional blood loss of more than 500 mL

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 58 | 407 | 53 | 402 | 52.1% | 1.08 [0.76 , 1.53] |
| Winikoff 2010 | 53 | 488 | 20 | 490 | 47.9% | 2.66 [1.62 , 4.38] |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **1.66 [0.69 , 4.02]** |
| Total events: | 111 | | 73 | | | |

Heterogeneity: Tau² = 0.36; Chi² = 8.46, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable

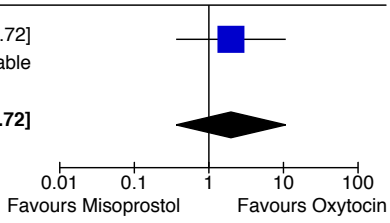



**Analysis 1.2**

Comparison 1: Misoprostol versus oxytocin, Outcome 2: Composite of maternal death or severe morbidity

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 4 | 407 | 2 | 402 | 100.0% | 1.98 [0.36 , 10.72] |
| Winikoff 2010 | 0 | 488 | 0 | 490 | | Not estimable |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **1.98 [0.36 , 10.72]** |
| Total events: | 4 | | 2 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable

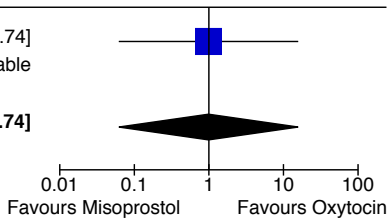



**Analysis 1.3**

Comparison 1: Misoprostol versus oxytocin, Outcome 3: Death

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 1 | 407 | 1 | 402 | 100.0% | 0.99 [0.06 , 15.74] |
| Winikoff 2010 | 0 | 488 | 0 | 490 | | Not estimable |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **0.99 [0.06 , 15.74]** |
| Total events: | 1 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable

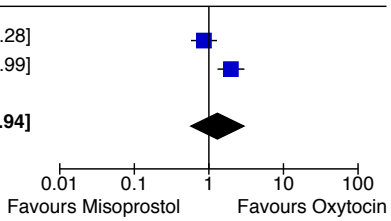



**Analysis 1.4**

Comparison 1: Misoprostol versus oxytocin, Outcome 4: Additional uterotonics

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 40 | 407 | 46 | 402 | 50.2% | 0.86 [0.58 , 1.28] |
| Winikoff 2010 | 61 | 488 | 31 | 490 | 49.8% | 1.98 [1.31 , 2.99] |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **1.30 [0.57 , 2.94]** |
| Total events: | 101 | | 77 | | | |

Heterogeneity: Tau² = 0.30; Chi² = 8.04, df = 1 (P = 0.005); I² = 88%
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable

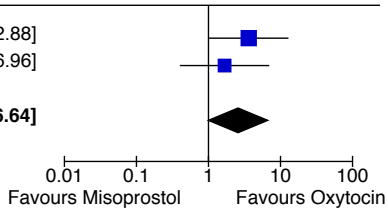



**Analysis 1.5**

Comparison 1: Misoprostol versus oxytocin, Outcome 5: Additional blood loss of more than 1000 mL

| Study or Subgroup | Favours Misoprostol Events | Favours Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 11 | 407 | 3 | 402 | 55.8% | 3.62 [1.02 , 12.88] |
| Winikoff 2010 | 5 | 488 | 3 | 490 | 44.2% | 1.67 [0.40 , 6.96] |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **2.57 [1.00 , 6.64]** |
| Total events: | 16 | | 6 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.96 (P = 0.05)
Test for subgroup differences: Not applicable

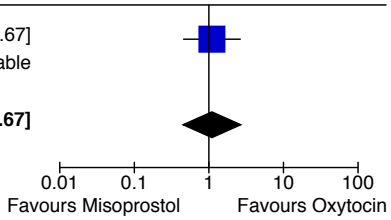



**Analysis 1.6**

Comparison 1: Misoprostol versus oxytocin, Outcome 6: Additional surgical procedures

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 10 | 407 | 9 | 402 | 100.0% | 1.10 [0.45 , 2.67] |
| Winikoff 2010 | 0 | 488 | 0 | 490 | | Not estimable |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **1.10 [0.45 , 2.67]** |
| Total events: | 10 | | 9 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable

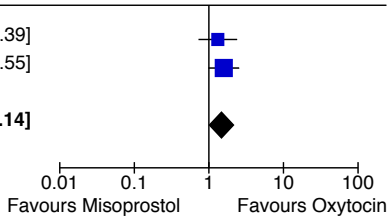



**Analysis 1.7**

Comparison 1: Misoprostol versus oxytocin, Outcome 7: Blood transfusion or other blood products

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 24 | 407 | 18 | 402 | 38.9% | 1.32 [0.73 , 2.39] |
| Winikoff 2010 | 41 | 488 | 26 | 490 | 61.1% | 1.58 [0.98 , 2.55] |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **1.47 [1.02 , 2.14]** |
| Total events: | 65 | | 44 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)
Test for subgroup differences: Not applicable

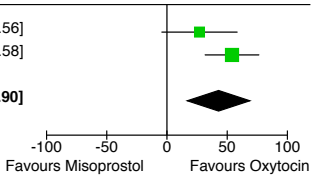



## Analysis 1.8

Comparison 1: Misoprostol versus oxytocin, Outcome 8: Mean additional blood loss

| Study or Subgroup | Misoprostol Mean [mL] | Misoprostol SD [mL] | Misoprostol Total | Oxytocin Mean [mL] | Oxytocin SD [mL] | Oxytocin Total | Weight | Mean Difference IV, Random, 95% CI [mL] |
|---|---|---|---|---|---|---|---|---|
| Blum 2010 | 279 | 251 | 407 | 252 | 205 | 402 | 41.3% | 27.00 [-4.56 , 58.56] |
| Winikoff 2010 | 244 | 186 | 488 | 190 | 174 | 490 | 58.7% | 54.00 [31.42 , 76.58] |
| **Total (95% CI)** | | | **895** | | | **892** | **100.0%** | **42.85 [16.79 , 68.90]** |

Heterogeneity: Tau² = 168.49; Chi² = 1.86, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 3.22 (P = 0.001)
Test for subgroup differences: Not applicable

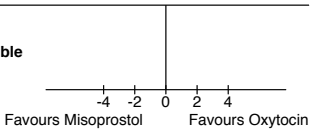



## Analysis 1.9

Comparison 1: Misoprostol versus oxytocin, Outcome 9: Change in haemoglobin

| Study or Subgroup | Misoprostol Mean [g/L] | Misoprostol SD [g/L] | Misoprostol Total | Oxytocin Mean [g/L] | Oxytocin SD [g/L] | Oxytocin Total | Weight | Mean Difference IV, Random, 95% CI [g/L] |
|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **0** | | | **0** | | **Not estimable** |

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

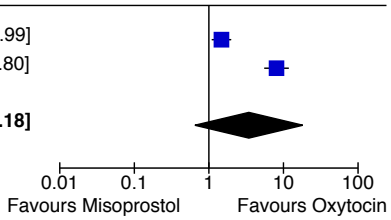



## Analysis 1.10

Comparison 1: Misoprostol versus oxytocin, Outcome 10: Fever

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 88 | 407 | 59 | 402 | 50.2% | 1.47 [1.09 , 1.99] |
| Winikoff 2010 | 217 | 488 | 27 | 490 | 49.8% | 8.07 [5.52 , 11.80] |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **3.43 [0.65 , 18.18]** |
| Total events: | 305 | | 86 | | | |

Heterogeneity: Tau² = 1.42; Chi² = 47.48, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable

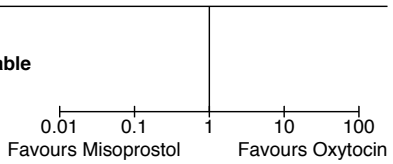



## Analysis 1.11

Comparison 1: Misoprostol versus oxytocin, Outcome 11: Hypothermia

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | 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

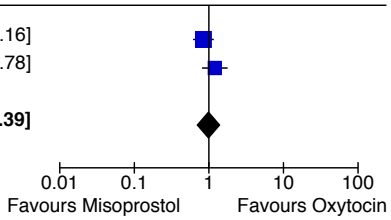



## Analysis 1.12

Comparison 1: Misoprostol versus oxytocin, Outcome 12: Nausea

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 59 | 407 | 69 | 402 | 55.8% | 0.84 [0.61 , 1.16] |
| Winikoff 2010 | 49 | 488 | 41 | 490 | 44.2% | 1.20 [0.81 , 1.78] |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **0.99 [0.70 , 1.39]** |
| Total events: | 108 | | 110 | | | |

Heterogeneity: Tau² = 0.03; Chi² = 1.84, df = 1 (P = 0.18); I² = 46%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable

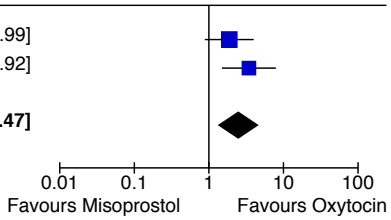



## Analysis 1.13

Comparison 1: Misoprostol versus oxytocin, Outcome 13: Vomiting

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 19 | 407 | 10 | 402 | 54.4% | 1.88 [0.88 , 3.99] |
| Winikoff 2010 | 24 | 488 | 7 | 490 | 45.6% | 3.44 [1.50 , 7.92] |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **2.47 [1.37 , 4.47]** |
| Total events: | 43 | | 17 | | | |

Heterogeneity: Tau² = 0.02; Chi² = 1.12, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 3.00 (P = 0.003)
Test for subgroup differences: Not applicable

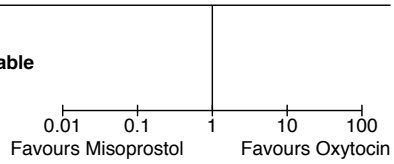



## Analysis 1.14

Comparison 1: Misoprostol versus oxytocin, Outcome 14: Hypertension

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | 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

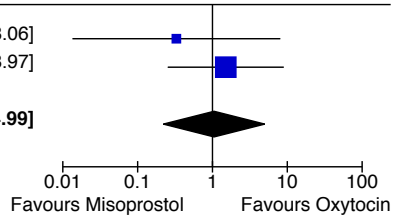



## Analysis 1.15

Comparison 1: Misoprostol versus oxytocin, Outcome 15: Headache

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 (1) | 0 | 407 | 1 | 402 | 23.8% | 0.33 [0.01 , 8.06] |
| Winikoff 2010 (2) | 3 | 488 | 2 | 490 | 76.2% | 1.51 [0.25 , 8.97] |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **1.05 [0.22 , 4.99]** |
| Total events: | 3 | | 3 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable




**Footnotes**

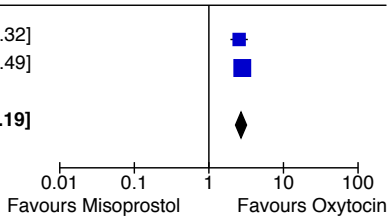
(1) Retrieved data from Mousa HA et al. 2014.
(2) Retrieved data from Mousa HA et al. 2014.

## Analysis 1.16

Comparison 1: Misoprostol versus oxytocin, Outcome 16: Shivering

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 152 | 407 | 59 | 402 | 40.2% | 2.54 [1.95 , 3.32] |
| Winikoff 2010 | 229 | 488 | 82 | 490 | 59.8% | 2.80 [2.25 , 3.49] |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **2.70 [2.28 , 3.19]** |
| Total events: | 381 | | 141 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 11.48 (P < 0.00001)
Test for subgroup differences: Not applicable

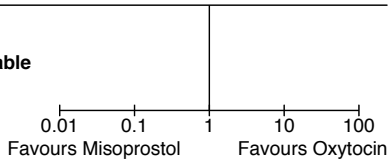



**Analysis 1.17**

Comparison 1: Misoprostol versus oxytocin, Outcome 17: Tachycardia

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | 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

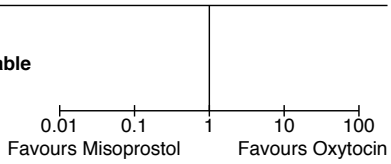



**Analysis 1.18**

Comparison 1: Misoprostol versus oxytocin, Outcome 18: Arrhythmia

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | 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

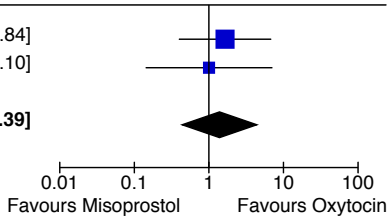



**Analysis 1.19**

Comparison 1: Misoprostol versus oxytocin, Outcome 19: Diarrhoea

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 2010 | 5 | 407 | 3 | 402 | 65.3% | 1.65 [0.40 , 6.84] |
| Winikoff 2010 | 2 | 488 | 2 | 490 | 34.7% | 1.00 [0.14 , 7.10] |
| **Total (95% CI)** | | **895** | | **892** | **100.0%** | **1.39 [0.44 , 4.39]** |
| Total events: | 7 | | 5 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable

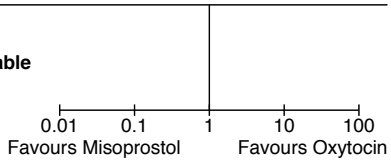



**Analysis 1.20**

Comparison 1: Misoprostol versus oxytocin, Outcome 20: Abdominal pain

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | 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

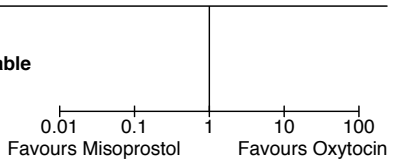


**Analysis 1.21**

Comparison 1: Misoprostol versus oxytocin, Outcome 21: Maternal sense of wellbeing

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

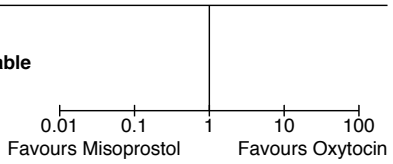



**Analysis 1.22**

Comparison 1: Misoprostol versus oxytocin, Outcome 22: Acceptability of intervention

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

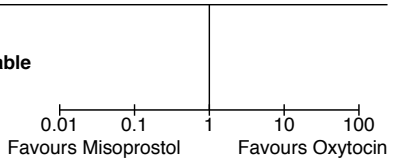



**Analysis 1.23**

Comparison 1: Misoprostol versus oxytocin, Outcome 23: Maternal satisfaction

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

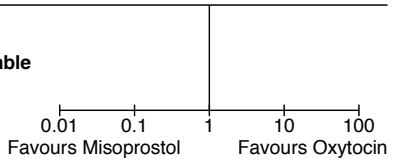



**Analysis 1.24**

Comparison 1: Misoprostol versus oxytocin, Outcome 24: Breastfeeding on discharge

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

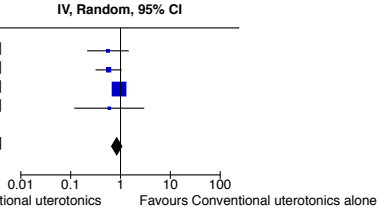



**Analysis 2.1**

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 1: Additional blood loss of more than 500 mL

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Hofmeyr 2004 | 6 | 117 | 11 | 120 | 5.9% | 0.56 [0.21 , 1.46] | |
| Walraven 2004 | 13 | 79 | 23 | 81 | 14.2% | 0.58 [0.32 , 1.06] | |
| Widmer 2010 | 149 | 703 | 162 | 714 | 77.8% | 0.93 [0.77 , 1.14] | |
| Zuberi 2008 | 2 | 27 | 4 | 32 | 2.1% | 0.59 [0.12 , 2.99] | |
| **Total (95% CI)** | | **926** | | **947** | **100.0%** | **0.84 [0.66 , 1.06]** | |
| Total events: | 170 | | 200 | | | | |

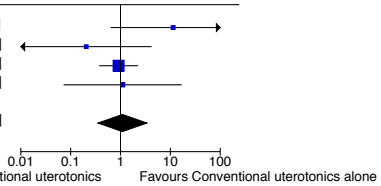
Heterogeneity: Tau² = 0.01; Chi² = 3.26, df = 3 (P = 0.35); I² = 8%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



## Analysis 2.2

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 2: Composite of maternal death or severe morbidity

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Hofmeyr 2004 | 5 | 117 | 0 | 121 | 13.3% | 11.37 [0.64 , 203.41] |
| Walraven 2004 | 0 | 79 | 2 | 81 | 12.2% | 0.20 [0.01 , 4.20] |
| Widmer 2010 | 9 | 705 | 10 | 717 | 59.9% | 0.92 [0.37 , 2.24] |
| Zuberi 2008 | 1 | 29 | 1 | 32 | 14.6% | 1.10 [0.07 , 16.85] |
| **Total (95% CI)** | | **930** | | **951** | **100.0%** | **1.09 [0.35 , 3.39]** |
| Total events: | 15 | | 13 | | | |

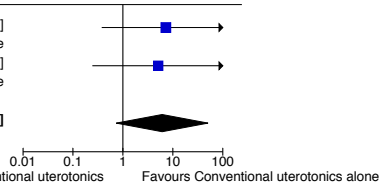



Heterogeneity: Tau² = 0.35; Chi² = 3.83, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.16 (P = 0.88)
Test for subgroup differences: Not applicable

## Analysis 2.3

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 3: Death

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Hofmeyr 2004 | 3 | 117 | 0 | 121 | 51.4% | 7.24 [0.38 , 138.60] |
| Walraven 2004 (1) | 0 | 79 | 0 | 81 | | Not estimable |
| Widmer 2010 | 2 | 705 | 0 | 717 | 48.6% | 5.08 [0.24 , 105.73] |
| Zuberi 2008 | 0 | 29 | 0 | 32 | | Not estimable |
| **Total (95% CI)** | | **930** | | **951** | **100.0%** | **6.10 [0.73 , 50.59]** |
| Total events: | 5 | | 0 | | | |



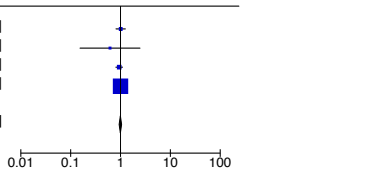

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)
Test for subgroup differences: Not applicable

**Footnotes**
(1) Retrieved data from Mousa HA et al. 2014.

## Analysis 2.4

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 4: Additional uterotonics

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Hofmeyr 2004 | 63 | 111 | 63 | 112 | 6.1% | 1.01 [0.80 , 1.27] |
| Walraven 2004 | 3 | 79 | 5 | 81 | 0.2% | 0.62 [0.15 , 2.49] |
| Widmer 2010 | 188 | 705 | 203 | 717 | 11.4% | 0.94 [0.80 , 1.12] |
| Zuberi 2008 | 29 | 29 | 32 | 32 | 82.3% | 1.00 [0.94 , 1.06] |
| **Total (95% CI)** | | **924** | | **942** | **100.0%** | **0.99 [0.94 , 1.05]** |
| Total events: | 283 | | 303 | | | |

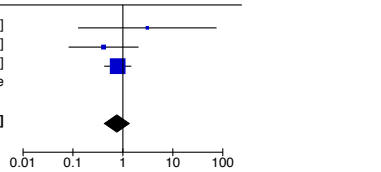



Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 3 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable

## Analysis 2.5

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 5: Additional blood loss of more than 1000 mL

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Hofmeyr 2004 | 1 | 117 | 0 | 120 | 3.2% | 3.08 [0.13 , 74.76] |
| Walraven 2004 | 2 | 79 | 5 | 81 | 12.6% | 0.41 [0.08 , 2.05] |
| Widmer 2010 | 17 | 703 | 22 | 714 | 84.1% | 0.78 [0.42 , 1.47] |
| Zuberi 2008 (1) | 0 | 27 | 0 | 32 | | Not estimable |
| **Total (95% CI)** | | **926** | | **947** | **100.0%** | **0.76 [0.43 , 1.34]** |
| Total events: | 20 | | 27 | | | |




Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable

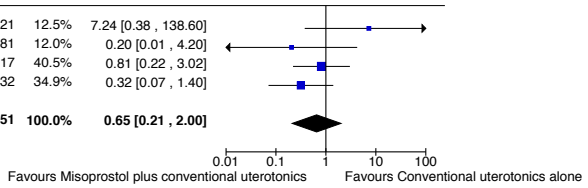
**Footnotes**
(1) Retrieved data from Mousa HA et al. 2014.

## Analysis 2.6

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 6: Additional surgical procedures

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Hofmeyr 2004 | 3 | 117 | 0 | 121 | 12.5% | 7.24 [0.38 , 138.60] |
| Walraven 2004 | 0 | 79 | 2 | 81 | 12.0% | 0.20 [0.01 , 4.20] |
| Widmer 2010 (1) | 4 | 705 | 5 | 717 | 40.5% | 0.81 [0.22 , 3.02] |
| Zuberi 2008 | 2 | 29 | 7 | 32 | 34.9% | 0.32 [0.07 , 1.40] |
| **Total (95% CI)** | | **930** | | **951** | **100.0%** | **0.65 [0.21 , 2.00]** |
| Total events: | 9 | | 14 | | | |

Heterogeneity: Tau² = 0.37; Chi² = 4.13, df = 3 (P = 0.25); I² = 27%
Test for overall effect: Z = 0.75 (P = 0.45)
Test for subgroup differences: Not applicable



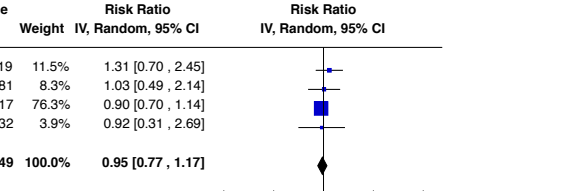

**Footnotes**
(1) Retrived data from Mousa HA et al. 2014.

## Analysis 2.7

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 7: Blood transfusion or other blood products

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Hofmeyr 2004 | 19 | 115 | 15 | 119 | 11.5% | 1.31 [0.70 , 2.45] |
| Walraven 2004 | 12 | 79 | 12 | 81 | 8.3% | 1.03 [0.49 , 2.14] |
| Widmer 2010 | 103 | 705 | 117 | 717 | 76.3% | 0.90 [0.70 , 1.14] |
| Zuberi 2008 | 5 | 29 | 6 | 32 | 3.9% | 0.92 [0.31 , 2.69] |
| **Total (95% CI)** | | **928** | | **949** | **100.0%** | **0.95 [0.77 , 1.17]** |
| Total events: | 139 | | 150 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable

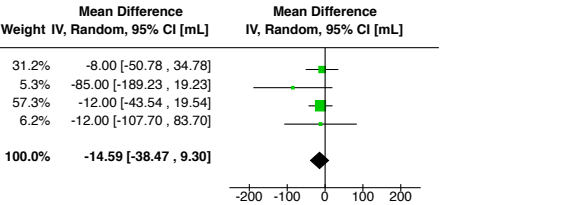



## Analysis 2.8

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 8: Mean additional blood loss

| Study or Subgroup | Misoprostol plus conventional uterotonics Mean [mL] | SD [mL] | Total | Conventional uterotonics alone Mean [mL] | SD [mL] | Total | Weight | Mean Difference IV, Random, 95% CI [mL] |
|---|---|---|---|---|---|---|---|---|
| Hofmeyr 2004 | 168 | 163 | 117 | 176 | 173 | 120 | 31.2% | -8.00 [-50.78 , 34.78] |
| Walraven 2004 | 325 | 264 | 79 | 410 | 397 | 81 | 5.3% | -85.00 [-189.23 , 19.23] |
| Widmer 2010 | 320 | 270 | 703 | 332 | 333 | 714 | 57.3% | -12.00 [-43.54 , 19.54] |
| Zuberi 2008 | 175 | 168 | 27 | 187 | 207 | 32 | 6.2% | -12.00 [-107.70 , 83.70] |
| **Total (95% CI)** | | | **926** | | | **947** | **100.0%** | **-14.59 [-38.47 , 9.30]** |

Heterogeneity: Tau² = 0.00; Chi² = 1.87, df = 3 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)
Test for subgroup differences: Not applicable

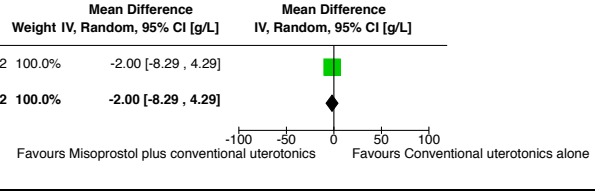



## Analysis 2.9

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 9: Change in haemoglobin

| Study or Subgroup | Misoprostol plus conventional uterotonics Mean [g/L] | SD [g/L] | Total | Conventional uterotonics alone Mean [g/L] | SD [g/L] | Total | Weight | Mean Difference IV, Random, 95% CI [g/L] |
|---|---|---|---|---|---|---|---|---|
| Zuberi 2008 | 20 | 11 | 29 | 22 | 14 | 32 | 100.0% | -2.00 [-8.29 , 4.29] |
| **Total (95% CI)** | | | **29** | | | **32** | **100.0%** | **-2.00 [-8.29 , 4.29]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.53)
Test for subgroup differences: Not applicable

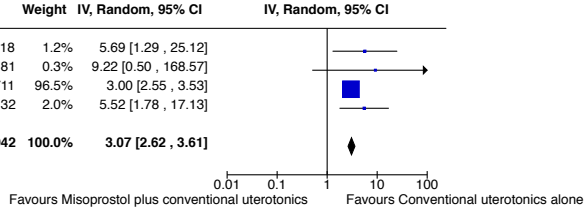



## Analysis 2.10

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 10: Fever

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Hofmeyr 2004 (1) | 11 | 114 | 2 | 118 | 1.2% | 5.69 [1.29 , 25.12] |
| Walraven 2004 (2) | 4 | 79 | 0 | 81 | 0.3% | 9.22 [0.50 , 168.57] |
| Widmer 2010 | 406 | 702 | 137 | 711 | 96.5% | 3.00 [2.55 , 3.53] |
| Zuberi 2008 (3) | 15 | 29 | 3 | 32 | 2.0% | 5.52 [1.78 , 17.13] |
| **Total (95% CI)** | | **924** | | **942** | **100.0%** | **3.07 [2.62 , 3.61]** |
| Total events: | 436 | | 142 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 2.32, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 13.72 (P < 0.00001)
Test for subgroup differences: Not applicable



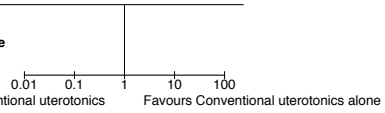

**Footnotes**
(1) The threshold here was 38.5
(2) Retrieved data from Mousa HA et al. 2014.
(3) The threshold here was 37.5

## Analysis 2.11

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 11: Hypothermia

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | 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

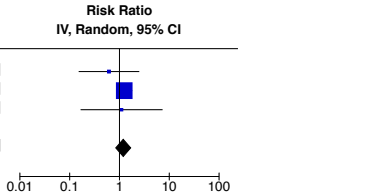



## Analysis 2.12

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 12: Nausea

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Walraven 2004 | 3 | 79 | 5 | 81 | 6.1% | 0.62 [0.15 , 2.49] |
| Widmer 2010 | 60 | 704 | 49 | 717 | 90.6% | 1.25 [0.87 , 1.79] |
| Zuberi 2008 | 2 | 29 | 2 | 32 | 3.3% | 1.10 [0.17 , 7.34] |
| **Total (95% CI)** | | **812** | | **830** | **100.0%** | **1.19 [0.84 , 1.68]** |
| Total events: | 65 | | 56 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable

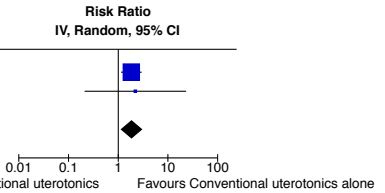



## Analysis 2.13

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 13: Vomiting

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Widmer 2010 | 45 | 704 | 25 | 717 | 96.0% | 1.83 [1.14 , 2.96] |
| Zuberi 2008 | 2 | 29 | 1 | 32 | 4.0% | 2.21 [0.21 , 23.08] |
| **Total (95% CI)** | | **733** | | **749** | **100.0%** | **1.85 [1.16 , 2.95]** |
| Total events: | 47 | | 26 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)
Test for subgroup differences: Not applicable

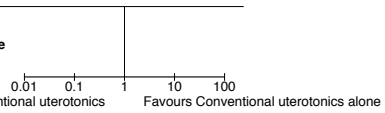



## Analysis 2.14

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 14: Hypertension

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | 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

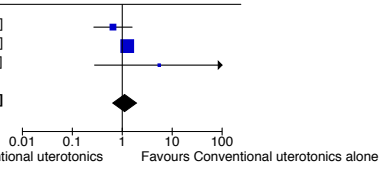



## Analysis 2.15

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 15: Headache

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Walraven 2004 | 7 | 79 | 11 | 81 | 25.7% | 0.65 [0.27 , 1.60] |
| Widmer 2010 (1) | 125 | 704 | 101 | 717 | 71.1% | 1.26 [0.99 , 1.60] |
| Zuberi 2008 | 2 | 29 | 0 | 32 | 3.2% | 5.50 [0.27 , 110.01] |
| **Total (95% CI)** | | **812** | | **830** | **100.0%** | **1.12 [0.65 , 1.93]** |
| Total events: | 134 | | 112 | | | |

Heterogeneity: Tau² = 0.09; Chi² = 2.92, df = 2 (P = 0.23); I² = 31%
Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Not applicable



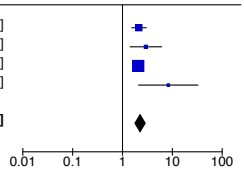

**Footnotes**
(1) Retrieved data from Mousa HA et al. 2014.

## Analysis 2.16

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 16: Shivering

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Hofmeyr 2004 | 63 | 116 | 30 | 118 | 27.8% | 2.14 [1.50 , 3.04] |
| Walraven 2004 | 23 | 79 | 8 | 81 | 9.1% | 2.95 [1.40 , 6.19] |
| Widmer 2010 | 514 | 704 | 252 | 717 | 60.2% | 2.08 [1.86 , 2.32] |
| Zuberi 2008 | 15 | 29 | 2 | 32 | 2.9% | 8.28 [2.07 , 33.13] |
| **Total (95% CI)** | | **928** | | **948** | **100.0%** | **2.25 [1.77 , 2.86]** |
| Total events: | 615 | | 292 | | | |

Heterogeneity: Tau² = 0.02; Chi² = 4.59, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 6.62 (P < 0.00001)
Test for subgroup differences: Not applicable




## Analysis 2.17

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 17: Tachycardia

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **Total (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |

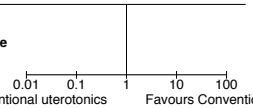
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable


## Analysis 2.18

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 18: Arrhythmia

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | 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

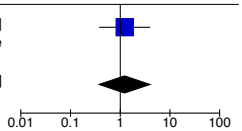



## Analysis 2.19

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 19: Diarrhoea

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Widmer 2010 | 6 | 704 | 5 | 717 | 100.0% | 1.22 [0.37 , 3.99] |
| Zuberi 2008 | 0 | 29 | 0 | 32 | | Not estimable |
| **Total (95% CI)** | | **733** | | **749** | **100.0%** | **1.22 [0.37 , 3.99]** |
| Total events: | 6 | | 5 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable

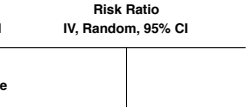



## Analysis 2.20

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 20: Abdominal pain

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | 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

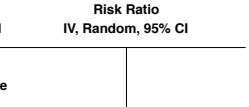



## Analysis 2.21

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 21: Maternal sense of wellbeing

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | 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

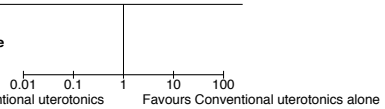


## Analysis 2.22

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 22: Acceptability of intervention

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | 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

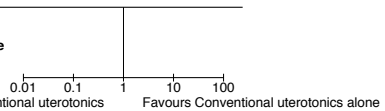



## Analysis 2.23

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 23: Maternal satisfaction

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | 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

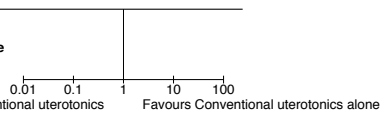



## Analysis 2.24

Comparison 2: Misoprostol plus conventional uterotonics versus conventional uterotonics alone, Outcome 24: Breastfeeding on discharge

| Study or Subgroup | Misoprostol plus conventional uterotonics Events | Total | Conventional uterotonics alone Events | 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

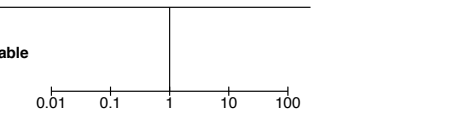



## Analysis 3.1

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 1: Additional blood loss of more than 500 mL

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | 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

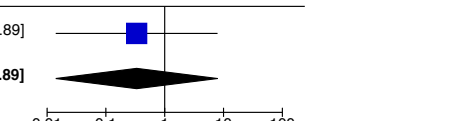



## Analysis 3.2

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 2: Composite of maternal death or severe morbidity

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Lokugamage 2001 | 0 | 32 | 1 | 32 | 100.0% | 0.33 [0.01 , 7.89] |
| **Total (95% CI)** | | **32** | | **32** | **100.0%** | **0.33 [0.01 , 7.89]** |
| Total events: | 0 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

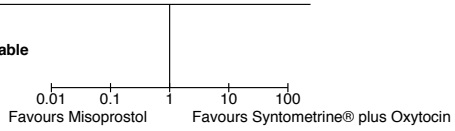



## Analysis 3.3

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 3: Death

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | 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

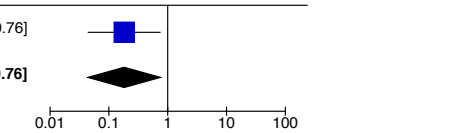



## Analysis 3.4

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 4: Additional uterotonics

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Lokugamage 2001 | 2 | 32 | 11 | 32 | 100.0% | 0.18 [0.04 , 0.76] |
| **Total (95% CI)** | | **32** | | **32** | **100.0%** | **0.18 [0.04 , 0.76]** |
| Total events: | 2 | | 11 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)
Test for subgroup differences: Not applicable

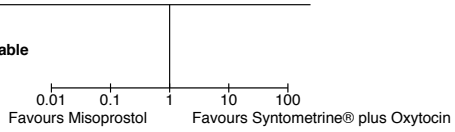



## Analysis 3.5

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 5: Additional blood loss of more than 1000 mL

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | 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

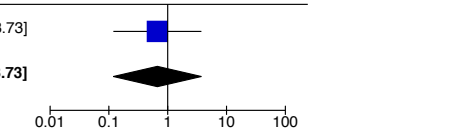



## Analysis 3.6

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 6: Additional surgical procedures

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Lokugamage 2001 | 2 | 32 | 3 | 32 | 100.0% | 0.67 [0.12 , 3.73] |
| **Total (95% CI)** | | **32** | | **32** | **100.0%** | **0.67 [0.12 , 3.73]** |
| Total events: | 2 | | 3 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable

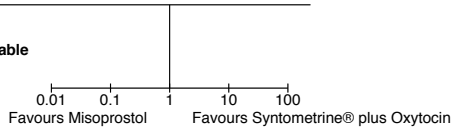



## Analysis 3.7

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 7: Blood transfusion or other blood products

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | 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

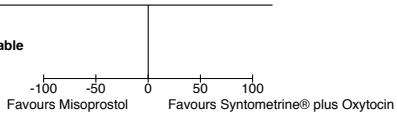



## Analysis 3.8

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 8: Mean additional blood loss

| Study or Subgroup | Misoprostol Mean [mL] | Misoprostol SD [mL] | Misoprostol Total | Syntometrine® plus Oxytocin Mean [mL] | Syntometrine® plus Oxytocin SD [mL] | Syntometrine® plus Oxytocin Total | Weight | Mean Difference IV, Random, 95% CI [mL] | Mean Difference IV, Random, 95% CI [mL] |
|---|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **0** | | | **0** | | **Not estimable** | |

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

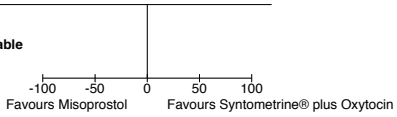



## Analysis 3.9

### Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 9: Change in haemoglobin

| Study or Subgroup | Misoprostol Mean [g/L] | Misoprostol SD [g/L] | Misoprostol Total | Syntometrine® plus Oxytocin Mean [g/L] | Syntometrine® plus Oxytocin SD [g/L] | Syntometrine® plus Oxytocin Total | Weight | Mean Difference IV, Random, 95% CI [g/L] | Mean Difference IV, Random, 95% CI [g/L] |
|---|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **0** | | | **0** | | **Not estimable** | |

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

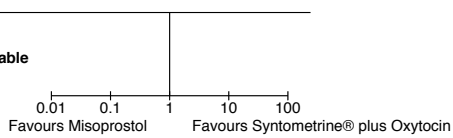



## Analysis 3.10

### Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 10: Fever

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Syntometrine® plus Oxytocin Events | Syntometrine® plus Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

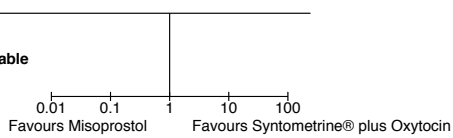



## Analysis 3.11

### Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 11: Hypothermia

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Syntometrine® plus Oxytocin Events | Syntometrine® plus Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

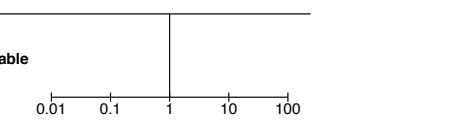



## Analysis 3.12

### Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 12: Nausea

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Syntometrine® plus Oxytocin Events | Syntometrine® plus Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

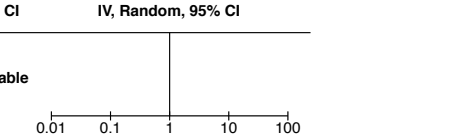



## Analysis 3.13

### Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 13: Vomiting

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Syntometrine® plus Oxytocin Events | Syntometrine® plus Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

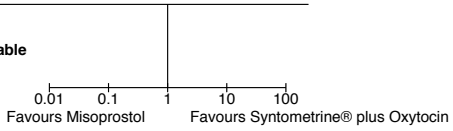



## Analysis 3.14

### Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 14: Hypertension

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Syntometrine® plus Oxytocin Events | Syntometrine® plus Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

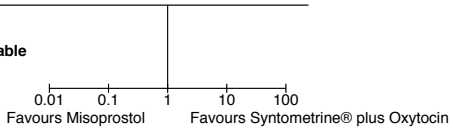



## Analysis 3.15

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 15: Headache

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Syntometrine® plus Oxytocin Events | Syntometrine® plus Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

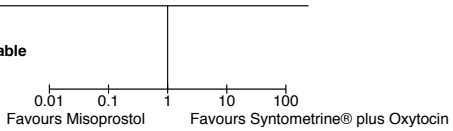



## Analysis 3.16

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 16: Shivering

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Syntometrine® plus Oxytocin Events | Syntometrine® plus Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

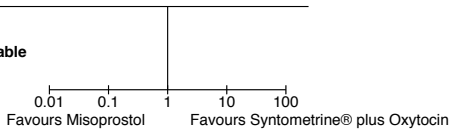



## Analysis 3.17

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 17: Tachycardia

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Syntometrine® plus Oxytocin Events | Syntometrine® plus Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

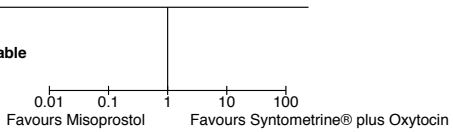



## Analysis 3.18

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 18: Arrhythmia

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Syntometrine® plus Oxytocin Events | Syntometrine® plus Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

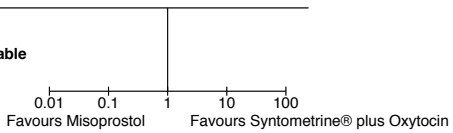



## Analysis 3.19

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 19: Diarrhoea

| Study or Subgroup | Misoprostol Events | Misoprostol Total | Syntometrine® plus Oxytocin Events | Syntometrine® plus Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

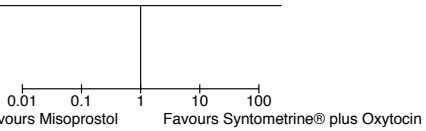



## Analysis 3.20

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 20: Abdominal pain

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | 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

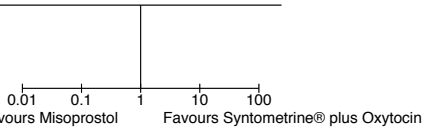



**Analysis 3.21**

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 21: Maternal sense of wellbeing

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | 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

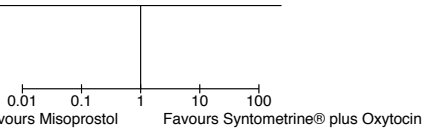



**Analysis 3.22**

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 22: Acceptability of intervention

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | 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

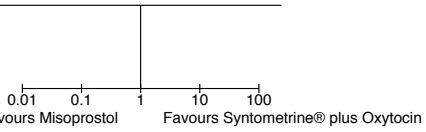



**Analysis 3.23**

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 23: Maternal satisfaction

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | 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

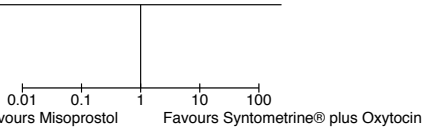



**Analysis 3.24**

Comparison 3: Misoprostol versus Syntometrine® plus oxytocin, Outcome 24: Breastfeeding on discharge

| Study or Subgroup | Misoprostol Events | Total | Syntometrine® plus Oxytocin Events | 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

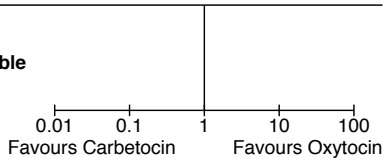



**Analysis 4.1**

Comparison 4: Carbetocin versus oxytocin, Outcome 1: Additional blood loss of more than 500 mL

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

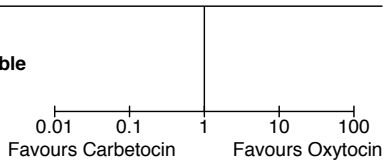



**Analysis 4.2**

Comparison 4: Carbetocin versus oxytocin, Outcome 2: Composite of maternal death or severe morbidity

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

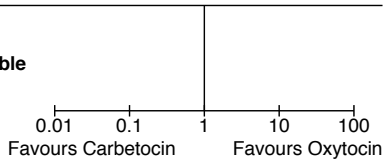



**Analysis 4.3**

Comparison 4: Carbetocin versus oxytocin, Outcome 3: Death

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

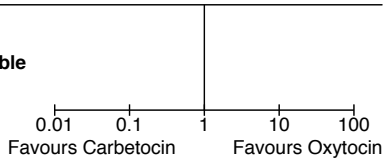



**Analysis 4.4**

Comparison 4: Carbetocin versus oxytocin, Outcome 4: Additional uterotonics

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

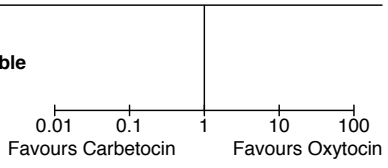



**Analysis 4.5**

Comparison 4: Carbetocin versus oxytocin, Outcome 5: Additional blood loss of more than 1000 mL

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

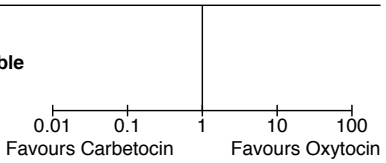



**Analysis 4.6**

Comparison 4: Carbetocin versus oxytocin, Outcome 6: Additional surgical procedures

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | 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

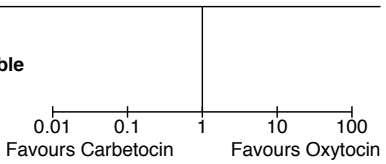



**Analysis 4.7**

Comparison 4: Carbetocin versus oxytocin, Outcome 7: Blood transfusion or other blood products

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | 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

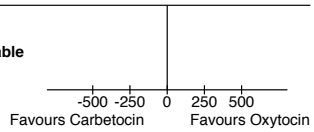



**Analysis 4.8**

Comparison 4: Carbetocin versus oxytocin, Outcome 8: Mean additional blood loss

| Study or Subgroup | Carbetocin Mean [mL] | Carbetocin SD [mL] | Carbetocin Total | Oxytocin Mean [mL] | Oxytocin SD [mL] | Oxytocin Total | Weight | Mean Difference IV, Random, 95% CI [mL] |
|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **0** | | | **0** | | **Not estimable** |

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

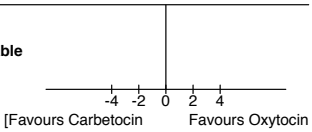



**Analysis 4.9**

Comparison 4: Carbetocin versus oxytocin, Outcome 9: Change in haemoglobin

| Study or Subgroup | Carbetocin Mean [g/L] | Carbetocin SD [g/L] | Carbetocin Total | Oxytocin Mean [g/L] | Oxytocin SD [g/L] | Oxytocin Total | Weight | Mean Difference IV, Random, 95% CI [g/L] |
|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **0** | | | **0** | | **Not estimable** |

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

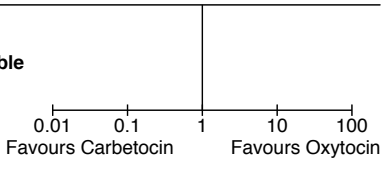



**Analysis 4.10**

Comparison 4: Carbetocin versus oxytocin, Outcome 10: Fever

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | 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

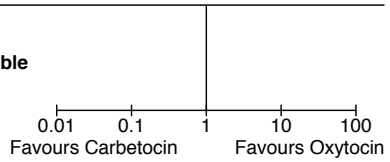



**Analysis 4.11**

Comparison 4: Carbetocin versus oxytocin, Outcome 11: Hypothermia

| Study or Subgroup | Carbetocin Events | Total | Oxytocin Events | Total | Weight | Risk Ratio IV, Random, 95% CI | 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

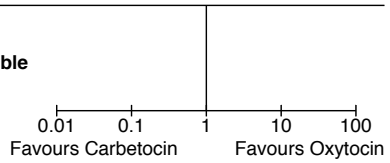



**Analysis 4.12**

Comparison 4: Carbetocin versus oxytocin, Outcome 12: Nausea

| Study or Subgroup | Carbetocin Events | Total | Oxytocin Events | Total | Weight | Risk Ratio IV, Random, 95% CI | 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

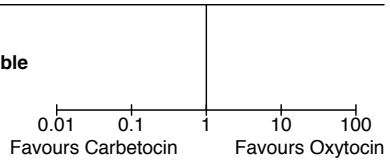



**Analysis 4.13**

Comparison 4: Carbetocin versus oxytocin, Outcome 13: Vomiting

| Study or Subgroup | Carbetocin Events | Total | Oxytocin Events | Total | Weight | Risk Ratio IV, Random, 95% CI | 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

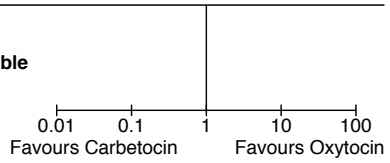



**Analysis 4.14**

Comparison 4: Carbetocin versus oxytocin, Outcome 14: Hypertension

| Study or Subgroup | Carbetocin Events | Total | Oxytocin Events | Total | Weight | Risk Ratio IV, Random, 95% CI | 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

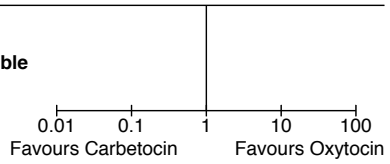



**Analysis 4.15**

Comparison 4: Carbetocin versus oxytocin, Outcome 15: Headache

| Study or Subgroup | Carbetocin Events | Total | Oxytocin Events | Total | Weight | Risk Ratio IV, Random, 95% CI | 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

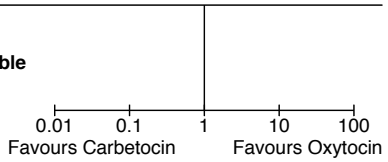



**Analysis 4.16**

Comparison 4: Carbetocin versus oxytocin, Outcome 16: Shivering

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

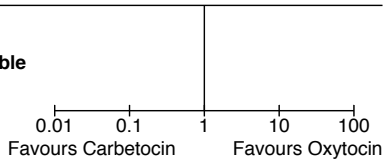



**Analysis 4.17**

Comparison 4: Carbetocin versus oxytocin, Outcome 17: Tachycardia

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

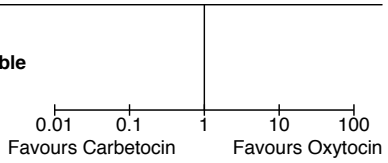



**Analysis 4.18**

Comparison 4: Carbetocin versus oxytocin, Outcome 18: Arrhythmia

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

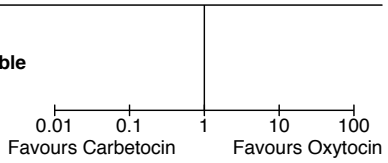



**Analysis 4.19**

Comparison 4: Carbetocin versus oxytocin, Outcome 19: Diarrhoea

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

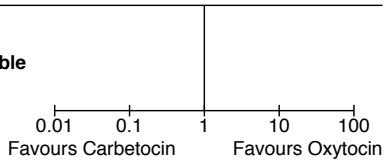



**Analysis 4.20**

Comparison 4: Carbetocin versus oxytocin, Outcome 20: Abdominal pain

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

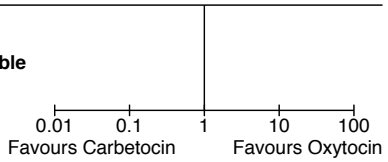



**Analysis 4.21**

Comparison 4: Carbetocin versus oxytocin, Outcome 21: Maternal sense of wellbeing

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

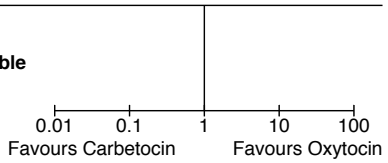



**Analysis 4.22**

Comparison 4: Carbetocin versus oxytocin, Outcome 22: Acceptability of intervention

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

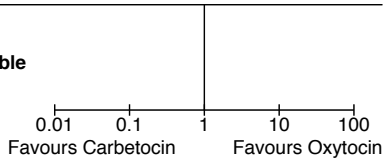



**Analysis 4.23**

Comparison 4: Carbetocin versus oxytocin, Outcome 23: Maternal satisfaction

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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

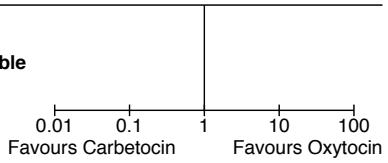



**Analysis 4.24**

Comparison 4: Carbetocin versus oxytocin, Outcome 24: Breastfeeding on discharge

| Study or Subgroup | Carbetocin Events | Carbetocin Total | Oxytocin Events | Oxytocin Total | Weight | Risk Ratio IV, Random, 95% CI | 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



# Chapter 6 - Volume of postpartum blood loss and the use of treatment regimen of uterotonic drug: a secondary analysis of Champion data

### *Preamble to Chapter 6*

In Chapter 5 I outlined the results of a Cochrane review for the best uterotonic medication to use for the treatment of PPH. In Chapter 6 I continue to investigate the best strategy to treat PPH. I carried out a cohort study to establish what blood volume lost prompts treatment for PPH.

### *Contributions*

Dr. Parry-Smith – conceived the idea, made substantial contribution to the design, acquisition, analysis and interpretation of the data and wrote the manuscript.

Associate Professor Tobias- contributed to the analysis and interpretation of data.

Dr. Gallos - contributed to the design and interpretation of data.

Prof. Coomarasamy- made substantial contribution to the design, proofread the manuscript and provided substantial edits.

## Abstract

### *Background*

There appears to be variations in the blood loss thresholds at which care providers initiate treatment. Medical or midwifery care provision at delivery might impact on treatment of blood loss. A failure to initiate treatment and recognise blood loss appropriately can lead to substandard care. A secondary analysis of trial data was undertaken to investigate the blood loss threshold that prompts administration of a treatment uterotonic drug within the first hour following delivery.

### *Methods*

The participants are the UK sub-population the WHO CHAMPION trial (ACTRN12614000870651). As soon as possible following delivery a plastic drape was placed under the woman's buttocks and blood loss was measured. In order to measure blood loss accurately a scale was used to weigh the blood collected. Treatment uterotonic use as a dichotomous outcome variable stratified by blood loss was fitted in a regression model. A stratified analysis by practitioners conducting delivery (instrumental vs. normal delivery) was undertaken.

### *Results*

The total number of participants eligible for inclusion in the database for analysis was 1,972 women. At a blood loss threshold of 500-599mL for women with normal vaginal delivery and instrumental delivery, 19.2% (95% CI; [15.9-22.6]) and 36.8% (95% CI; [32.4-41.2]) respectively received treatment uterotonic drugs. At a blood loss threshold of 1000-1099mL for women with normal vaginal delivery and instrumental delivery, 64.5% (95% CI; [54.0-75.0]) and 67.4% (95% CI; [59.3-75.3]) respectively received treatment uterotonic drugs. Once the threshold of 700mL of

blood loss is crossed, there is no significant difference in the use of uterotonic treatment drugs regardless of the mode of delivery.

### *Conclusion*

The study demonstrated that more than 60% of patients who had a PPH did not receive treatment uterotonic medication at a loss of 500-599mL, while at 1000-1099mL a third of women were not treated. Significantly more women received treatment for PPH following an instrumental assisted birth conducted by an obstetrician compared to those women having normal birth 36.8% vs 19.2%. The difference observed in treatment of PPH by mode of delivery is blunted as haemorrhage volume is increased and abolished by 700mL. Further work to establish how best to recognise and trigger treatment is required and in particular to explore the differences in PPH treatment observed in normal vaginal and instrumental births.

## Background

The CHAMPION trial was a phase three, randomized, double-blind, active controlled, multinational, multicentre, non-inferiority trial using room temperature stable (RTS) carbetocin for the prevention of postpartum haemorrhage (PPH) during the third stage of labour in women delivering vaginally (ACTRN12614000870651). The trial aim was to evaluate the effectiveness of carbetocin (RTS) 100 µg administered intramuscularly (IM), compared to oxytocin 10 IU IM. The aims of the trial were twofold: to evaluate the non-inferiority of the two uterotonic medications after vaginal delivery with blood loss of 500mL or more or the use of additional uterotonics as the composite endpoint at one hour and two hours after delivery. The second aim was to evaluate non-inferiority of the two medications in the prevention of severe PPH ≥1000 mL blood loss at one hour and up to two hours for those women continuing to bleed after the first hour. The decision to administer and treat excessive bleeding with further uterotonic medication was based on the carers' individual assessment and usual clinical practice.

Birmingham Women's Hospital was the only UK site of the 22 centers across 10 countries that recruited into the CHAMPION trial. The trial was conducted according to the published protocol by Widmer and colleagues and the primary study was published in the New England Journal of Medicine in August 2018 (33,70). I coordinated the day-to-day trial activity that included: recruitment, general trial management, serious and adverse event reporting, data collection, and liaison with the trial contract research organisation monitoring team. I also led the team processing the data for the local Birmingham trial site as a co-investigator under the guidance and mentorship of Professor Coomarasamy, the Birmingham site Principal Investigator, during the first year and a half of my Doctorate of Medicine studies.

Each site owns their locally collected trial data. The trial study team has given permission for the use of local primary data to conduct analysis and investigate secondary questions, which are not part of the primary aims and objectives of the trial.

It is recognised that effective management of PPH rests on early identification and treatment (29). PPH recognition is, however, challenging and blood loss can be underestimated by as much as 49% of the total volume loss (30).

The decision to treat excessive blood loss following delivery is a dynamic process and the practitioner uses a range of information including clinical assessment, blood loss estimation and speed of blood flow (31). The use of a drape placed under the patient following delivery is a recognised technique to quantify blood loss accurately, but seems not to reduce the rate of PPH (32). PPH diagnosis and treatment in a timely fashion has been the subject of much research and recently bundles of care have been suggested, because deaths continue to occur even in well trained and resourced settings (34).

Postpartum vigilance to detect uterine atony every 15 minutes for 2 hours is recommended by the WHO. In the CHAMPION trial, there was an objective assessment of blood loss at one hour and two hours by weighing drapes placed under the buttocks. If a participant at one-hour or two-hour postpartum thresholds has a blood loss measured in excess of 500mL but has not received further uterotonic medication, this may demonstrates a failure of recognition and treatment of PPH.

### Hypothesis

PPH treatment with a uterotonic drug is not provided to many women even after they have lost over 500mL of blood (current definition of PPH). The mode of delivery and practitioner present impacts on treatment of PPH.

### Main objectives

The main objectives of this study were:

- To investigate the blood loss threshold that prompts administration of a treatment uterotonic drug within the first hour following delivery; and
- To investigate if instrumental or normal vaginal delivery affects the blood loss threshold for treatment of PPH.

## Methods

### Data collection

The participants were the CHAMPION trial patients at the UK site who received the Investigational Medicinal Product (IMP) in accordance with the trial protocol, with the exception of those who received the IMP >3 minutes after birth of the baby were included (70). Patients were excluded if no data were collected on the time of birth, the estimated blood loss, or caesarean delivery. The database for analysis was derived from the cleaned and verified electronic case report forms extracted into Microsoft Excel.

The time of birth was documented on the trial case report form (CRF); the data source was the electronic clinical record system- K2 Guardian$^{TM}$ (K2 Medical Systems Ltd. Plymouth UK). The K2 system provides full electronic capture of patient information in real time during childbirth at the bedside via a touchscreen.

The K2 system uses a sequential series of questions to accurately document clinical data. Only registered users, including midwives or medical staff with appropriate K2 training can enter information in the K2 system and these data are verified by use of passwords or biometrics and checked with internal controls for consistency.

Blood loss was recorded and measured as set out in the trial protocol and accompanying manual of operations. The IMP was administered as soon as possible after the birth of the baby, and once the cord was clamped 1-3 minutes after delivery a plastic drape was placed under the woman's buttocks and blood loss measured for one or two hours after delivery if bleeding continued beyond an hour. In order to measure blood loss accurately scales with a digital record/sticker of the weight was attached to the paper CRF. All blood, clots, and blood soaked gauze swabs were placed in the drape for measurement. The weight of the drape and blood loss was recorded as one measurement and conversion to blood volume in mL and average empty drape weight taken into account for the final blood volumes reported. The use of treatment uterotonic medication, termed further uterotonic was recorded up to the time of discharge.

## Data analysis

I conducted descriptive statistics and data analysis with assistance from Associate Professor Aurelio Tobias. The use of additional uterotonics as a dichotomous outcome variable is the main outcome and I stratified this by blood loss categories. A margins effect at the mean (MEM) regression model with 95% confidence intervals was fitted to each blood loss increment. A stratified analysis by practitioners conducting delivery (instrumental vs. normal delivery) was undertaken. All statistical analyses were performed using Stata (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

## Results

The total number of participants eligible for inclusion in the database for analysis was 1,972 women. The median blood loss was 353mL (50-3040mL). The crude percentage of women who had a PPH of over 500mL was 30.9% (*N*=610). The percentage of women who received a treatment uterotonic drug by blood loss increments of 99mL is given in Table 8.

**Table 8-** Use of treatment uterotonic drug by blood loss increments for operative and normal delivery combined.

| Blood loss increments | Uterotonic treatment drug started | |
|---|---|---|
| | % | *N*=total women with blood loss |
| 0-99mL | 5.1 | 6 |
| 100-199mL | 7.7 | 306 |
| 200-299mL | 9.1 | 464 |
| 300-399mL | 10.9 | 341 |
| 400-499mL | 20.6 | 244 |
| 500-599mL | 30.7 | 128 |
| 600-699mL | 42.0 | 122 |
| 700-799mL | 36.4 | 101 |
| 800-899mL | 54.1 | 70 |
| 900-999mL | 56.7 | 48 |
| 1000-1099mL | 83.4 | 30 |
| 1100-1199mL | 60.0 | 28 |
| 1200-1299mL | 62.5 | 15 |

| | | |
|---|---|---|
| **1300-1399mL** | 81.8 | 15 |
| **1400-1499mL** | 83.3 | 15 |
| **1500mL+** | 100.0 | 39 |

At a blood loss threshold of 500-599mL and 1000-1099mlL, 30.7% (95%CI; [21.7-39.7]) and 83% (95% CI; [66.1-100.0]) of women, respectively, received treatment uterotonic drugs for all types of vaginal delivery (Figure 7)

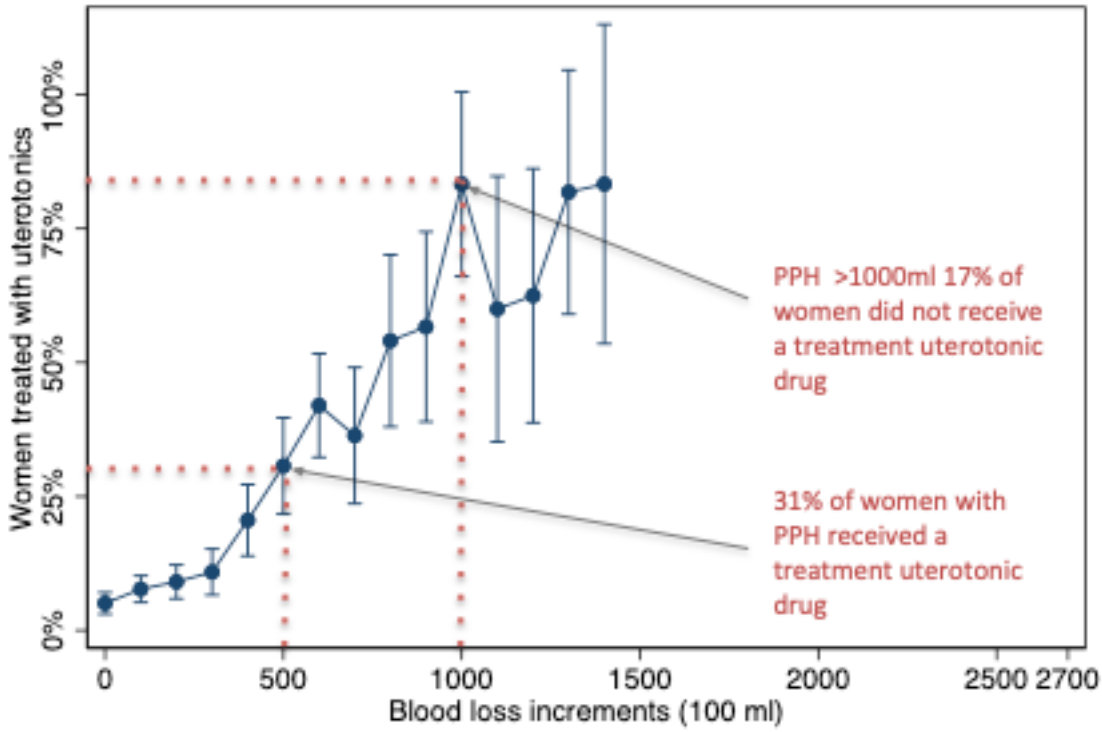



Figure 7- Treatment of PPH all types of vaginal delivery

At a blood loss threshold of 500-599mL for women with normal vaginal delivery and instrumental delivery, 19.2% (95% CI; [15.9-22.6]) and 36.8% (95% CI; [32.4-41.2]) received treatment by uterotonic drugs, respectively (Figure 8).

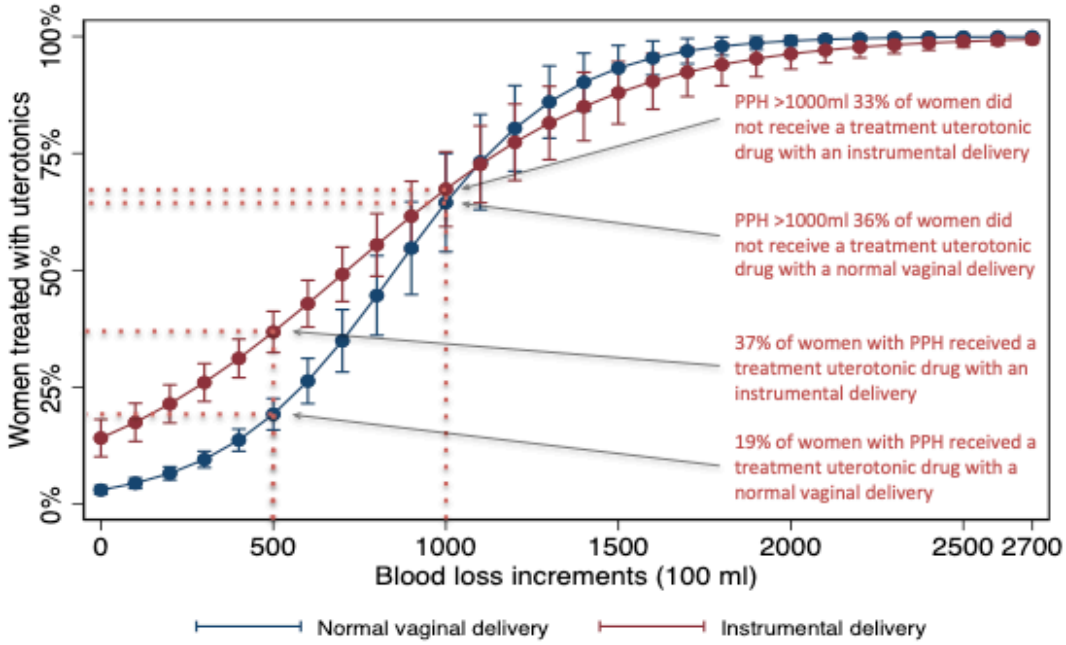



Figure 8 Treatment of PPH by normal vaginal and instrumental deliver.

Figure 8 shows a margins effect at the mean regression model with 95% confidence interval fitted to each blood loss increment of 100mL. The model shows blood loss increments of 100mL at one hour after delivery and what prevalence of patients received a treatment uterotonic drug, stratified by mode of delivery

At a blood loss threshold of 1000-1099mL for women with normal vaginal delivery and instrumental delivery, 64.5% (95% CI; [54.0-75.0]) and 67.4% (95% CI; [59.3-75.3]) received treatment by uterotonic drugs, respectively (Figure 8).

### Maternal and baby demographics

The median maternal age was 30 years (16-45 years), median parity was 1 (0-10) and 4.8% (*N*=94) women previously had a PPH. The median gestation was 39 weeks (27-43 weeks). The median birth weight was 3320g (1800-5119g).

## Discussion

### Summary of findings

This is the first study to my knowledge, to report the prevalence of use of uterotonic treatment drugs by carefully recorded blood volume in a fully monitored clinical trial environment within the UK. Blood loss of 1500mL needs to be reached before women delivering by both instrumental and normal delivery are reliably given treatment uterotonic drugs. The use of a treatment uterotonic drugs is different up to a volume of 700mL of blood loss, with those having an instrumental delivery more likely to receive treatment than those with a normal vaginal delivery. Once the threshold of 700mL of blood loss is crossed, there is no significant difference in the use of uterotonic treatment drugs regardless of the mode of delivery. The 500mL threshold for diagnosis of PPH at an hour following delivery triggers the use of treatment uterotonic drugs in less than half of cases (19.2% for normal delivery, and 36.8% for instrumental delivery).

### Strengths and weaknesses

The primary study benefited from a detailed trial protocol and careful measurement of blood loss combined with a rigorous external monitoring and data integrity checks. The use of treatment uterotonic medication was recorded on the CRF and verified for all cases with the primary source data. The blood loss estimation using under buttock drapes is a consistent and reliable estimation technique for recording blood

loss following delivery. Selection and outcome bias is unlikely as neither the participants nor the practitioners involved in the care of the patients were aware that prevalence of uterotonic regimen use would be investigated nor blood loss estimation used in this context either.

By its nature this type of secondary cohort study derived from a primary randomised control trial is only able to prompt hypothesis generation and associations at best, not least because the initial trial was not designed to answer the question posed. A weakness is that treatment uterotonic drug use is used as a surrogate marker to compare practice with the assumption that the majority of PPH is caused by uterine atony and drug use is a key component of management. However in cases of retained placenta or tissue, trauma, and coagulopathy that might cause PPH the use of a treatment uterotonic drug it is unlikely to be of benefit nor a key component of management.

## Implications for clinical practice

Improvements in the recognition and assessment of PPH leading to its prompt treatment are required. If less than half of those who bleed more than 500mL are receiving treatment regime uterotonic medication this highlights the need for improvement. A system to alert practitioners and start treatment of PPH is required that functions better than the current practice in the unit. The suggestion that accurate measurement of blood using under buttock drapes alone is the key to early recognition and treatment is not supported by the data presented in this study. Exploration of the factors that contribute towards improved but still low levels of treatment uterotonic drug use for instrumental delivery rather than normal vaginal delivery is important to explore. If normal vaginal delivery treatment of PPH was brought in-line with those reported in the instrumental delivery population an

improvement of 18% (19-37%) would be required. This study was not designed to investigate the factors that contribute to the increased treatment of PPH in those women having an instrumental delivery, though presence of more staff at the time of delivery and recognition of increased risk of bleeding following instrumental delivery might be contributing factors among many others.

## Conclusion

The study demonstrated that less than half of patients who had a PPH received treatment uterotonic medication. Further work to establish how best to recognise and trigger treatment is required and in particular to explore the differences in PPH treatment observed in normal vaginal and instrumental births.

## Ethics approval

Local ethical permission from Birmingham University has been granted for the secondary analysis Reference number ERN-17-0486. In addition, the CHAMPION trial ethics approval for the primary study made provision for secondary analysis.

# Chapter 7 - Postpartum haemorrhage and risk of mental health disease: population based longitudinal study using linked primary and secondary care databases

### *Preamble to Chapter 7*

In Chapter 6 I established that less than half of patients who had a PPH of 500mL received treatment uterotonic medication. The thesis so far has addressed strategies of prevention and treatment; the final chapters will investigate the long-term effects of PPH. In Chapter 7 I will report a population based longitudinal study on the risk of mental health disease following a PPH.

### *Contributions*

Dr. Parry-Smith – conceived the idea, made substantial contribution to the design, acquisition, analysis and interpretation of the data and wrote the manuscript.

Dr. Nirantharakumar- contributed to the design, interpretation of data and provided substantial edits to the manuscript.

Dr. Sumilo- contributed to the design, interpretation of data and provided substantial edits to the manuscript.

Dr. Subramanian, Mr Gokhale and Mr Okoth contributed to the acquisition, analysis and interpretation of data.

Prof. Coomarasamy proofread the manuscript and provided substantial edits.

## Abstract

### *Introduction*

Mental health is increasingly recognised as an important factor before, during and after pregnancy. There is, however, a gap in the literature investigating the impact of obstetric complications such as postpartum haemorrhage (PPH) on subsequent mental illness

### *Methods*

We conducted a retrospective open cohort study utilizing linked primary care (The Health Improvement Network (THIN)) and English secondary care (Hospital Episode Statistics (HES)) databases, from 1st January 1997 to 31st January 2018. A total of 42,327 women were included: 14,109 of them were exposed to PPH during the study period and 28,218 unexposed controls were matched for age and date of delivery. Hazard ratios (HRs) for mental illness among women with and without exposure to PPH were estimated after controlling for covariates (age, BMI, smoking status, ethnicity, birth weight, mode of delivery) using multivariate Cox regression models.

### *Results*

Women who had had PPH were at an increased risk of developing postnatal depression (adjusted HR: 1.13, 95%CI: 1.04-1.24, p=0.007) compared to women unexposed to PPH. No increase in risk was observed for other mental illnesses, including depression (adjusted HR: 1.00, 95%CI: 0.96-1.05, p=0.85) severe mental illness (adjusted HR: 0.74, 95%CI: 0.45-1.22, p=0.239) post-traumatic stress disorder (PTSD) (adjusted HR: 1.15, 95%CI: 0.72-1.83, p=0.56) and anxiety (adjusted HR: 0.99, 95%CI: 0.90-1.09, p=0.88).

### *Conclusion*

PPH is associated with a significant increase in the risk of developing postnatal depression. Active monitoring for postnatal depression should form an integral part of the follow-up package in women who suffered a PPH.

## Introduction

For a substantial number of women, factors associated with mental health before, during and after pregnancy have critical impacts on their general wellbeing and relationship with the children. Some of these factors are the biological consequences of the birth itself and others involve social situations surrounding the birth. These factors range from mild in severity to life-threatening emergencies. One of such more severe complications that can occur after birth is postpartum haemorrhage (PPH). PPH is widely defined as blood loss following birth in excess of 500 mL (3). The Hospital Episode Statistics 2017-18 data show that there were over 117,000 (19%) episodes of PPH in over 625,000 women delivering a baby in England that financial year (79). It is clear that there are gaps in the literature with no published cohort studies yet (although some are planned) examining this relationship.(80) The investigation of psychological and physical health after PPH is limited, in contrast to the many papers addressing prevention, treatment and risk factors for PPH itself (9). A systematic review by Zatt et al. postulates a link between PPH and post-traumatic stress disorder (PTSD) and negative psychological responses, but concludes that quality of the existing literature is too inconsistent to determine a definite link (81). Of the additional literature which does exist exploring mental health outcomes following PPH, one nested case control study examined the association between PPH and post-partum depressive (PPD) symptoms and found no such positive association.(82) Although when examining specifically the role of anaemia at discharge, negative self-reported delivery experiences and depressed mood during the pregnancy, these were seen as strong predictor of PPD. (82)

The rationale for the development of mental illness following PPH is clear and could be rooted in the traumatic experience of PPH which in itself could give rise to future

ill health and adverse life events, such as long-term depression and divorce (83,84). The fear and anxiety of recurrence of PPH as reported by Sentilhes et al. led to 21% of women deciding not to have another child and of those who did, 60% reported intense anxiety throughout the pregnancy (84). However, as highlighted there has been no large-scale systematic investigation into the mental health outcomes of women who had a PPH compared to those who did not, which leaves a large gap in the literature and more importantly, a gap for potential early detection and intervention of mental illness following childbirth.

To address the gap in our knowledge of the mental health risks following a PPH, we carried out a large retrospective cohort study examining the long-term risk of developing mental illness among women who suffered a PPH compared to women who did not.

## Methods

### Study design and data sources

This study is a population based retrospective open cohort study utilising linked primary care (The Health Improvement Network (THIN)) and secondary care (Hospital Episode Statistics (HES)) databases. THIN is a large population wide database in the UK that contains electronic medical records of over 17 million patients from 787 general practices (163 of them linked to the HES database containing information on admissions to NHS hospitals in England). The linked records were used in order to capture information on exposure (PPH) from HES (as PPH is better recorded in secondary care), and the long-term mental health outcomes recorded in primary care. THIN and HES databases, on their own and linked, have been extensively used for epidemiological studies, including longitudinal

studies that examine long-term outcomes in women with exposures to a variety of events during pregnancy (49–51).

## Study population

Women aged between 16 and 46 who had a record of delivery in HES between 1st January 1990 and 31st January 2018 (index delivery) were eligible to be included if they were registered with their general practice for at least 12 months and their general practice had been using electronic medical records for a minimum of 12 months and shown acceptable mortality recording in the previous 12 months or before (49). These three criteria ensured data quality and sufficient time for maximum and accurate documentation of all covariates. The THIN-HES data linkage was performed by NHS Digital using patient-sensitive de-anonymized data that was then anonymized and received by our team. Once linked, women with a HES record of PPH associated with the index delivery were identified to form the exposed cohort. For each woman exposed to PPH, we randomly selected two unexposed women matched for age (± 2 year) and delivery date (± 1 year). Cohort selection for this study is described in Figure 9.

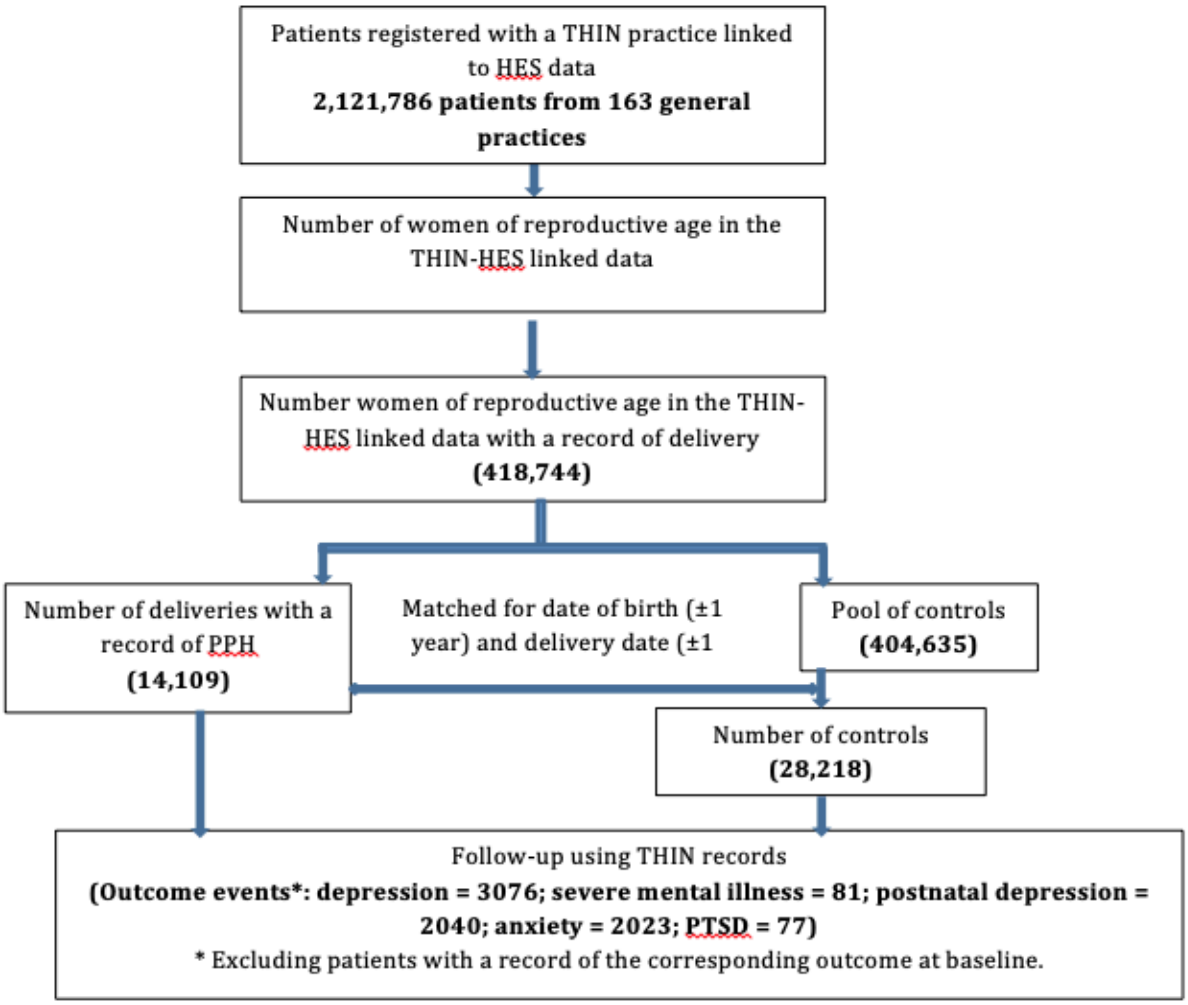



**Figure 9-.** Cohort selection for the study

## Follow-up period

Index date was the date of delivery for all women. Patients were followed up using THIN records until the earliest of the following: date they left the general practice, date they died, date the general practice ceased to contribute to the THIN database, date the outcome of interest was recorded and study end date (31st December 2018).

## Exposure definition

Exposure PPH was defined using ICD 10 codes recorded in HES. ICD 10 codes used to identify PPH have previously been used in national audits and other epidemiological studies (39,85).

## Outcomes

Outcome were identified using THIN Read codes, a hierarchical coding system to document symptoms, signs and diagnosis in primary care (86). Depression following PPH was the primary outcome of interest and was coded separately from postnatal depression. Anxiety, post-traumatic stress disorder (PTSD), and severe mental illness and postnatal depression following PPH were secondary outcomes. All outcomes have previously been studied using THIN and some are included in the Quality Outcome Framework in UK, a payment incentivised process which requires mandatory maintenance of disease registers for these conditions (87–92).

## Covariates

Covariates were selected on the basis of biological plausibility and previous literature. Information on the following covariates was extracted from THIN: age, Body Mass Index (BMI), ethnicity and socio-economic status.

Age was categorized as 16-19, 20-29, 30-39 and >40 years. BMI was categorized according to the World Health Organization's (WHO) classification as <18 kg/m2, 18-24 kg/m2, 25-29 kg/m2 and >30 kg/m2. Socio-economic status in THIN is recorded as Townsend deprivation quintile graded from 1 to 5 with increasing degree of deprivation.

Information on the mode of delivery (spontaneous, caesarean and other delivery methods) and birthweight of the baby was obtained from National Clinical Coding Standards (OPCS) recorded in HES. Birthweight (BW) of the baby was categorized into <1000g (Extremely low BW), 1001-1500g (Very low BW), 1501-2500g (Low BW), 2501-4000g (Normal BW), 4001-4500g (High BW) and >4500g (Very high BW).

Ethnicity data were derived from THIN and, when missing, HES records were used. Missing records of BMI, Townsend score, birthweight and ethnicity were allocated into the 'missing-category' of the corresponding covariate.

## Data analysis

Baseline data stratified by exposure are reported as mean (SD) or median (IQR) for continuous variables depending upon the normality of the distribution and as frequency and proportions for categorical variables. Cox regression model was used to obtain crude and adjusted hazard ratios (HRs and aHRs) of mental health outcomes among women with PPH compared to women without PPH, taking into account the covariates described earlier. In an exploratory analysis, we also looked at the hazard of being prescribed relevant medications such as antidepressants, anxiolytics, and antipsychotics among those with PPH compared to those without PPH. For this, women with a corresponding prescription in the previous year prior to index delivery, indicative of active mental health illness alone were excluded. All analyses were performed in Stata 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) . For each outcome analysis, women with a Read code recording (in THIN) of the outcome of interest prior to the indexed delivery were excluded.

Two-sided P value < 0.05 was considered statistically significant.

## Results

A total of 42,327 women were included in our study: 14,109 women who had a PPH during index delivery were matched to 28,218 women unexposed to PPH. Baseline summary statistics stratified by the exposure status are included in Table 9. Mean age at delivery was 30.90 (SD 5.72) and 30.85 (SD 5.68) years for women exposed and unexposed to PPH, respectively. Follow-up period was similar between women exposed and unexposed to PPH [Median (IQR) follow-up in years: 4.13 (1.72-7.58) and 4.15 (1.78-7.63), respectively]. BMI recorded at baseline was very slightly higher among the women exposed to PPH compared to women without PPH [Median (IQR): 24.1 (21.5-28.0) and 23.7 (21.2-27.4) respectively]. There was no marked difference in socio-economic status and ethnicity of women with and without PPH. Women with PPH were less likely to be smokers compared to women who did not experience PPH during delivery [2,409 (17.07%) vs 5,906 (20.93%)]. There were also differences in the delivery methods between the two groups; higher proportion of women with PPH underwent caesarean section [5,173 (36.66%) vs 7,020 (24.88%)] and other non-spontaneous delivery methods [5,576 (39.52%) vs 16,422 (58.20%)]. Finally, women with PPH were more likely to have delivered very high BW babies compared to women without PPH [2,706(19.18%) vs 5,621 (19.92%)].

**Table 9-** Baseline Characteristics Table

| | Women with PPH (exposed) (*N*=14,109) | Women without PPH (unexposed) (*N*=28,218) |
|---|---|---|
| Age [Mean(***SD***)] | 30.90 (5.72) | 30.85 (5.68) |
| BMI (kg/m2) [Median(IQR)] | 24.1 (21.5-28.0) | 23.7 (21.2-27.4) |
| BMI categories [n(%)] | | |
| < 18 kg/m2 | 239 (1.69%) | 635 (2.25%) |
| 18-24 kg/m2 (reference) | 6,742 (47.79%) | 14,015 (49.67%) |
| 25-29 kg/m2 | 3,100 (21.97%) | 5,711 (20.24%) |
| >=30 kg/m2 | 2,164 (15.34%) | 3,717 (13.17%) |
| Missing | 1,864 (13.21%) | 4,140 (14.67%) |
| Townsend deprivation quintile [n(%)] | | |
| 1 (reference) | 3,341 (23.68%) | 6,316 (22.38%) |
| 2 | 2,573 (18.24%) | 5,035 (17.84%) |
| 3 | 3,087 (21.88%) | 6,216 (22.03%) |
| 4 | 2,741 (19.43%) | 5,582 (19.78%) |
| 5 | 1,567 (11.11%) | 3,349 (11.87%) |
| Missing | 800 (5.67%) | 1,720 (6.10%) |
| Smoking Status [n(%)] | | |
| Non-Smoker (reference) | 8,473 (60.05%) | 16,060 (56.91%) |
| Ex-Smoker | 2,887 (20.46%) | 5,552 (19.68%) |
| Smoker | 2,409 (17.07%) | 5,906 (20.93%) |
| Missing | 340 (2.41%) | 700 (2.48%) |
| Baseline Comorbidities [n(%)] | | |
| Hypertensive disorders (pre-eclampsia, pregnancy induced and pre-existing hypertension) | 298 (2.11%) | 518 (1.84) |
| Hypertensive disorders of pregnancy (pregnancy induced hypertension and pre-eclampsia) | 128 (0.91%) | 227 (0.80%) |
| Pre-existing hypertension | 186 (1.32%) | 306 (1.08%) |

| | | |
|---|---|---|
| Gestational Diabetes | 352 (2.49%) | 598 (2.12%) |
| Pre-existing diabetes | 120 (0.85%) | 200 (0.71%) |
| Depression | 2,110 (14.95%) | 4,597 (15.97%) |
| Anxiety | 1,298 (9.20%) | 2,539 (9.00%) |
| Post traumatic stress disorder | 52 (0.37%) | 109 (0.39%) |
| History of post natal depression | 431 (3.05%) | 677 (2.40%) |
| Mode of delivery [*N*(%)] | | |
| Spontaneous (reference) | 5,576 (39.52%) | 16,422 (58.20%) |
| Caesarean | 5,173 (36.66%) | 7,020 (24.88%) |
| Other delivery methods | 3,360 (23.81%) | 4,776 (16.93%) |
| Ethnicity [*N*(%)] | | |
| Caucasians (reference) | 10,949 (77.60%) | 22,023 (78.05%) |
| South-Asians | 695 (4.93%) | 1,340 (4.75%) |
| Afro-Carribeans | 502 (3.56%) | 894 (3.17%) |
| Mixed race | 193 (1.37%) | 373 (1.32%) |
| Other race | 490 (3.47%) | 953 (3.38%) |
| Missing | 1,280 (9.07%) | 2,635 (9.34%) |

## Risk of depression

After excluding 6,617 women with a record of depression at baseline [2,110 (14.9%) and 4,507 (15.97%) among the exposed and the unexposed], 980 (8.17%) women exposed to PPH and 2,096 (8.84%) women unexposed to PPH received a diagnosis of depression during follow-up, with an incidence rate of 17.2 and 18.6 per 1000 person years. There was no significant difference in the hazard of depression diagnosis between women who were exposed and unexposed to PPH after adjustment for covariates (aHR: 0.94 (95%CI: 0.87-1.01, p=0.103), although the crude estimate showed a marginal reduction in the hazard of depression diagnosis (HR: 0.92 (95% CI: 0.86-1.00, p=0.043)]. After excluding women without a prescription of any antidepressants in the 1 year preceding index delivery, there was

no significant difference in the incidence of being prescribed medication for the treatment of depression between women who were exposed and unexposed to PPH [HR=0.99 (95% CI: 0.95-1.04), p=0.807, including after adjustment for covariates aHR: 1.00 (95%CI: 0.96-1.04, p=0.974]

### Risk of severe mental illness

After excluding 187 women with a record of severe mental illness at baseline [55 (0.39%) and 132 (0.47%)], 21 (0.19%) women exposed to PPH and 60 (0.21%) women unexposed to PPH received a diagnosis of severe mental illness during follow-up, with an incidence rate of 0.29 and 0.42 per 1000 person years. See Table 10. There was no significant difference in the hazard of severe mental illness between women who were exposed and unexposed to PPH [HR=0.70 (95% CI: 0.43-1.15, p=0.162, including after adjustment for covariates aHR: 0.65 (95%CI: 0.40-1.08, p=0.095]. There was a small but insignificant reduction in the risk of being prescribed antipsychotic medication for the treatment of severe mental illness between women who were exposed and unexposed to PPH , which became statistically significant when adjusted for covariates [HR=0.94 (95% CI: 0.88-1.00), p=0.070], aHR: 0.92 (95%CI: 0.86-0.98, p=0.016].

### Risk of postnatal depression (PND)

After excluding women with a history of postnatal depression, 731 (5.34%) women exposed to PPH and 1,309 (4.75%) women unexposed to PPH developed PND during follow-up, with an incidence rate of 11.1 and 9.8 per 1000 person years. There was a significant increase in the hazard of PND among women who were

exposed to PPH compared to those matched controls unexposed to PPH [HR: 1.13 (95%CI: 1.03-1.23, p=0.009), including after adjustment for covariates aHR: 1.10 (95%CI: 1.01-1.21, p=0.037].

### Risk of anxiety

After excluding 3,837 women with a record of anxiety at baseline [1,298(9.20%) and 2,539 (9.00%) among those with and without PPH], 662 (5.17%) women exposed to PPH and 1,361 (5.30%) women unexposed to PPH developed anxiety during follow-up, with an incidence rate of 10.5% and 10.8% per 1000 person years. There was no significant difference in the risk of anxiety between women who were exposed and unexposed to PPH [HR= 0.97 (95% CI: 0.88-1.07), p=0.541), including after adjustment for covariates aHR: 0.99 (95%CI: 0.90-1.09, p=0.881]. There was no significant difference in the risk of being prescribed medication for the treatment of anxiety between women who were exposed and unexposed to PPH [HR=1.02 (95% CI: 0.96-1.10, p=0.495, including after adjustment for covariates aHR: 1.03 (95%CI: 0.96-1.11, p=0.387].

### Risk of post traumatic stress disorder (PTSD)

28 (0.20%) women exposed to PPH and 49 (0.17%) women unexposed to PPH newly developed PTSD during follow-up, with an incidence rate of 0.39 and 0.34 per 1000 person years. There was a 15% increase in the risk of PTSD in women who had PPH compared to women unexposed to PPH [HR=1.15 (95% CI: 0.72-1.82, p=0.561, including after adjustment for covariates aHR: 1.17 (95%CI: 0.73-1.89, p=0.511], although the confidence intervals were wide and the risk difference ranged from a negative to a substantial positive association.

**Table 10-** Crude and adjusted hazard rate ratio for mental health disease among women who were exposed PPH compared to women unexposed to PPH

| | | Exposed to PPH | Unexposed women |
|---|---|---|---|
| Depression^ | **Total *n*** | 11,999 | 23,711 |
| | **Outcomes *N(%)*** | 980 (8.17%) | 2,096 (8.84%) |
| | **Follow up (person-years)** | 59,954 | 112,360 |
| | **Hazard rate ratio (95%CI); *p*-value** | 0.92 (0.86-1.00), *p*=0.043 | |
| | **Adjusted Hazard rate ratio (95%CI) ; *p*-value^** | 0.94 (0.87-1.01); *p*=0.092 | |
| Severe mental illness* | **Total *N*** | 14,054 | 28,086 |
| | **Outcomes *N(%)*** | 21 (0.19%) | 60 (0.21%) |
| | **Follow up (person-years)** | 71,589 | 143,359 |
| | **Hazard rate ratio (95%CI); *p*-value** | 0.70 (0.43-1.15), *p*=0.162 | |
| | **Adjusted Hazard rate ratio (95%CI); *p*-value*** | 0.65 (0.40-1.08); *p*=0.095 | |
| Postnatal depression* | **Total *N*** | 13,668 | 27,541 |
| | **Outcomes *N (%)*** | 731 (5.34%) | 1,309 (4.75%) |
| | **Follow up (person-years)** | 65,891 | 133,446 |
| | **Hazard rate ratio (95%CI); *p*-value** | 1.13 (1.03-1.23); *p*=0.009 | |
| | **Adjusted Hazard rate ratio (95%CI); *p*-value*** | 1.10 (1.01-1.21); *p*=0.037 | |

| | | | |
|---|---|---|---|
| Anxiety^ | **Total *N*** | 12,811 | 25,679 |
| | **Outcomes *N(%)*** | 662 (5.17%) | 1,361 (5.30%) |
| | **Follow up (person-years)** | 62,975 | 125,834 |
| | **Hazard rate ratio (95%CI); *p*-value** | 0.97 (0.88-1.07, *p*=0.541) | |
| | **Adjusted Hazard rate ratio (95%CI) ; *p*-value*** | 0.99 (0.90-1.09); *p*=0.881 | |
| Post traumatic stress disorder* | **Total *N*** | 14,057 | 28,109 |
| | **Outcomes *N(%)*** | 28 (0.20%) | 49 (0.17%) |
| | **Follow up (person-years)** | 71,565 | 143,530 |
| | **Hazard rate ratio (95%CI); *p*-value** | 1.15 (0.72-1.83); p=0.561 | |
| | **Adjusted Hazard rate ratio (95%CI); *p*-value*** | 1.17 (0.73-1.89); p=0.511 | |

^adjusted for age category, BMI category, smoking status, ethnicity, birth weight category, delivery method.

* adjusted for age category, BMI category, smoking status, ethnicity, and delivery method.

## Discussion

To our knowledge, this is the first UK population-wide longitudinal study to date investigating mental health outcomes following PPH that includes over 14,000 episodes of PPH and over 150,000 person years of follow-up. Women who experienced PPH were found to be at increased risk of developing postnatal depression. The risk of developing PTSD following a PPH was increased also,

though with considerable uncertainly around the estimate. Women who experienced PPH, however, were not at a higher risk of developing non-pregnancy related depression and anxiety compared to those who did not experience PPH.

Postnatal depression according to the ICD-10 classification occurs within six weeks of giving birth. The prevalence of PND depending on the criteria used for diagnosis ranges from 10-30% and is thought to be higher still at 40% in women with risk factors such as premature babies (93,94). A recognized risk factor for developing PND is a prior depressive episode, though we excluded from analysis women with prior mental illness, that said up to 40% of women will have new onset depression following birth for the first time (93). One hypothesis to explain the increased risk of PND rather than other mental health outcomes (anxiety, depression, PTSD, severe mental illness) could be that there is transient increase in stress secondary to PPH often with an increased length of hospital stay and comorbidity (anaemia, renal impairment, coagulopathy) which is largely resolved by the first six weeks following birth and with no subsequent increased appreciable risk to ongoing mental health thereafter (9).

Although not formally classed as a severe mental illness outcome, postnatal depression has frequently been linked with serious adverse effects on women's wellbeing and bonding with their new-borns. These effects can be long-lasting and impact upon the children's critical years of development. Albeit a rare occurrence, in the most extremely severe cases of postnatal depression, cases of infanticide and suicide are reported in relation to an acute depressive episode and there is evidence showing increased suicidal ideation in general in mothers with postnatal depression (95). The smaller yet statistically significant difference seen in prescriptions for

antipsychotic medication being less likely in those who had a PPH than those who did not aHR: 0.93 (95%CI: 0.87-1.05, p=0.048) is unlikely to be of clinical relevance, but might reflect the ease of access to general practice while recovering from a PPH.

Considering the association demonstrated in our findings, the investigation of mental illness outcomes following childbirth and in particular those births complicated by a PPH is clearly warranted

## Strengths and weaknesses

The findings of this study should be considered in light of its strengths and limitations. Due to the linked nature of the dataset this study has several unique strengths including its sample size, population-wide coverage, and controlling for confounding by using the matched controlled study design and adjusting for a wide range of relevant covariates. A major strength was accounting for prior depression and other mental illness diagnoses in the population, so that that a known confounding factor was mitigated when investigating outcomes. Investigation of diagnosis of mental illnesses and subsequent prescriptions issued for treatment also allowed the outcomes to be investigated by two techniques, strengthening the reliability.

However, when conducting epidemiological studies, the accuracy of such studies largely relies upon the accuracy of documenting by the primary and secondary care clinician. There has yet to be a recorded study validating the Read or ICD-10 codes for PPH or mental illness in UK primary/secondary care. However, our code lists have been selected with the support of experts in code list selection, clinicians in primary care and those trained in Psychiatry. Additionally, by linking the dataset we aimed to reduce the possibility of misclassification bias. However, due to difficulties

in accounting for measurement of blood loss intrinsically linked with the definition of PPH, we were only able to identify those women who had the presence of such records. Additionally, although we were able to control for many important confounding factors, there are still other confounders not well recorded in primary care which may be related to poor post-natal and mental health outcomes which may include exposure to abuse and education status (90).

### Implications for clinical practice

In clinical practice, vigilance in those women who have had a PPH needs to be raised and assessment for postnatal depression should be considered as part of the general follow-up strategy given the associated increased risk following PPH. The current NICE guidance gives advice that each postnatal contact, women should be asked about their emotional wellbeing, however we advise that particular attention is paid to this subgroup of mothers by clinicians due to their increased risk of mental illness. (96)

## Conclusion

PPH is associated with an increase in the risk of developing postnatal depression. Our findings are potentially impactful on determining the focus of follow-up by health visitors in women who had a PPH after childbirth. This group of women should be deemed as at an increased risk for postnatal depression and careful assessment needs to be put in place for early detection and intervention

## Ethics approval

The IQVIA Scientific Review Committee (SRC) and Independent Scientific Ethical Advisory Committee (ISEAC) approved the study. ISEAC Reference number: 18THIN035.

# Chapter 8 - Postpartum haemorrhage and risk of hypertension and cardiovascular disease: population based longitudinal study using linked primary and secondary care databases

### *Preamble to Chapter 8*

In Chapter 7 I reported there is no appreciable long-term effect of PPH on mental health, but there is an increased risk of developing postnatal depression. In Chapter 8 in order to investigate the long-term effects of PPH on cardiovascular disease I carried out a population based longitudinal study.

### *Contributions*

Dr. Parry-Smith – conceived the idea, made substantial contribution to the design, acquisition, analysis and interpretation of the data and wrote the manuscript.

Dr. Nirantharakumar and Dr Sumilo- contributed to the design, interpretation of data and provided substantial edits to the manuscript.

Dr. Subramanian, Mr Gokhale and Mr Okoth contributed to the acquisition, analysis and interpretation of data.

Prof. Coomarasamy proofread the manuscript and provided substantial edits.

## Abstract

### *Introduction*

There is increasing recognition that various obstetric conditions can impact on future cardiovascular health, but no studies have investigated the relationship between postpartum haemorrhage (PPH) and cardiovascular outcomes.

### *Methods*

We conducted an open cohort study utilising linked primary care (The Health Improvement Network (THIN)) and English secondary care (Hospital Episode Statistics (HES)) databases, from 1st January 1997 to 31st January 2018. A total of 42,327 women were included: 14,109 of them exposed to PPH during the study period and 28,218 matched for age and date of delivery, and unexposed to PPH. Hazard ratios (HRs) for cardiovascular outcomes among women who had and did not have PPH were estimated after controlling for covariates using multivariate Cox regression models.

### *Results*

During a median follow-up of over 4 years there was no significant difference in the risk of hypertensive disease after adjustment for covariates [aHR: 1.03 (0.87-1.22); *p*=0.71]. We also did not observe a statistically significant difference in the risk of composite cardiovascular disease (CVD) (ischemic heart disease, heart failure, stroke or transient ischemic attack) between the exposed and the unexposed cohort [aHR: 0.86 (0.52-1.43; *p*=0.57].

### *Conclusion*

Over a median follow-up of 4 years we did not observe an association between PPH and hypertension or cardiovascular disease.

## Introduction

The widely used definition of postpartum haemorrhage (PPH) is blood loss in excess of 500mL following birth (3). In 2017-18 there were 626,203 deliveries in NHS hospitals in England, of which 19% were complicated by PPH (79). Over 100,000 women a year in England suffer a PPH but the long term health consequences beyond a year of experiencing PPH, aside from future fertility and mental health illness, have not been studied to date (35,97). The majority of the recognised risk factors for PPH are pregnancy-related, such as placental abruption and hypertensive disorders of pregnancy, which are also overarching risk factors for later development of cardiovascular disease (CVD) (98,99).

Disease unmasked in or around pregnancy such as pregnancy induced hypertension, gestational diabetes mellitus (GDM), preterm labour, and diseases of placentation including fetal growth restriction, and placental abruption have previously been demonstrated to identify women at high risk of long-term cardiovascular risk, as shown in a number of cohorts of women with adverse pregnancy outcomes (100–110).

Given that hypertensive disorders of pregnancy increase the likelihood of PPH, it is possible that PPH is also a risk factor for later development of hypertension post-partum. Hypertensive disease in pregnancy causes poor placentation; this combined with the higher mean arterial blood pressure could pre-dispose to brisker blood loss after delivery (111). The PPH episode might therefore unmask the potential for endothelial or vascular dysfunction that may not have manifested as hypertensive disease in pregnancy, therefore remaining as a latent threat for hypertension and CVD in later life (37). The risk of poor cardiovascular health in women who have undergone PPH is thus a possibility and warrants investigation.

To address the gap in our knowledge of the risks following a PPH, we did a cohort study examining the long-term risk of developing hypertension and cardiovascular disease among those women who suffered a PPH compared to those women who did not.

## Methods

### Study design and data sources

This study is a population based retrospective open cohort study utilising linked primary care (The Health Improvement Network (THIN)) and secondary care (Hospital Episode Statistics (HES)) databases. THIN is a large population-based database in the UK that contains electronic medical records of over 17 million patients from 787 general practices (163 of them linked to the HES database). The linkage of databases was performed in order to capture information on exposure (PPH) from HES, the long-term cardiovascular outcomes from THIN and important covariates from both THIN (demographics) and HES (records during hospital admission). THIN and HES databases, on their own and linked have been extensively used for epidemiological studies, including longitudinal studies that examine long-term outcomes in women with exposures during pregnancy (49–51).

### Study population

Women aged between 16 and 46 years who had a record of delivery in HES (which contains information on admissions to NHS hospitals in England) between 1st January 1990 and 31st January 2018 (index delivery) were eligible to be included. Patients in THIN were considered for data linkage 12 months after registration with their practice and where the practice had been using electronic medical records for a minimum of 12 months and had shown acceptable mortality recording in the previous 12 months or before (49). These three criteria ensured data quality and sufficient

time for maximum and accurate documentation of all covariates. The THIN-HES data linkage was performed by NHS Digital using patient-sensitive de-anonymized data that was then anonymised and received by our team. Once linked, women with a HES record of PPH associated with the index delivery were identified to form the exposed cohort. For each woman exposed to PPH, we randomly selected two controls matched for date of birth (± 1 year) and delivery date (± 1 year). Cohort selection for this study is described in Figure 10.

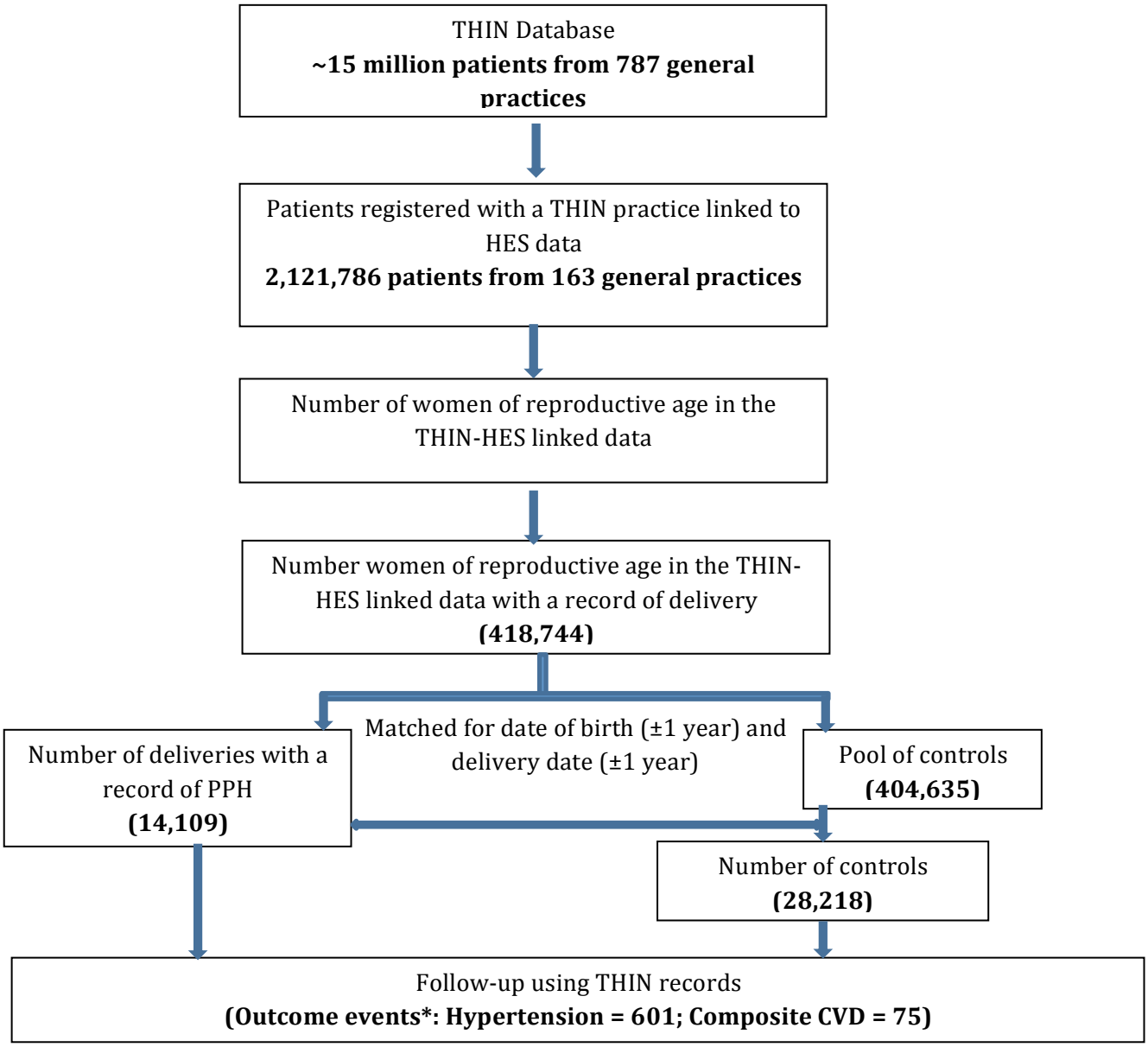



Figure 10- Cohort selection for the study. *Excluding patients with a record of the corresponding outcome at baseline.

## Follow-up period

Index date was the date of delivery for all women. Patients were followed up using THIN records until the earliest of the following: date they left the general practice, date they died, date the general practice ceased to contribute to the THIN database, date the outcome of interest was recorded, and study end date (31st December 2017).

## Exposure definition

Exposure PPH was defined using ICD-10 codes recorded in HES. ICD-10 codes used to identify PPH have previously been used in national audits and other epidemiological studies (39,85).

## Outcomes

Outcome ascertainment was performed using THIN Read Code records, a hierarchical coding system to document symptoms, signs, and diagnosis in primary care (86). Hypertension following PPH was the primary outcome of interest. Composite cardiovascular disease (CVD: ischemic heart disease, stroke or TIA and heart failure) and individual components of composite CVD following PPH were secondary outcomes. All outcomes have previously been studied extensively using THIN and are part of the Quality Outcome Framework in UK, that requires mandatory maintenance of disease registers for these conditions and are thus expected to be documented rigorously (87,88,100).

## Covariates

Covariates that are independent predictors of outcome other than the exposure of interest were selected on the basis of biological plausibility and previous literature. Information on the following covariates was extracted from THIN: age, Body Mass Index (BMI), socio-economic status, smoking status, diagnoses of hypertensive disorders (pre-existing or pregnancy induced hypertension and pre-eclampsia), gestational diabetes and pre-existing diabetes, and prescription records of lipid lowering drugs.

Age was categorized as 15-19, >20-29, >30-39, and >40 years. BMI was categorized according to the World Health Organization's (WHO) classification as <18 $kg/m^2$, 18-24 $kg/m^2$, >25-29 $kg/m^2$, and >30 $kg/m^2$. Socio-economic status in

THIN is recorded as Townsend deprivation quintile graded from 1 to 5 with increasing degree of deprivation.

Information on the mode of delivery (spontaneous, caesarean, and other delivery methods) was obtained from National Clinical Coding Standards (OPCS) recorded in HES.

Ethnicity data were derived from THIN and, when missing, HES records were used. Missing records of BMI, Townsend score, and ethnicity were allocated into the 'missing-category' of the corresponding covariate.

### Data analysis

Baseline data stratified by exposure are reported as mean (*SD*) or median (IQR) for continuous variables depending upon the normality of the distribution and as frequency and proportions for categorical variables. Cox regression model was used to obtain crude and adjusted hazard ratios (HRs and aHRs) taking into account the covariates described earlier. All analyses were performed in Stata 14.0. For each outcome analysis, women with a Read code recording (in THIN) of the outcome of interest prior to the indexed delivery were excluded.

## Results

A total of 42,327 women were included in our study: 14,109 women exposed to PPH during index delivery and 28,218 women unexposed to PPH. Baseline summary statistics stratified by the exposure status are provided in Table 11. Mean age at delivery was 30.90 (*SD* 5.72) and 30.85 (*SD* 5.68) years for women exposed and unexposed to PPH, respectively. Follow-up period was similar between women exposed and unexposed to PPH [Median (IQR) follow-up in years: 4.13 (1.72-7.58) and 4.15 (1.78-7.63), respectively]. BMI recorded at baseline was higher among the

women exposed to PPH compared to women without PPH [Median (IQR): 24.1 (21.5-28.0) and 23.7 (21.2-27.4) respectively]. There was no significant difference in socio-economic status and ethnicity of women with and without PPH. Women who experienced PPH were less likely to be smokers compared to women who did not experience PPH during delivery [2,409 (17.07%) vs 5,906 (20.93%)]. The proportion of women with a record of pre-existing hypertension and diabetes and proportion prescribed with lipid-lowering drugs were similar between the two groups. However, there was a slightly higher proportion of women with GDM among the exposed compared to the unexposed [352 (2.49%) vs 597 (2.12%) respectively]. There were also differences in the delivery methods between the two groups; higher proportion of women with PPH underwent caesarean section [5,173 (36.66%) vs 7,020 (24.88%)] and other non-spontaneous delivery methods [5,576 (39.52%) vs 16,422 (58.20%)].

**Table 11-** Baseline Characteristics Table

| | Women with PPH (exposed) (*N*=14,109) | Women without PPH (unexposed) (*N*=28,218) |
|---|---|---|
| Age [Mean(***SD***)] | 30.90 (5.72) | 30.85 (5.68) |
| BMI (kg/m$^2$) [Median(IQR)] | 24.1 (21.5-28.0) | 23.7 (21.2-27.4) |
| BMI categories [*N*(%)] | | |
| < 18 kg/m$^2$ | 239 (1.69%) | 635 (2.25%) |
| 18-24 kg/m$^2$ (reference) | 6,742 (47.79%) | 14,015 (49.67%) |
| 25-29 kg/m$^2$ | 3,100 (21.97%) | 5,711 (20.24%) |
| >=30 kg/m$^2$ | 2,164 (15.34%) | 3,717 (13.17%) |
| Missing | 1,864 (13.21%) | 4,140 (14.67%) |
| Townsend deprivation quintile [*N*(%)] | | |
| 1 (reference) | 3,341 (23.68%) | 6,316 (22.38%) |
| 2 | 2,573 (18.24%) | 5,035 (17.84%) |
| 3 | 3,087 (21.88%) | 6,216 (22.03%) |
| 4 | 2,741 (19.43%) | 5,582 (19.78%) |
| 5 | 1,567 (11.11%) | 3,349 (11.87%) |
| Missing | 800 (5.67%) | 1,720 (6.10%) |
| Smoking Status [*N*(%)] | | |
| Non-Smoker (reference) | 8,473 (60.05%) | 16,060 (56.91%) |
| Ex-Smoker | 2,887 (20.46%) | 5,552 (19.68%) |
| Smoker | 2,409 (17.07%) | 5,906 (20.93%) |
| Missing | 340 (2.41%) | 700 (2.48%) |
| Baseline Comorbidities [*N*(%)] | | |
| Hypertensive disorders (pre-eclampsia, pregnancy induced and pre-existing hypertension) | 298 (2.11%) | 518 (1.84) |
| Hypertensive disorders of pregnancy (pregnancy induced hypertension and pre-eclampsia) | 128 (0.91%) | 227 (0.80%) |
| Pre-existing | 186 (1.32%) | 306 (1.08%) |

| | | |
|---|---|---|
| hypertension | | |
| Gestational Diabetes | 352 (2.49%) | 598 (2.12%) |
| Pre-existing diabetes | 120 (0.85%) | 200 (0.71%) |
| Combined cardiovascular disease | 22 (0.16%) | 44 (0.16%) |
| Ischemic heart disease | 3 (0.02%) | 7 (0.02%) |
| Heart failure | 0 (0.00%) | 2 (0.01%) |
| Stroke/TIA | 19 (0.13%) | 39 (0.14%) |
| Baseline Drug prescription [*N*(%)] | | |
| Lipid-lowering drugs | 51 (0.36%) | 115 (0.41%) |
| Mode of delivery [*N*(%)] | | |
| Spontaneous (reference) | 5,576 (39.52%) | 16,422 (58.20%) |
| Caesarean | 5,173 (36.66%) | 7,020 (24.88%) |
| Other delivery methods | 3,360 (23.81%) | 4,776 (16.93%) |
| Ethnicity [*N*(%)] | | |
| Caucasians (reference) | 10,949 (77.60%) | 22,023 (78.05%) |
| South-Asians | 695 (4.93%) | 1,340 (4.75%) |
| Afro-Carribeans | 502 (3.56%) | 894 (3.17%) |
| Mixed race | 193 (1.37%) | 373 (1.32%) |
| Other race | 490 (3.47%) | 953 (3.38%) |
| Missing | 1,280 (9.07%) | 2,635 (9.34%) |

## Risk of hypertension

218 (1.6%) women exposed to PPH and 383 (1.4%) women unexposed to PPH developed hypertension during follow-up, with an incidence rate of 3.12 and 2.72 per 1000 person-years, respectively. There was no significant difference in the risk of hypertension between women who were exposed and unexposed to PPH [HR: 1.14 (95%CI: 0.97-1.35, $p$=0.118), including after adjustment for covariates [aHR: 1.03 (0.87-1.22); $p$=0.710] see table 12.

**Table 12-** Crude and adjusted hazard rate ratio for hypertension and cardiovascular disease among women who were exposed PPH compared to women unexposed to PPH

| | | Exposed to PPH | Unexposed women |
|---|---|---|---|
| **Hypertension** | **Total *N*** | 13,923 | 27,912 |
| | **Outcomes *N (%)*** | 218 (1.57%) | 383 (1.37%) |
| | **Follow up (person-years)** | 69,944 | 140,703 |
| | **Hazard rate ratio (95%CI); *p*-value** | 1.14 (0.97-1.35); *p*=0.118 | |
| | **Adjusted Hazard rate ratio (95%CI); *p*-value^** | 1.03 (0.87-1.22); *p*=0.710 | |
| **Composite CVD (Ischemic heart disease, heart failure, stroke/transient ischemic attack)** | **Total *N*** | 14,087 | 28,174 |
| | **Outcomes *N (%)*** | 23 (0.16%) | 52 (0.18%) |
| | **Follow up person-years)** | 71,666 | 143,724 |
| | **Hazard rate ratio (95%CI); *p*-value** | 0.88 (0.54-1.44); *p*=0.621 | |
| | **Adjusted Hazard rate ratio (95%CI); *p*-value*** | 0.86 (0.52-1.43); *p*=0.572 | |

^adjusted for age category, BMI category, smoking status, ethnicity, Townsend deprivation quintile, baseline record of hypertensive disorders of pregnancy (pregnancy induced hypertension and pre-eclampsia), gestational diabetes, pre-existing diabetes, baseline prescription of lipid lowering drugs and delivery method.

*adjusted for age category, BMI category, smoking status, ethnicity, Townsend deprivation quintile, baseline record of hypertensive disorders (pre-existing/ pregnancy induced hypertension and pre-eclampsia), gestational diabetes, pre-existing diabetes, baseline prescription of lipid lowering drugs and delivery method.

### Risk of CVD

23 (0.16%) women exposed to PPH and 52 (0.18%) women unexposed to PPH developed at least one of the three components of the composite cardiovascular outcome during follow-up. After adjustment for covariates, there was no significant difference in the risk of composite CVD between the exposed and the unexposed cohort [aHR: 0.86 (0.52-1.43; *p*=0.572]. When the individual components of the CVD were analysed as outcomes, none of these individual outcomes were significantly different between the exposed and the unexposed cohort [aHR- ischemic heart disease: 1.00 (0.30-3.32); *p*=0.995, heart failure: 0.76 (0.25-2.31); *p*=0.634) and stroke or TIA: 0.80 (0.43-1.47); *p*=0.461] (see Figure 11).

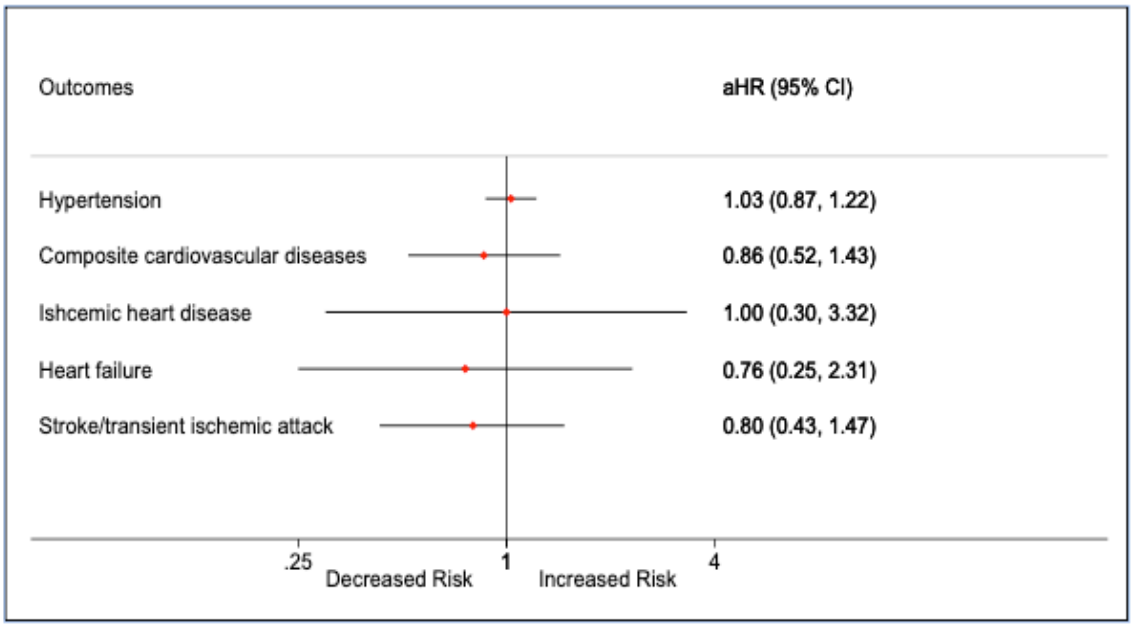



**Figure 11-** Adjusted Hazard ratios for different cardiovascular outcomes following exposure to PPH

## Discussion

To our knowledge, this is the first population wide longitudinal study to date investigating cardiovascular risk following PPH and includes over 14,000 episodes of

PPH and over 210,000 person-years of follow-up. Women who experienced PPH were found not to be at increased risk of developing hypertension nor composite cardiovascular disease (heart failure, stroke or TIA and ischemic heart disease) when compared to women who did not experience PPH.

The hypothesis that having PPH might unmask a latent risk of developing future cardiovascular disease is, as discussed in the introduction, plausible though not supported in the follow up period of this study. PPH is thought to occur more frequently in those women with pre-existing congenital heart disease (112). In episodes of severe PPH requiring admission to intensive care, myocardial ischemia-induced injury was associated with severe PPH, though there was no long term follow up of these women (113). Cardiovascular disease is a leading cause of death among women, and when combined with the high prevalence of PPH following childbirth, an association could have been of importance at individual and population levels. Our study provides reassurance for women who have had a PPH with regard to future cardiovascular risk (114).

## Strengths and weaknesses

This study has several strengths including its sample size, population wide coverage, and controlling for confounding by using the matched controlled study design and adjusting for a wide range of relevant covariates.

Measurement of blood loss and definition of postpartum haemorrhage, however, are a challenge with recognized underestimation of blood loss. We were only able to identify women who had PPH and cardiovascular disease if it was coded in the database.

A previous study identified increased cardiovascular risk following maternal placental syndromes at between 3-5 years following delivery (114). The follow-up period in our study was similar between women exposed and unexposed to PPH but the follow-up time frame could have been too short to observe an effect as relatively few women had a diagnosis of cardiovascular disease.

### Implications for clinical practice

Long-term morbidity and disease as a consequence of PPH deserves vigilance but there is no particular cause for concern regarding an increase in cardiovascular risk in this patient group.

## Conclusion

Over a median follow-up of 4 years we did not observe an association between PPH and hypertension or cardiovascular disease.

## Ethics approval

The IQVIA Scientific Review Committee (SRC) and Independent Scientific Ethical Advisory Committee (ISEAC) approved the study. ISEAC Reference number: 18THIN035.

# Chapter 9 – Conclusion

In this thesis, I outlined an approach to address some key strategies to manage postpartum haemorrhage. I divided the thesis into chapters with three key themes; prevention, treatment, and complications, while trying to explore new questions and solutions to a persistent problem: how best to reduce the burden of blood loss following childbirth.

As PPH rates have risen in the developed world, evaluating commonly used prescription drugs that might change the risk of having a PPH seemed a sensible strategy. In Chapter 2 I shared the results of a nested case control study addressing the question of oral contraceptive use as a risk factor for PPH. The study outlined in Chapter 2 concluded that the use of oral progesterone only contraceptive medication within 18 months of conception might be associated with, an as yet unproven, increase in the risk of PPH. Progesterone is thought to play a role in suppression of uterine contractility and it is conceivable that progesterone receptor expression is altered by pre-conception exogenous progesterone contraceptive medication. This is the first time in the literature, that this question has been addressed at such a scale.

I continued the exploration of commonly used prescription drugs as a risk factor for PPH in Chapter 3. In Chapter 3 I shared the results of another nested case-control study. The literature to date suggested that SSRI use might increase the risk of PPH. The study I undertook did not show an increase in the risk of PPH, with third trimester SSRI use. The study is the first UK population based study of its kind.

In Chapter 4 I continued with the theme of prevention. The question of when best to administer prophylactic uterotonic medication to reduce blood loss after delivery seems sensible to investigate given the widespread guidance and practice for immediate administration despite a limited evidence base. Many researchers have not formally addressed the question perhaps because of existing consensus and reasonable belief that the earlier a drug is given the better the outcome. However, I have throughout this thesis questioned consensus in order to find new strategies to manage PPH. The cohort study derived from the UK sub-population of the WHO CHAMPION trial suggested that administration of uterotonic medication immediately following delivery should be revisited. A short delay is unlikely to be detrimental and may be beneficial. The delay in uterotonic medication to work in concert with the dynamic nature of the third stage of labour and regional contraction and relaxation of the uterus makes physiological sense. The study is the first of its kind.

The thesis pivots from prevention to treatment in Chapter 5. In Chapter 5 I share the results of a Cochrane review on uterotonic agents for first-line treatment of PPH. The chapter identified a lack of trial evidence for all uterotonic agents used as first line treatment and highlighted gaps in the literature. The key findings were that misoprostol, increased the risk of women requiring a blood transfusion when compared with oxytocin, and that misoprostol when used in combination with conventional drugs is associated with a significant increase in side effects without being more effective.

Treatment of PPH can only occur if it is correctly identified and the requirement for action initiated. In Chapter six I shared a further cohort study whose participants were the UK sub-population of the WHO CHAMPION study. The study demonstrated

that more than 60% of patients who had a PPH did not receive treatment uterotonic medication at a loss of 500-599mL, while at 1000-1099mL a third of women were not treated. Significantly more women received treatment for PPH following an instrumental assisted birth conducted by an obstetrician compared to those women having a normal birth.

In Chapters 7 and 8 the thesis addressed the question of long term complications following a PPH. In Chapter 7 I presented a cohort study investigating the consequence of a PPH on mental health. The key finding was that PPH is associated with an increased risk of developing postnatal depression. The study is the largest of its kind and the finding biologically plausible.

In Chapter 8 I share the results of a cohort study investigating the consequence of PPH on cardiovascular health. The key finding was over a median follow up of four years no association between PPH and hypertension or cardiovascular disease was observed. The study was the first time the association between PPH and cardiovascular health has been addressed at a population level.

## Implications for future practice

My thesis has allowed me to explore in detail key areas of prevention, treatment, and consequence of PPH. There are a number of clinical points that can be made from the findings of my thesis. SSRI prescribing in late pregnancy was not associated with an increase in odds of PPH. SSRI use in pregnancy is increasingly common as is PPH. While all drugs should be prescribed with caution in pregnancy, the study suggested that no excessive concern should be attached to the risk of bleeding following delivery in those taking SSRI medication. Women should not stop taking SSRI medication for fear of developing a PPH. The thesis also suggests that the

need to immediately administer prophylactic uterotonic medication following birth is not warranted and may in fact be detrimental to blood loss minimisation.

Clinicians may wish to reconsider which drugs they use to treat a PPH and decide whether misoprostol is appropriate as a first line drug in their own settings. Misoprostol used as a first-line treatment of PPH increased the risk of blood transfusion compared to oxytocin and is associated with more side effects. All clinicians need to reflect on recognition and prompt treatment of PPH, given the finding that more than 60% of patients who had a PPH did not receive treatment uterotonic medication. Less than half of those sustaining a PPH received a treatment uterotonic medication at a loss of 500-599mL. The findings that significantly more women received treatment for PPH following an instrumental delivery conducted by an obstetrician compared to those women having a normal birth should prompt further research to establish why this difference exists. Multidisciplinary team training and PPH recognition and action drills might prove useful as part of a comprehensive practice intervention which is being evaluated currently in the Obstetric Bleeding strategy for Wales, OBS Cymru programme. Finally PPH is associated with an increase in the risk of developing postnatal depression. The finding is important in determining the focus of follow-up by health visitors and GPs in women who had a PPH after childbirth. This group of women should be deemed as at an increased risk for postnatal depression and careful assessment needs to be put in place for early detection and intervention with clear communication between maternity teams and primacy care on discharge following birth.

## Implications for public policy

My thesis establishes that strategies to manage PPH should include work to confirm known risk factors in the case of SSRI medication and identify novel risk factors in the case of contraceptive medication. Policy should focus on strategies to ensure timely identification of PPH and appropriate treatment. Finally policy makers should recognise the potential long-term effects of PPH and ensure this is credited as an emerging area of concern given the risk to maternal mental health demonstrated in this thesis. Given the scale of PPH and the findings of this thesis, policy makers should prioritise PPH mitigation strategies and research urgently.

## Implications for research

My thesis establishes that contraception medication prior to conception warrants further study. The association with progesterone only contraception and PPH also generates further hypotheses for future research. Equally, the finding that SSRI medication is not associated with an increase in PPH needs to be further investigated in other data sets using the same rigorous methods I have detailed; given that my findings are contrary to the existing limited literature. I have discussed collaboration with colleagues in Canada who have expertise in pharmaco-epidemiology who are interested in taking this work forward based on the work presented in my thesis.

The best time to administer prophylactic uterotonic medication and the possibility that delay may be beneficial and in keeping with the physiology of the third stage of labour will appeal to many researchers and women alike. Delaying uterotonic medication and timing it to coincide with the physiological contraction waves of the uterus is biologically plausible. A randomised controlled trial comparing immediate vs delayed administration of prophylactic uterotonic medication accepting an alpha risk

of 0.05 and beta risk of 0.2 would require 273 women in each arm to recognise a statistically significant difference of 50mls with an anticipated dropout rate of 0%. A feasibility study based on the cohort study reported in my thesis and the sample size above should be considered and I intend to work up the study as a research proposal.

There is a lack of evidence for all available drugs for treating excessive bleeding after childbirth and especially for commonly used drugs, such as injectable prostaglandins, ergometrine, and Syntometrine. This lack of evidence requires further research. A study comparing oxytocin vs injectable prostaglandin for the treatment of PPH is seeking trial sites and I intend to contribute as a principal investigator by enrolling my hospital into the trial. I also intend to regularly update the Cochrane review presented in my thesis. The finding that less than half of women who have a PPH received treatment requires a package of work to understand the barriers present that prevent prompt recognition and treatment. Colleagues in Birmingham are taking this work forward and I am collaborating with them.

The long term effects following a PPH are little studied and this thesis shows that consideration of further identification of health problems in this key group of women is required, with particular emphasis on their mental health. I intend to continue collaboration with colleagues in Birmingham as our expertise develops in using large patient databases to address these key public health questions.

## Appendices

Appendix 1

Gynecologic and Obstetric Surgery: Challenges and Management Options, First Edition. Edited by Arri Coomarasamy, Mahmood I. Shafi, G. Willy Davila and Kionh K. Chan. 2016 Published by John Wiley and Sons, Ltd

Page 119. Chapter 40 and 169 are co-authored by Dr Parry-Smith and cover the management of massive haemorrhage

Appendix 2

Page 121. THIN database research protocol and approval

**An epidemiological study exploring novel risk factors and long-term health effects of Postpartum Haemorrhage**

**Background:**

The widely used definition of post partum haemorrhage (PPH) is blood loss following birth in excess of 500 mL (WHO, 2012). PPH treatment is usually characterised by interventions to remedy the cardinal cause(s) of haemorrhage. The treatment particularly focuses on uterine tone, as well as steps to exclude and repair any trauma, remove the placenta and membranes in entirety, and correct the clotting cascade (Coomarasamy *et al.*, 2016).

The contribution of PPH to maternal mortality is well recognised and documented in developed countries and in sub-Saharan Africa where haemorrhage accounts for 13.4% and 33.9% respectively of the overall causes of maternal mortality (Khan *et al.*, 2006). The decline in PPH in low resource countries is welcomed and driven by a decrease in the number of pregnancies per women, increased income per head, higher maternal educational attainment and increasing access to skilled birth attendants (Hogan *et al.*, 2010). The incidence of atonic PPH is however increasing in many well-resourced countries, for example in Canada the rate increased from 4.8% to 6.3% from 2001 to 2009 (Mehrabadi *et al.*, 2013). In the UK, PPH occurred in 13.8% of all deliveries 2013-14, with a doubling of PPH reported between 2003 and 2013 (Winter, 2015; Nair, Kurinczuk and Knight, 2016). The paradox of decreasing PPH in low resource settings and increase in well-resourced settings requires investigation, not least to ensure that gains made in low resource settings are maintained as the resource levels improve.

An explanation of the increase in PPH observed in well-resourced settings has been sought. Maternal obesity, nulliparity, gestational weight and ethnicity have all been demonstrated to contribute to the increased risk of PPH in a New Zealand cohort study (Fyfe *et al.*, 2012). In the USA a large population based study of 8.5 million hospital deliveries demonstrated the following risk factors for increased rate of PPH: increased maternal age, fibroids, preeclampsia, amnionitis, placenta praevia or abruption, cervical laceration, instrumental delivery and caesarean delivery, fetal macrosomia (Kramer *et al.*, 2013). In the UK Briley and colleagues identified similar risk factors but

also found that index of multiple deprivation, multiparity without caesarean section and administration of steroids for fetal reasons contributed to PPH (Briley *et al.*, 2014). The UK confidential enquiries into maternal deaths and morbidity reports repeatedly identify PPH, prediction, recognition and management as an area that requires improvement (Knight *et al.,* , 2017). However, despite the contribution of these recognised risk factors the doubling of severe PPH in a decade was not explained by a mirrored change in risk factors in the USA (Kramer *et al.*, 2013). A study identifying novel risk factors for PPH is required to explain and potentially mitigate the rise in PPH seen in well-resourced settings.

An approach to identifying potential novel risk factors for PPH is contingent on a plausible biological explanation. Some authors speculate that the increased use of selective serotonin reuptake inhibitors might cause novel drug interactions that lead to modulation of vascular tone and platelet aggregation causing PPH (Joseph *et al.*, 2015). Serotonin receptors are present in the myometrium, their disruption by anti-depressant drugs could contribute to poor muscle contraction and atonic PPH (Cordeaux *et al.*, 2009). The increase in atonic PPH , the most common type, could be viewed through the prism of smooth muscle dysfunction. The role of smooth muscle in uterine contraction is well described despite the underlying mechanisms being incompletely understood (Bru-Mercier *et al.*, 2012). Two recent systematic reviews have concluded that there may be an association between anti-depression medication and PPH, but the numbers of studies were small and none have been conducted in a UK setting (Bruning *et al.*, 2015; Jiang *et al.*, 2016). The review by Brunning and colleagues made use of only four studies and was inconclusive. The review by Jiang and colleagues contained eight studies and concluded that use of antidepressants during pregnancy was associated with a 32% increase in the odds of PPH. Limitations common to both studies included exposure to antidepressants during pregnancy only rather than prior to conception as well and adjustment for few confounding factors.

Oestrogen and progesterone in relation to pregnancy have recently been studied mainly in the context of of pre-term birth and increasing maternal obesity. Oestrogen and progesterone levels in the context of obesity and their role in myometrium contractility and the complex pathobiology at work have been well described (Carlson, Hernandez and Hurt, 2015). Progesterone has been used extensively in pre-term birth treatment; its effect on the myometrium is to reduce contractility. Exposure to higher doses of the drug in oral contraceptives might well impact on PPH with modulation of oestrogen and progesterone receptors (Anderson *et al.*, 2009). Zhang and colleagues demonstrate both clinically and in vivo that obesity impairs uterine contractility, the effects of high circulating cholesterol are postulated as an explanation (Zhang *et al.*, 2007). The metabolic effects of the combined oral contraceptive pill and to a lesser extent progesterone only are profound, with a tendency towards higher cardiometabolic risk (Wang *et al.*,

2016). It is therefore reasonable to investigate the use of exogenous hormonal contraception prior to pregnancy as a novel risk factor for PPH.

In 2015/16 in the UK over 7 million prescriptions were dispensed in community pharmacies for oral contraceptives (Health and Medicine, 2016). Anti-depressant prescriptions for both Citalopram (14 million) and Amitriptyline (12 million) have doubled in the previous decade (Health and Social Care Information Centre, 2013). The role of these widely used medications in PPH should therefore be examined.

The contribution of post partum haemorrhage (PPH) to maternal mortality is well recognised and documented. The immediate morbidity associated with PPH is also widely reported and captured in the maternal morbidity outcome indicator (Roberts et al., 2008). The investigation of psychological and physical health after PPH is limited as shown by the six studies included in a recent systematic review, in stark contrast to the many papers addressing prevention, treatment and risk factors for PPH (Carroll et al., 2016). The long term health consequences beyond a year of PPH and health implications aside from future fertility and mental health have been little studied to date (Gizzo et al., 2013; Ricbourg et al., 2015).

The majority of the recognized risk factors for PPH are specific to pregnancy, however preeclampsia is associated with hypertensive changes before and after pregnancy (Garovic and August, 2014). Given the risk of hypertensive disorders of pregnancy increasing the likelihood of PPH, it seems sensible to follow up women with PPH with regards to developing hypertension in later years as an independent risk factor itself. Likewise detailed follow up of mental health and psychiatric diagnosis following PPH is prudent given this association is already postulated in the literature.

An approach to identifying potential long terms ill effects of PPH as for novel risk factors is contingent on a plausible biological explanation. Hypertensive disease in pregnancy causes poor placentation, this combined with the higher mean arterial blood pressure could pre-dispose to brisker blood loss after delivery (Magnussen et al., 2009). The PPH episode might therefore unmask the potential for endothelial or vascular dysfunction that would otherwise remain a latent threat. The risk of poor cardiovascular health in women who have undergone PPH is a possibility on this basis. Development of mental illness following PPH could also be rooted in the experience of PPH and give rise to future ill health (Dunning, Harris and Sandall, 2016)

**Study 1: Exploring Novel risk factors for Postpartum Haemorrhage – a nested case-control study**

**Aims and hypotheses**

The aims of this study are to investigate if exposure to either antidepressant medication or exogenous hormonal contraception increases the odds of developing a PPH. We hypothesize that women exposed to either antidepressant or contraceptive medications are at increased risk of developing PPH.

**Study design**

Nested case-control study

**Data source**

The Health Improvement Network (THIN) is a large UK based primary care database. The THIN database has been extensively used in epidemiology studies and is representative of the UK population. In addition to information recorded in primary care we will use linked Hospital Episode Statistics (HES) data, as diagnosis of PPH is largely made and recorded in hospital settings.

**Sample selection**

All women between the ages of 15 and 49 years old that had a live birth between 2005-17and were registered for 36 consecutive months with the general practice contributing to THIN will be included. Known abnormal placentation, specifically placenta praevia, accreta, increeta, and percrreta will be excluded, as atonic PPH is the primary mechanism of interest. We will exclude women with a pregnancy code 21 months before the current pregnancy to ensure adequate exposure to contraception and order to reduce the likelihood of two pregnancies within a three-year period. See figure 1.

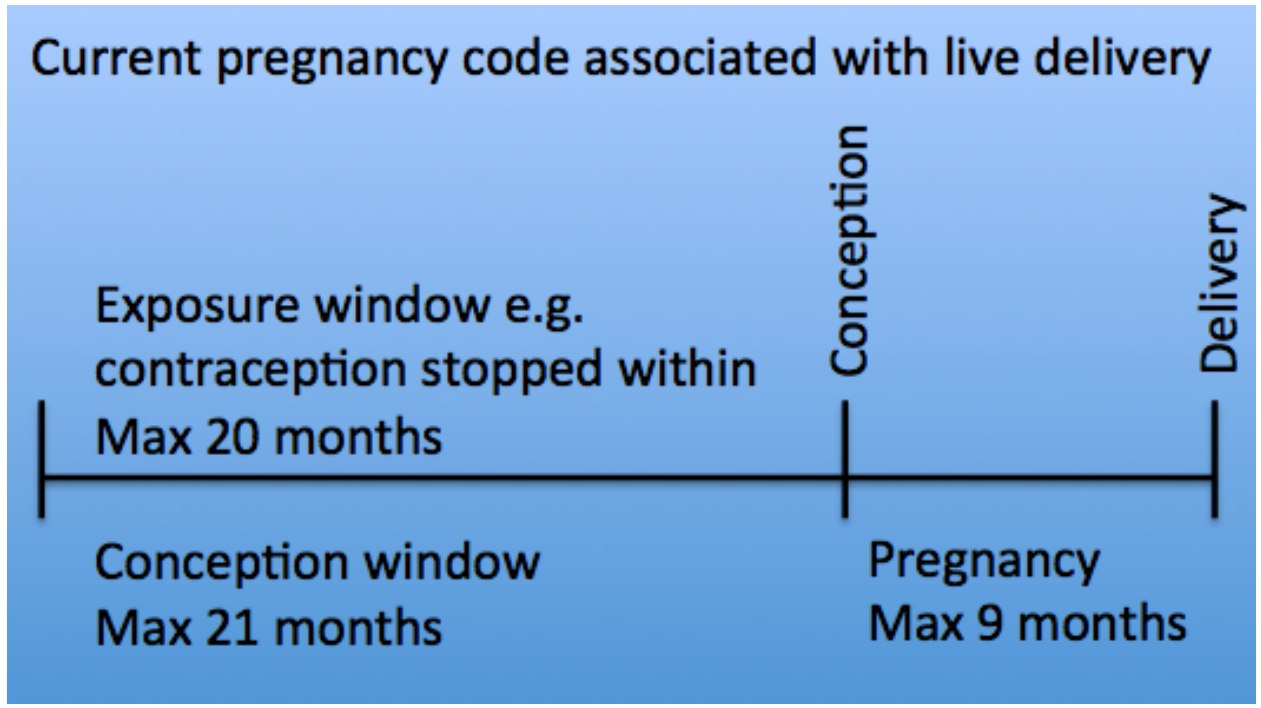



*Fig.1 Cohort exposure diagram*

*Selection of cases*

All women who have a diagnosis of PPH documented in either the THIN or HES data sets will be selected if they meet the inclusion criteria. We will use OPCS, ISC-10 codes in HES and READ codes in primary care for diagnosis and exposures of interest. We will expect that around 13% of the cohort will have a PPH recorded in HES linked data in line with the previously reported HES statistics.

*Selection of controls*

From the same cohort we will randomly select up to four controls matched for age, body mass index and Townsend score (a measure for deprivation). We will match registration date within 12 months and delivery date within 6 months.

Exposures - antidepressant and contraceptive medication

Women taking antidepressant or contraceptive medication will have a prescription drug code recorded on the THIN database alongside the date of the prescription. Prescriptions 30 months prior to the index outcome of PPH will be used to define exposure. 30 months includes 9 months gestation and a 21 months conception window (including time for return of ovulation, following cessation of contraceptive). We have chosen 30 months to ensure that only one term pregnancy can be likely achieved within the exposure timeframe.

Antidepressant medication codes will be classified as Monoamine oxidase inhibitors (MAOI), Selective serotonin reuptake inhibitors (SSRI), tricyclic (TCA) and 'other' antidepressants. The contraceptive codes will be divided into combined oral contraceptives (COCP), Progesterone only pills (POP), Intrauterine device (IUD), Intrauterine system (IUS), parenteral progesterone and contraceptive patches.

**Covariates**

Covariates that are independent predictors of outcome other than the exposure of interest will be selected on the basis of biological plausibility and previous literature as described above. These include maternal age, Body Mass Index (BMI), Townsend score, smoking status, hypertension (pre-existing and pregnancy induced), fibroids, parity, mode of delivery (caesarean and instrumental), ethnicity and pre-eclampsia.

**Statistical analysis and power calculation**

6000 patients will allow a 20% and 10% increase in PPH secondary to anti-depressant and contraceptive use respectively to be detected (alpha 0.05, 80% power). Baseline data of each category will be reported as mean (standard deviation) for continuous variables and as proportions for categorical variables. We will use conditional logistic regression to estimate ORs with 95% CIs for PPH. Where missing data exists we will create a separate category so that all available data is utilised in the analysis. All analysis will be performed in STATA 14.0.

**Limitations**

Measurement of blood loss and definition of post partum haemorrhage, is a challenge with recognised underestimation of blood loss.

A prescription issued for medication is not synonymous with taking the medication as prescribed.

The drug codes recorded can be incomplete.

**Study 2: Long term health effects of Postpartum Haemorrhage – a population-based open-cohort study**

## Aims

The aims of this study are to investigate if exposure to PPH increases the risk of mental and cardiovascular health problems.

## Study design

A population based open cohort study.

## Data source

The Health Improvement Network (THIN) in addition to information recorded in primary care we will use linked Hospital Episode Statistics (HES) data, as diagnosis of PPH is largely made and recorded in hospital settings.

## Study population

Women who have delivered between the ages of 15 and 49 years between 2005 and 2017. Patients will be selected if they have been registered at their practice for at least 12 months before entry to the study. Individuals with a diagnosis code for cardiovascular or mental health disease any time prior to delivery will be excluded as appropriate (e.g. those with mental health disease can be in the cohort investigating cardiovascular health and vice versa). For each woman exposed to PPH we will randomly select one to four control individuals matched for age, body mass index, smoking, and delivery within 6 months, Townsend score and registration year with a general practice contributing to THIN.

## Follow-up period

All women will be followed up for the maximum period available within the database.

## Outcomes

*Primary outcomes*

Hypertension or depression following PPH.

*Secondary outcomes*

Renal and cardiovascular disease, anxiety, post traumatic stress disorder, and psychosis following PPH.

Any women taking antidepressant or anti-hypertensive medication will have a prescription drug code recorded on the THIN database alongside the date of the prescription. The drug read codes will be generated from the THIN database codes and cross-referenced with the British National formulary. Antidepressant medication codes and anti-hypertensive codes plus diagnosis codes of hypertension, depression, anxiety, post traumatic stress disorder and psychosis will be used.

**Covariates**

Covariates that are independent predictors of outcome other than the exposure of interest will be selected on the basis of biological plausibility and previous literature. These included age, Body Mass Index (BMI), Townsend score (a measure for deprivation), smoking status, prior hypertension (pre-existing and pregnancy induced), prior mental illness, fibroids, parity, mode of delivery (caesarean and instrumental), ethnicity and pre-eclampsia.

**Statistical analysis**

Baseline data of each category will be reported as mean (standard deviation) for continuous variables and as proportions for categorical variables. Crude Incidence Rate Ratio (IRR) or Hazard Ratios (HR) and adjusted Incidence Rate Ratio (aIRR) or Hazard Ratios (aHR) will be calculated by applying Poisson regression/Cox regression offsetting for the person years of follow-up. Where missing data exists we will create a separate category so that all available data is utilised in the analysis. In order to demonstrate a 15% difference in the risk outcomes at an alpha of 0.05 and power of 0.8 a sample size of 1800 will be required. All analysis was performed in STATA 14.0.

**Limitations**

Measurement of blood loss and definition of post partum haemorrhage, is a challenge with recognized underestimation of blood loss.

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# ISEAC & SRC Feedback

**Researcher Name:** Dana Sumilo
**Organisation:** University of Birmingham
**ISEAC Reference Number:** 18THIN035
**Date:** 10th August 2018
**Study title:** An epidemiological study exploring novel risk factors and long-term health effects of Postpartum Haemorrhage.

**Committee opinion:** Approved

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**The following feedback has been supplied by ISEAC & SRC chairs.**

*Notes from the Chair:*

*Approved*

Approved documents:

| Approved document | Version | Date |
|---|---|---|
| SRC_Protocol_18THIN035_v1_29-03-2018 | 1 | 29/ |
| SRC_responses_18THIN035 | | |

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We are pleased to inform you of this approval allows you to proceed with the study.

Once the study has been completed and published, it is important for you to inform IQVIA in order for us to report back to NHS Digital.

Please remember to use the following statement in your published work:

**"Copyright © 2018, re-used with the permission of The Health & Social Care Information Centre. All rights reserved"**

References to all published studies are added to our website enabling other researchers to become aware of your work. In order to identify your study as using the relevant database, we recommend that you include the name of the database within your study title.

Copies of your full publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

pp. Mustafa Dungarwalla, IQVIA
(on behalf of, **ISEAC & SRC Chair**)

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