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

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

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Abstract

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

Ioannis Gallos,[1]* Helen Williams,[1] Malcolm Price,[2] Karen Pickering,[2] Abi Merriel,[1] Aurelio Tobias,[1] David Lissauer,[1] Harry Gee,[1] Özge Tunçalp,[3] Gillian Gyte,[4,5] Vidhya Moorthy,[1] Tracy Roberts,[2] Jonathan Deeks,[2] Justus Hofmeyr,[6] Metin Gülmezoglu[3] and Arri Coomarasamy[1]

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Background: Postpartum haemorrhage (PPH) is the leading cause of maternal mortality worldwide. Prophylactic uterotonic drugs can reduce blood loss and are routinely recommended. There are several uterotonic drugs for preventing PPH, but it is still debatable which drug or combination of drugs is the most effective.

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

Methods: The Cochrane Pregnancy and Childbirth's Trials Register (1 June 2015), ClinicalTrials.gov and the World Health Organization (WHO)'s International Clinical Trials Registry Platform (ICTRP) were searched for unpublished trial reports (30 June 2015). In addition, reference lists of retrieved studies (updated October 2017) were searched for randomised trials evaluating uterotonic drugs for preventing PPH. The study estimated relative effects and rankings for preventing PPH, defined as blood loss of $\geq$ 500 ml and $\geq$ 1000 ml. Pairwise meta-analyses and network meta-analysis were performed to determine the relative effects and rankings of all available drugs and combinations thereof [ergometrine, misoprostol (Cytotec®; Pfizer Inc., New York, NY, USA), misoprostol plus oxytocin (Syntocinon®; Novartis International AG, Basel, Switzerland), carbetocin (Pabal®; Ferring Pharmaceuticals, Saint-Prex, Switzerland), ergometrine plus oxytocin (Syntometrine®; Alliance Pharma plc, Chippenham, UK), oxytocin, and a placebo or no treatment]. Primary outcomes were stratified according to the mode of birth, prior risk of PPH, health-care setting, drug dosage, regimen and route of drug administration. Sensitivity analyses were performed according to study quality and funding source, among others. A model-based economic evaluation compared the relative cost-effectiveness separately for vaginal births and caesareans with or without including side effects.

Results: From 137 randomised trials and 87,466 women, ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were found to reduce the risk of PPH blood loss of ≥ 500 ml compared with the standard drug, oxytocin [ergometrine plus oxytocin: risk ratio (RR) 0.69, 95% confidence interval (CI) 0.57 to 0.83; carbetocin: RR 0.72, 95% CI 0.52 to 1.00; misoprostol plus oxytocin: RR 0.73, 95% CI 0.6 to 0.9]. Each of these three strategies had 100% cumulative probability of being ranked first, second or third most effective. Oxytocin was ranked fourth, with an almost 0% cumulative probability of being ranked in the top three. Similar rankings were noted for the reduction of PPH blood loss of ≥ 1000 ml (ergometrine plus oxytocin: RR 0.77, 95% CI 0.61 to 0.95; carbetocin: RR 0.70, 95% CI 0.38 to 1.28; misoprostol plus oxytocin: RR 0.90, 95% CI 0.72 to 1.14), and most secondary outcomes. Ergometrine plus oxytocin and misoprostol plus oxytocin had the poorest ranking for side effects. Carbetocin had a favourable side-effect profile, which was similar to oxytocin. However, the analysis was restricted to high-quality studies, carbetocin lost its ranking and was comparable to oxytocin. The relative cost-effectiveness of the alternative strategies is inconclusive, and the results are affected by both the uncertainty and inconsistency in the data reported on adverse events. For vaginal delivery, when assuming no adverse events, ergometrine plus oxytocin is less costly and more effective than all strategies except carbetocin. The strategy of carbetocin is both more effective and more costly than all other strategies. When taking adverse events into consideration, all prevention strategies, except oxytocin, are more costly and less effective than carbetocin. For delivery by caesarean section, with and without adverse events, the relative cost-effectiveness is different, again because of the uncertainty in the available data.

Limitations: There was considerable uncertainty in findings within the planned subgroup analyses, and subgroup effects cannot be ruled out.

Conclusions: Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin are more effective uterotonic drug strategies for preventing PPH than the current standard, oxytocin. Ergometrine plus oxytocin and misoprostol plus oxytocin cause significant side effects. Carbetocin has a favourable side-effect profile, which was similar to oxytocin. However, most carbetocin trials are small and of poor quality. There is a need for a large high-quality trial comparing carbetocin with oxytocin; such a trial is currently being conducted by the WHO. The relative cost-effectiveness is inconclusive, and results are affected by uncertainty and inconsistency in adverse events data.

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

Funding: Funding for this study was provided by the National Institute for Health Research Health Technology Assessment programme in a research award to the University of Birmingham and supported by the UK charity Ammalife (UK-registered charity 1120236). The funders of the study had no role in study design, data collection, data synthesis, interpretation or writing of the report.

Contents

List of tables

List of figures

List of abbreviations

CEAC	cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPCG	Cochrane Pregnancy and Childbirth Group
Hb	haemoglobin
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IU	international units
NCT	National Childbirth Trust
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	network meta-analysis
OR	odds ratio
PPH	postpartum haemorrhage
PPI	patient and public involvement
PRIME	Public and Researcher Involvement in Maternity and Early pregnancy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCOG	Royal College of Obstetricians and Gynaecologists
RR	risk ratio
RTS	room temperature stable
SUCRA	surface under the cumulative ranking curve
WHO	World Health Organization
WTP	willingness to pay

Plain English summary

Postpartum haemorrhage (PPH) is the most common reason why mothers die in childbirth worldwide. Although most healthy women can cope well with blood loss after birth, some do not, and this can pose a serious risk to their health and even life. To reduce blood loss after birth, the routine administration of a drug to contract the uterus (uterotonic) has become standard practice across the world. This research seeks to identify which is the most effective and cost-effective drug.

Different drugs have been used for reducing the occurrence of PPH. They include oxytocin, misoprostol, ergometrine, carbetocin, and combinations of these drugs, each with different effectiveness and side effects. The study synthesised the available evidence to compare all of these drugs and combinations thereof. After putting the results of all available comparisons together in a network, a ranking among them was calculated, and provided robust effectiveness and side-effect profiles for each drug and their associated costs.

The study included 137 randomised trials, involving a total of 87,466 women. The results suggested that ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin are the most effective strategies for preventing PPH and are more effective than the currently recommended drug, oxytocin. Each of these three strategies had almost 100% probability of being ranked first, second or third most effective. Oxytocin was ranked fourth with an almost 0% probability of being ranked in the top three. Ergometrine plus oxytocin and misoprostol plus oxytocin were the worst drug combinations for side effects, with carbetocin having the most favourable side-effect profile. Carbetocin could prevent approximately one further event of PPH out of three in comparison with oxytocin. However, existing carbetocin studies were small and of poor quality. There is need for a large high-quality study comparing carbetocin with the current standard treatment of oxytocin for the prevention of PPH. The cost analyses of the alternative drug strategies remain inconclusive.

Scientific summary

Background

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

Objectives

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

Methods

A systematic review was performed of randomised trials of pregnant women following a vaginal birth or caesarean section conducted in hospital and community settings. Included were trials of uterotonics administered prophylactically by health-care professionals for preventing PPH via any systemic route (sublingual, subcutaneous, intramuscular, rectal, oral, intravenous bolus and/or infusion) compared with another uterotonic or with placebo or no treatment. All drugs were stratified according to the mode of birth, prior risk of PPH, health-care setting, specific dosage, regimen and route of drug administration, to detect inequalities in subgroups that could affect comparative effectiveness. The study estimated relative effects and ranking of the competing interventions according to the prevention of PPH blood loss of $\geq$ 500 ml and $\geq$ 1000 ml as primary outcomes. Secondary outcomes included maternal mortality or morbidity, requirement for additional uterotonics, transfusion or manual removal of placenta, mean volumes of blood loss, mean durations of the third stage, changes in haemoglobin (Hb) measurements and patient-reported outcomes, such as clinical signs of excessive blood loss and side effects such as nausea, vomiting, hypertension, headache, tachycardia, hypotension, abdominal pain, fever and shivering in the first 24 hours post partum.

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

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

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

Results

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

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

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

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

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

Conclusions

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

Study registration

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

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Chapter 1 Background

Existing knowledge

Postpartum haemorrhage

An estimated 289,000 women worldwide died during childbirth in 2013.[1] Postpartum haemorrhage (PPH) is the leading direct cause of maternal death worldwide, accounting for up to one-third of all maternal deaths.[2] PPH is very common, affecting 1 in 10 women at childbirth in Europe and 67,000 women in England alone every year.[3,4] In the UK, death from PPH is usually averted, but it remains an important cause of severe morbidity (e.g. when receiving a blood transfusion) and surgery, including hysterectomy.[5]

The third stage of labour, defined as the period of time from birth until the birth of the placenta, and the immediate postpartum period are the most hazardous phases of childbirth because of the risk of PPH. The World Health Organization (WHO) defines PPH as blood loss exceeding 500 ml in the first 24 hours after birth.[6] Though healthy women can physiologically adapt to this amount of blood loss, for women with a coexisting disease, such as anaemia, it can cause considerable morbidity and mortality. The primary cause of PPH, as defined by WHO, is uterine atony, which accounts for 75% of cases.[7] Even though risk factors for adverse maternal outcomes from severe haemorrhage have been identified,[8] PPH is often unpredictable because it occurs in the absence of identifiable clinical or historical risk factors.[9] Therefore, effective prevention of PPH is advocated for all women during childbirth.[6] The routine administration of uterotonic drugs during the third stage of labour is a key intervention that prevents PPH, although there is uncertainty about which drug may be the most effective.

Uterotonic drugs

The active management of the third stage of labour refers to a package of interventions. The administration of uterotonic drugs to prevent PPH is the main intervention within this package and can prevent two-thirds of PPH.[6,10] Uterotonics are also essential for the treatment of PPH, but treatment is not the focus of this review.

Several different uterotonic drugs have been used for preventing PPH. These drugs include ergometrine, misoprostol (Cytotec®; Pfizer Inc., New York, NY, USA), misoprostol plus oxytocin (Syntocinon®; Novartis International AG, Basel, Switzerland), carbetocin (Pabal®; Ferring Pharmaceuticals, Saint-Prex, Switzerland), ergometrine plus oxytocin and oxytocin when used alone.

Oxytocin

Oxytocin is the most widely used uterotonic drug. At low doses, it produces rhythmic uterine contractions that are indistinguishable in frequency, force and duration from those observed during spontaneous labour; however, at higher dosages, it causes sustained tetanic uterine contractions.[11] It has a short half-life, approximately 3–5 minutes, and can be used as an infusion to maintain uterine contraction. When used intramuscularly, the latent phase lasts 2–5 minutes, but the uterine activity can last 2–3 hours.[11] However, oxytocin cannot be used orally. Oxytocin is unstable at room temperature and it requires cold storage and transport. It cannot be given intravenously as a large bolus, because it can cause severe hypotension.[12] Owing to its antidiuretic effect, water intoxication can occur with prolonged infusion of oxytocin.[11] Oxytocin has a favourable side-effect profile for common side effects, such as nausea and vomiting, but the evidence is scarce.[13]

Ergometrine

Ergometrine and methylergometrine are ergot alkaloids that increase the uterine muscle tone by causing continuous tetanic contractions. It takes 2–5 minutes after intramuscular injection for the drug to become effective and the plasma half-life is 30–120 minutes.[14] However, ergometrine and methylergometrine are

unstable in heat and cannot be used orally.[15] They are vasoconstrictive and increase the risk of hypertension post partum.[16] Other side effects with ergot alkaloids are pain after birth, nausea and vomiting.[16]

Misoprostol

Misoprostol is a prostaglandin E1 analogue that is licensed for the prevention and treatment of gastric ulcers. It is widely used off-label as a uterotonic agent.[17] It is water soluble and heat stable.[18] It takes 9–15 minutes after sublingual, oral, vaginal and rectal use for the drug to be effective. The half-life is about 20–40 minutes. Oral and sublingual routes have the advantage of rapid onset of action, whereas the vaginal and rectal routes result in prolonged activity and greater bioavailability.[19] However, misoprostol is associated with side effects, such as diarrhoea, abdominal pain, nausea and vomiting, shivering and pyrexia.[17]

Carbetocin

Carbetocin is a newer long-acting synthetic analogue of oxytocin with agonist properties. After intravenous injection, it produces tetanic uterine contractions within 2 minutes, lasting for approximately 6 minutes followed by rhythmic contractions for 60 minutes.[20] When carbetocin is administered by an intramuscular injection the tetanic contractions last for approximately 11 minutes and the rhythmic contractions for 120 minutes.[20] Carbetocin is heat stable and the side-effect profile appears to be similar to oxytocin.[21]

Combinations of uterotonic drugs

The use of combinations of uterotonic drugs is also popular and the most commonly used preparation is oxytocin plus ergometrine. This combination is suggested to be associated with a statistically significant reduction of PPH blood loss of $\geq$ 500 ml when compared with oxytocin alone, attributable to the additive ergometrine effect.[22] Another combination is oxytocin plus misoprostol, which is also found to be associated with a small reduction in PPH blood loss of $\geq$ 500 ml.[17] However, both these combinations are associated with significant side effects and, despite the small difference in PPH, there is no difference found for severe PPH when compared with oxytocin. This has led the WHO to recommend oxytocin over these combinations.[6]

The WHO recommends that all women giving birth should be offered uterotonics during the third stage of labour for the prevention of PPH; oxytocin [given intramuscularly/intravenously at a dose of 10 international units (IU)] is the uterotonic drug of choice.[6] Other injectable uterotonics and misoprostol are recommended as alternatives for the prevention of PPH in settings where oxytocin is not available.

Costs to the National Health Service

Treatment of PPH costs the NHS £32–180M per year. The National Institute for Health and Care Excellence (NICE) recently estimated the costs of treating PPH to be between £488 and £2700 for each woman, depending on the severity of PPH.[23] Treating PPH also has societal implications, as it can reduce economic productivity by causing physical disability or a psychological burden to parents and families. A relative risk reduction of 34% in PPH occurrence can represent a saving of £10–60M per year for the NHS, with important benefits for public health.

Existing research

Before conducting the search through Cochrane, a scoping literature search was conducted for trials and reviews of the use of uterotonics for preventing PPH. The databases MEDLINE, EMBASE, Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, ISI Proceedings, ISRCTN Register and *meta*Register of Current Controlled Trials were searched from the respective database inception to July 2014. The search terms aimed to capture trials assessing the effectiveness of uterotonic drugs to prevent PPH include 'post-partum period of haemorrhage', 'third stage of labour', 'caesarean section' and 'obstetric delivery' AND ('Oxytocin', 'misoprostol', 'ergometrine', 'syntometrine', 'carbetocin' and 'prostaglandins'). The scoping literature search had identified 445 randomised trials that could be eligible for inclusion in the network meta-analysis (NMA). There were five separate Cochrane reviews,[13,16,17,21,22] including an aggregate total of 115 trials and 77,447 participants,

that have compared a uterotonic drug against another or with a placebo or no treatment. These meta-analyses were suggesting that oxytocin plus ergometrine [odds ratio (OR) 0.82, 95% confidence interval (CI) 0.71 to 0.95], oxytocin plus misoprostol [risk ratio (RR) 0.71, 95% CI 0.53 to 0.95] and carbetocin (RR 0.66, 95% CI 0.42 to 1.06) may be more effective than oxytocin in preventing PPH. The Cochrane reviews were pairwise meta-analyses and, therefore, could only compare two drugs that have been compared directly in head-to-head trials (direct evidence), did not make use of the large amount of indirect evidence available and could not always be used for drawing inferences across all the possible comparisons. In the absence of a single randomised controlled trial comparing all uterotonic drugs, uncertainty remained over their relative effectiveness and ranking.

The existing Cochrane reviews were also becoming out of date. In total, 58 new trials ($n = 22,071$ participants) were identified that could be eligible for inclusion in these reviews and 43 active randomised trials ($n = 63,326$ participants) due for completion before the end of 2015 (*Table 1*). These were assessed for inclusion in the NMA in addition to the existing evidence (see *Figure 1*).

A systematic review and a NMA were performed synthesising all available, up-to-date direct and indirect evidence of relative treatment effects in a single coherent analysis for all uterotonic drugs. Indirect evidence is obtained when the relative effectiveness of two competing drugs is inferred through a common comparator, even though this pair may not have been compared directly.[24] The NMA aimed to provide robust estimates or relative effectiveness, side-effect profile and the relative ranking for each uterotonic drug with a model-based economic evaluation.

TABLE 1 Cochrane reviews comparing uterotonic drugs for preventing PPH

Cochrane review (first author and date of publication)	Included trials (number of participants)	Latest search update	Available comparisons	Trials awaiting classification (number of participants)	Active trials to be completed by December 2015 (number of participants)
Liabsuetrakul *et al.*,[16] 2007	6 ($n = 1996$)	30 April 2011	Ergometrine vs. placebo or no treatment	2 ($n = 340$)	0
McDonald *et al.*,[22] 2004	6 ($n = 9332$)	30 April 2007	Oxytocin plus ergometrine vs. oxytocin	4 ($n = 946$)	3 ($n = 6860$)
Su *et al.*,[21] 2012	11 ($n = 2635$)	1 March 2011	Carbetocin vs. oxytocin	20 ($n = 5898$)	17 ($n = 41,583$)
			Carbetocin vs. oxytocin plus ergometrine		
Tunçalp *et al.*,[17] 2012	72 ($n = 52,678$)	7 January 2011	Misoprostol vs. oxytocin	24 ($n = 10,666$)	15 ($n = 8067$)
			Misoprostol vs. ergometrine		
			Misoprostol vs. placebo or no treatment		
			Misoprostol vs. oxytocin plus ergometrine		
			Misoprostol vs. oxytocin plus misoprostol		
Westhoff *et al.*,[13] 2013	20 ($n = 10,806$)	21 May 2013	Oxytocin vs. placebo or no treatment	8 ($n = 4221$)	8 ($n = 6816$)
			Oxytocin vs. ergometrine		
			Oxytocin plus ergometrine vs. ergometrine		
Total	115 ($n = 77,447$)			58 ($n = 22,071$)	43 ($n = 63,326$)

Objectives

Primary

To identify the most effective and cost-effective uterotonic drug(s) to prevent PPH, and to generate a clinically useful ranking of available uterotonics according to their effectiveness.

Secondary

1. To provide the relative effectiveness and side-effect profile of each drug for the primary outcomes within (1) treatment subgroups (different dosages and regimens and routes of administration of each uterotonic drug), and (2) population subgroups (prior risk of PPH, mode of birth and health-care setting).
2. To produce effectiveness and side-effect hierarchies of all uterotonic drugs considered, and to estimate the probability that each drug is the best for each outcome.
3. To evaluate the cost-effectiveness for each drug for preventing PPH overall and in the subgroups defined earlier in the UK.

Chapter 2 Review methods

Criteria for considering studies for this review

Types of studies

All randomised controlled comparisons or cluster trials of effectiveness or side-effects of uterotonic drugs for preventing PPH were included. Quasi-randomised trials and crossover trials were excluded.

Types of participants

The review included studies of pregnant women following a vaginal birth or caesarean section conducted in hospital and community settings.

Types of interventions

The study considered trials of uterotonic drugs, described by the WHO (ergometrine, misoprostol, misoprostol plus oxytocin, carbetocin, ergometrine plus oxytocin, oxytocin and a placebo or no treatment), administered prophylactically by health-care professionals for preventing PPH via any systemic route (sublingual, subcutaneous, intramuscular, rectal, oral, intravenous bolus and/or infusion) compared with another uterotonic drug or with a placebo or no treatment. Trials were included in which non-pharmacological co-interventions, such as controlled cord traction, cord clamping or uterine massage, were performed as a randomised intervention in all arms of the trial and the effects of such co-interventions were tested through a sensitivity analysis. All drugs were stratified according to mode of birth, prior risk of PPH, health-care setting and specific dosage, regimen and route of drug administration to detect inequalities in subgroups that could affect comparative effectiveness.

Multiarm trials that compared different dosages, regimens or routes of one uterotonic drug, but also compared any of these drugs versus another uterotonic drug, were included. Intervention arms of different dosages, regimens or routes of administration of the same uterotonic drug were merged together for the global analysis of all outcomes and treated as separate independent comparisons for only the relevant subgroup analysis according to dosage, regimen and route of drug administration, while considering the correlation between the comparisons. Trials comparing exclusively different dosages, regimens or routes of drug administration of the same uterotonic drug were excluded. The review was restricted to studies evaluating uterotonic drugs administered systemically at the birth of the baby to prevent PPH. Studies considering non-uterotonic drugs, uterotonic drugs administered locally (e.g. via intraumbilical or intrauterine routes) or at a later stage of birth (e.g. for the treatment of PPH or for retained placenta) were excluded.

For this review, it was assumed that any woman that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the eligible uterotonic drugs.

Types of outcome measures

The study estimated the relative effects and ranking of the competing interventions according to the following outcomes.

Primary outcomes

The primary outcomes of the review were:

- PPH blood loss of $\geq$ 500 ml
- PPH blood loss of $\geq$ 1000 ml.

Secondary outcomes

The secondary outcomes of the review were:

- maternal deaths
- maternal deaths or severe morbidity events adapted from the WHO's 'near-miss' criteria[25] to include major surgery [laparotomy, uterine artery ligation, internal iliac artery ligation, B-Lynch suture, hysterectomy, extensive vaginal repair, admission to the intensive care unit or vital organ failure (temporary or permanent)]
- additional uterotonics requirement
- transfusion requirement
- manual removal of the placenta
- mean volume of blood loss (ml)
- mean duration of the third stage of labour (minutes)
- change in haemoglobin (Hb) measurements before and after birth (g/l)
- clinical signs of excessive blood loss (as defined by the triallists)
- neonatal unit admission requirement
- breastfeeding at discharge
- side effects, such as nausea, vomiting, hypertension, headache, tachycardia, hypotension, abdominal pain, fever and shivering, in the first 24 hours post partum.

There are two primary outcomes for this NMA: a PPH blood loss of $\geq$ 500 ml and $\geq$ 1000 ml. The former is the WHO's definition[6] of PPH, but the latter was considered as one of the three critical outcomes (together with blood transfusion and maternal death) for the WHO's recommendations[6] for PPH prevention in which outcomes were rated by an independent panel.

Data sources

Electronic searches

The trials search co-ordinator for the pregnancy and childbirth group performed the search (September 2015) using their trials register, which contained trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) weekly searches of MEDLINE (via Ovid)
2. weekly searches of EMBASE (via Ovid)
3. monthly searches of the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EBSCO*host*)
4. hand-searches of 30 journals and the proceedings of major conferences
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central e-mail alerts.

Details of the search strategies for CENTRAL, MEDLINE, EMBASE and CINAHL, the list of hand-searched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialised Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group (CPCG).[26] Trials identified through the searching activities described above are each assigned to a review topic (or topics). The trials search co-ordinator searched the register for each review using the topic list rather than keywords (see *Appendix 1*).

In addition, ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform (ICTRP) were searched for unpublished trial reports. The search terms we used are given in *Appendix 1*.

Searching other resources

Additional relevant references cited in papers, identified through the above search strategy, were retrieved and the full texts of trials initially identified as abstracts were searched. Information was sought from primary authors to investigate whether or not these studies met the study's eligibility criteria, and to obtain outcome and study data. Trials that compared at least two of the drugs were eligible and all possible comparisons formed by the drugs of interest were searched for. No language or date restrictions were applied.

Study selection

Three review authors retrieved and independently assessed for inclusion all the potential studies that were identified (IDG, AM and HW). Any disagreements were resolved through discussion or, if required, in consultation with a fourth person (AC). A study flow diagram was created to map out the number of records identified, included and excluded (*Figure 1*).

Data extraction

An electronic form was designed on Microsoft Access® 2010 (Microsoft Corporation, Redmond, WA, USA) to extract data. For eligible studies, at least three review authors independently extracted the data using a blank electronic form (IDG, HW, AM, DL, HG or OT). Discrepancies were resolved through discussion or, if required, another person (AC) was consulted. Data were entered into Stata® version 14 (StataCorp LP, College Station, TX, USA) and Review Manager software 5.2 [2014 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark)] and checked for accuracy. When information was unclear, an attempt was made to contact authors of the original reports to provide further details.

Data extracted

Outcome data

From each included study the number of participants, the gestational age and parity of participants, and any exclusion criteria were extracted. In addition, the interventions being compared and their respective primary and secondary outcomes were extracted. All relevant arm-level data were extracted (e.g. number of events and number of patients for binary outcomes).

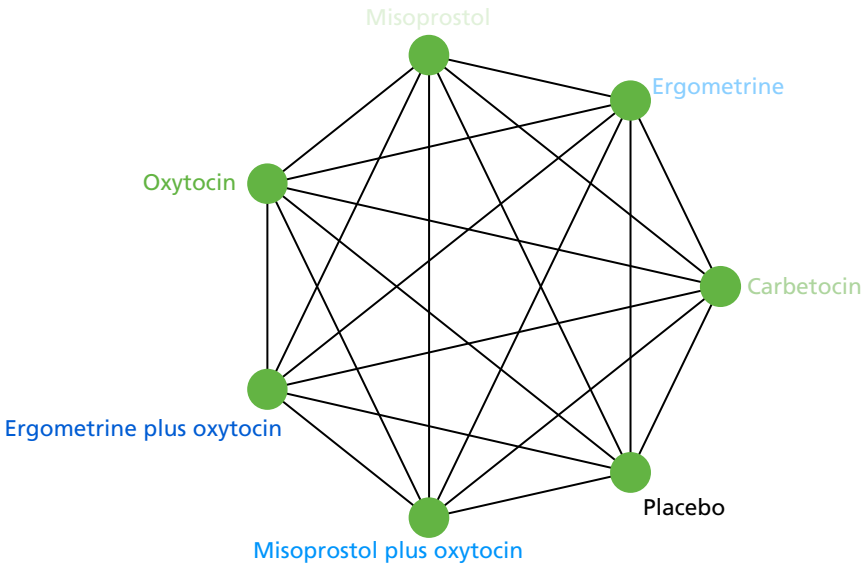

FIGURE 1 Network plot of eligible drug comparisons for the prevention of PPH.

Data on potential effect modifiers

From each included study the following data were extracted that may have acted as effect modifiers:

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

Other data

From each included study the following additional information was extracted:

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

Critical appraisal

At least three (IDG, HW, AM, DL, HG or OT) review authors independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[27] Any disagreements were resolved by discussion or by involving a third assessor (AC).

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

For each included study, the methods used to generate the allocation sequence in sufficient detail to allow an assessment of whether or not the study should produce comparable groups were described. Trials rated as being at a high risk of bias for allocation sequence generation were excluded from the review (any non-random process, e.g. odd or even date of birth, hospital or clinic record number).

The methods were assessed as being at:

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

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

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

The methods were assessed as being at:

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

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

For each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received were described. Studies were considered as being at a low risk of bias if they were blinded or, if judged, that the lack of blinding would be unlikely to have affected the results.

The methods were assessed as being at a:

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

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

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

The methods used to blind outcome assessment were assessed as being at a:

- low, high or unclear risk of bias.

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

For each included study, and for each primary outcome, the completeness of data, including attrition and exclusions from the analysis, was described. The reasons were stated for attrition and exclusions and the numbers included in the analysis at each stage (compared with the total randomised participants), and a judgement was made on whether missing data were balanced across groups or were related to outcomes.

The methods to handle incomplete outcome data were assessed as being at a:

- low risk of bias (e.g. no missing outcome data or missing outcome data balanced across groups and < 10% of missing outcome data)
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups, 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation or > 10% of missing outcome data)
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

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

The methods were assessed as being at a:

- low risk of bias (in which it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review had been reported)
- high risk of bias (in which not all the study's prespecified outcomes had been reported, one or more reported primary outcomes were not prespecified, outcomes of interest were reported incompletely and so could not be used, or the study failed to include results of a key outcome that would have been expected to have been reported)
- unclear risk of bias.

(6) Other bias [checking for bias caused by problems not covered by (1) to (5)]

For each included study any important concerns about other possible sources of bias, such as the source of funding and potential conflicts of interest, were described.

The interests were assessed as being at a:

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

Another source of bias could be generated by the method of measuring blood loss. An assessment was made of the method described in each study and it was classified as being at a:

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

(7) Overall risk of bias

Explicit judgements were made about whether or not studies were rated as being at a high risk of bias, according to the criteria given in the Cochrane handbook.[27] With reference to (1)–(6), the likely magnitude and direction of the bias, and whether or not the magnitude and direction of the bias was considered to have an impact on the findings were assessed. For the primary outcomes, quality items and judged trials were rated as being at a 'low risk of bias' if they were double-blinded and had allocation concealment, with little loss to follow-up (< 10%). Trials were judged as being at an 'intermediate risk of bias' if they demonstrated adequate allocation concealment, with assessor blinding and little loss to follow-up (< 10%). Alternatively, trials were considered to be at a 'high risk of bias'. See *Sensitivity analysis* for information about how this risk of bias has impacted the results.

Measures of treatment effect

Relative treatment effects

Relative treatment effects were summarised for dichotomous outcomes as the RR and 95% CIs. For continuous scales of measurement, the mean difference with 95% CIs was used.[28]

Relative treatment ranking

The ranking probabilities were estimated for all treatments of being at each possible rank for each intervention, then a treatment hierarchy was obtained using the surface under the cumulative ranking curve (SUCRA).[29] The SUCRA index can also be expressed as a percentage interpreted as the percentage of effectiveness or side effects of a treatment that would be ranked first without uncertainty.

Unit of analysis

Cluster randomised trials

Cluster randomised trials were included in the analyses along with individually randomised trials. The standard errors of the trials were adjusted using the methods described in the Cochrane handbook using an estimate of the intracluster correlation coefficient derived from the trial.[27] It was considered reasonable to combine the results from cluster randomised and individually randomised trials, as there is little heterogeneity between the study designs and any interaction between the relative effects of interventions and the choice of randomisation unit is considered to be unlikely. However, performed sensitivity analyses were performed to assess the validity of this assumption for the primary outcomes.

Crossover trials

This type of trial was not deemed appropriate for this intervention.

Multiarm trials

Multiarm trials were included and the correlation between the effect sizes were accounted for in the NMA. Multiarm studies were treated as multiple independent comparisons in pairwise meta-analyses.

Dealing with missing data

For included studies, levels of attrition were noted. The impact of including studies with high levels of missing data was explored in the overall assessment of treatment effect by using sensitivity analyses. For all outcomes, analyses were carried out, as far as possible, on a modified intention-to-treat basis, that is, all participants randomised to each group were included 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. The number of participants randomised minus any participants whose outcomes are known to be missing was used as the denominator for each outcome in each trial. No assumptions or imputations were made for the missing outcomes. If any participants were inappropriately excluded by the triallists from the analysis, and the data were available, these participants were reincluded in the analyses.

Assessment of clinical and methodological heterogeneity within treatment comparisons

To evaluate the presence of clinical heterogeneity, descriptive statistics were generated for each trial and study population characteristics across all included trials that compare each pair of interventions. The presence of clinical heterogeneity was assessed within each pairwise comparison by comparing these characteristics.

Assessment of transitivity across treatment comparisons

The assumption of transitivity was assessed by comparing the distribution of potential effect modifiers across the different pairwise comparisons. In this context it was expected that the transitivity assumption holds assuming the following: (1) the common treatment used to compare different uterotonics indirectly is similar when it appears in different trials (e.g. oxytocin is administered in a similar way in oxytocin vs. misoprostol trials and in oxytocin vs. oxytocin plus ergometrine trials); and (2) all pairwise comparisons do not differ with respect to the distribution of effect modifiers (e.g. the design and study characteristics of oxytocin vs. misoprostol trials are similar to oxytocin vs. oxytocin plus ergometrine trials). The assumption of transitivity is evaluated epidemiologically by comparing the clinical and methodological characteristics of sets of studies grouped by treatment comparisons.

Assessment of reporting biases

Potential reporting bias was evaluated for the primary outcomes by assessing the sensitivity of results to exclusion of studies with < 400 participants.

Data synthesis

Methods for direct treatment comparisons

Initially, standard pairwise meta-analyses were performed using a random-effects model,[30] in Stata, for every treatment comparison with at least two studies.

Methods for indirect and mixed comparisons

The NMA was performed within a frequentist framework using multivariate meta-analysis models.[31] All analyses were carried out using Stata statistical software, version 14. The network suite of Stata commands designed for this purpose was used.[32] The a priori belief was that a random-effects model is more appropriate because a degree of clinical heterogeneity between trials was expected.

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity

In pairwise meta-analyses different heterogeneity variances were estimated for each pairwise comparison. In the NMA, a common estimate was assumed for the heterogeneity variance across the different comparisons, by defining a proportional between-studies variance–covariance matrix.[31]

Measures and tests for heterogeneity

The presence of heterogeneity was statistically assessed within each pairwise comparison for the primary outcomes using the I^2-statistic, which measures the percentage of variability that cannot be attributed to random error.[33] The assessment of statistical heterogeneity in the entire network is based on the magnitude of the heterogeneity variance parameter estimated from the multivariate meta-analysis model.

Assessment of statistical inconsistency

To check the assumption of consistency in the entire network, the 'design-by-treatment' interaction model, as described by Higgins *et al.*,[34] was used. This model accounts for a different source of inconsistency that can occur when studies with different designs (i.e. two-arm trials vs. three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach, the presence of inconsistency was inferred from any source in the entire network based on a chi-squared test.

Investigation of heterogeneity and inconsistency

When important heterogeneity and/or inconsistency was found, the possible sources for primary outcomes were explored. Databases were rechecked for mistakes and inconsistencies in data extraction and entry. When sufficient studies were available, multivariate meta-analyses or subgroup analyses were performed by using the following potential effect modifiers as possible sources of inconsistency and/or heterogeneity:

- Population – prior risk of PPH (high vs. low), mode of birth (vaginal birth vs. caesarean section) and setting (hospital vs. community).
- Intervention – dose, regimen and route.
- Quality of the studies – studies are rated as being at a 'low risk of bias' if they are double-blinded and have allocation concealment with little loss to follow-up (< 10%). The concealed studies with assessor blinding and little loss to follow-up (< 10%) are rated as being at an 'intermediate risk of bias' and the rest are rated as being at a 'high risk of bias'. Assessor blinding was considered to be very important, in order to eliminate any risk of bias in subjective measurements or estimates of blood loss (not all studies measure this outcome objectively). Protocol publication was considered in advance of the results to be an unsuitable criterion for sensitivity analyses, because protocol publication has only became widespread in recent years.
- Funding source – high versus low risk of bias.
- Whether or not an objective method of outcome assessment was employed (objective vs. subjective) Objective methods of blood loss measurement were considered to be all methods that employed a measurement of the blood loss. This is in contrast to subjective methods, in which a health-care professional is estimating the blood loss, usually visually.
- Trial size – excluding small studies, in recognition of the greater likelihood for small studies than large or multicentre studies to suffer publication bias. In terms of trial size, there is evidence that smaller studies can exaggerate estimated benefits.[35] However, the cut-off point for deciding the definition of a small study can vary between research topics. For this topic, it appears that trials with > 400

participants were more likely to be rated as being of higher quality, prospectively registered and, overall, being rated as at a low risk of bias.
- Randomisation unit – cluster versus individual.

Subgroup analysis

For the primary outcomes, the following subgroup analyses were carried out:

- population – prior risk of PPH (high vs. low), mode of birth (vaginal birth vs. caesarean section) and setting (hospital vs. community)
- intervention – dose, regimen and route.

Subgroup differences were assessed by evaluating the relative effects and assessing model fit.

Sensitivity analysis

For the primary outcomes, sensitivity analysis was performed for the following:

- the quality of the studies (as described previously)
- funding source (as described previously)
- whether or not an objective method of outcome assessment was employed
- trial size (as described previously)
- trials that randomised participants to co-interventions, such as uterine massage or controlled cord traction
- trials with > 10% missing data
- trials published before 1990
- randomisation unit (cluster vs. individual)
- choice of relative effect measure (RR vs. OR)
- use of fixed-effects versus random-effects model.

Differences were assessed by evaluating the relative effects and assessing model fit.

Changes to the protocol

Preliminary protocol development

1. 26 February 2014: meta-analytic title registration (not including cost-effectiveness analysis) with the Cochrane Collaboration.
2. 5 September 2014: submission of the initial study proposal, including cost-effectiveness analysis, to the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme.
3. 10 January 2015: submission of a more detailed study proposal, including cost-effectiveness analysis to the NIHR HTA programme (recommendation for funding 5 February 2015).

Publication of protocol

1. 22 April 2015: finalisation of the comprehensive study protocol, including cost-effectiveness analysis, for the NIHR HTA programme, version 1.0
2. 30 April 2015: typographic corrections only to the comprehensive study protocol, including cost-effectiveness analysis for the NIHR HTA programme, version 1.1
3. 18 May 2015: publication of the meta-analytic protocol (not including the cost-effectiveness analysis) by the Cochrane Collaboration [contents in accordance with *(4) Incomplete outcome data (checking for possible attrition bias caused by the amount, nature and handling of incomplete outcome data)* and *(5) Selective reporting (checking for reporting bias)* above; available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011689/pdf (accessed 25 April 2018)].

Changes post publication

1. November 2016: submission of the NMA and cost-effectiveness analysis to the NIHR HTA programme, with meta-analysis performed in Stata rather than WinBUGS (MRC Biostatistics Unit, Cambridge, UK) for reasons of future reproducibility.

Patient and public involvement

The study team undertook patient and public involvement (PPI) primarily as consultation and collaboration to ensure that the study objectives and outcomes appropriately reflected the priorities of maternity service users. This was also undertaken to disseminate any findings of relevance to women of reproductive age and a wider public. The study team sought, and drew on, the contributions of lay stakeholders to conceive and develop the project, with facilitation from Gillian Gyte, who is the consumer editor of the CPCG and is a long-standing member of the National Childbirth Trust (NCT). Comments and suggestions were collected from the CPCG consumer panel via editorial feedback to the systematic review protocol prior to publication of this document and, subsequently, from the CPCG consumer panel and NCT representatives. Gillian Gyte established a study-specific PPI group (a group of women with experience of childbirth and willing to comment on provisional drafts of this report and the Cochrane review). The group comprised 10 women, six of whom had experienced PPH. These women also contributed to the *Plain English summary* of this report and the plain language summary of the Cochrane review.[36] Comments and suggestions were also collected from the Public and Researcher Involvement in Maternity and Early pregnancy (PRIME) research group. The comments and suggestions were collected, in April 2016, from 19 members, at a face-to-face meeting of the PRIME research group.

Overall, the women and parents who contributed to the study articulated the belief that reducing the occurrence of PPH is a top priority for preserving maternal well-being and endorsed the study objectives to identify the most effective uterotonic agent with minimal side effects. The women and parents encouraged the research team to evaluate additional outcomes, including women's views regarding the drugs used, clinical signs of excessive blood loss, abdominal pain after birth, neonatal unit admissions and breastfeeding.

Chapter 3 Results

Study selection

The results of the search strategy are summarised in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (*Figure 2*). Included in this systematic review are 137 randomised trials for a total of 87,466 women (see *Appendix 2* for details).[37–173] Excluded, with reasons, are 133 randomised trials; the specific references and reasons for exclusion are given in *Appendices 3–6*.

The authors were contacted from 93 primary randomised trials for additional data or clarifications and, for 38 randomised trials, they were able to add to this review data not reported in the published reports (see *Appendix 7* for unpublished data from triallists). In October 2017, an updated CPCG Register search was carried out that retrieved an additional 85 trial reports listed under studies awaiting classification.

Study characteristics

Study characteristics of participants and interventions for the 137 included studies are reported in *Appendix 2*. Most studies were reported in English and seven translations were obtained (four Spanish, two French, two Turkish and one Chinese). The studies were conducted in various countries and often involved more than one country. The UK was the country where most studies were conducted (i.e. 11 studies). A number of multiarm trials were identified: two five-arm trials, five four-arm trials and 14 three-arm trials (see *Appendix 3*). The median size of the trials was 250 participants (interquartile range 140–602 participants).

Included trials involved women undergoing a vaginal birth in 102 out of 137 trials (74.5%) and 35 trials (25.5%) involved women undergoing elective or emergency caesareans. Women included in the trials were judged to be at high risk for PPH in 42 out of 137 trials (30.7%), at low risk in 42 out of 137 trials (30.7%) and at either high or low risk in 48 out of 137 trials (35%). The risk for PPH was not specified in five trials (3.6%). There were 132 trials conducted in the hospital setting (96.4%), with only four community trials (2.9%) and one (0.7%) with a mixed setting.

The gestational ages included in the trials were not specified in 67 out of 137 trials (48.9%) and, when it was specified, 32 trials (23.4%) included term pregnancies with the remaining 38 trials (27.7%) including women with both preterm and term pregnancies. There were 81 trials (59.1%) that included women with a singleton pregnancy, 21 trials (15.3%) that included women with either singleton or multiple pregnancies and 35 trials (25.6%) did not specify this criterion. Three trials (2.2%) included only nulliparous or primigravida women, 34 trials (24.8%) included women of varying parity and 100 trials (73%) did not specify the parity of the

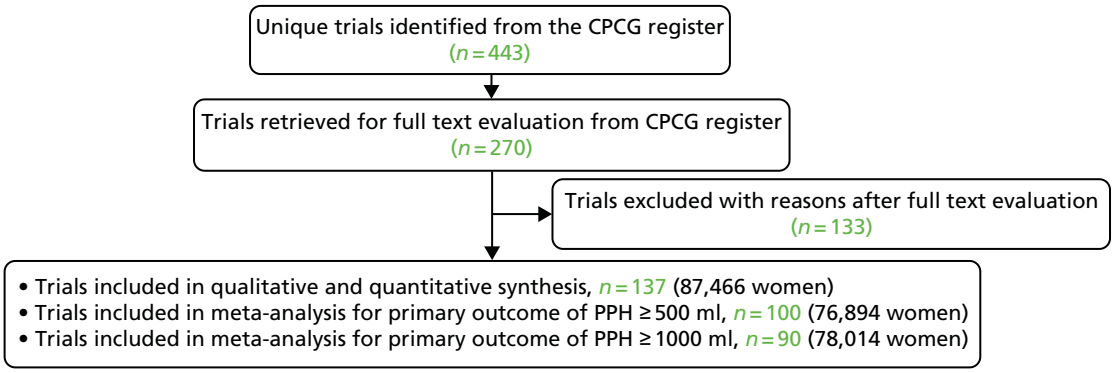

FIGURE 2 The PRISMA study flow diagram.

women included in the trials. Exclusion criteria varied significantly and often encompassed women with significant medical comorbidities.

Risk of bias in included studies

Summaries of the methodological quality of the included studies are presented for each of the domains that were assessed across all studies (*Figure 3*) and for each included study (*Figure 4*).

Random sequence generation

Trials with evidence of inadequate random sequence generation were excluded from this review. As a result, 99 out of 137 included trials (72.3%) were found to have used an adequate method of generating the random sequence and were rated as being at a low risk of bias. However, 38 trials (27.7%) did not report the method used in sufficient detail and the risk of bias was rated as being unclear.

Allocation concealment

Out of 137 trials, 70 (51.1%) reported adequate methods for allocation concealment and were rated as being at a low risk of bias, and 67 trials (48.9%) did not provide enough information to assess allocation concealment and the risk of bias was rated as being unclear.

Blinding of participants and personnel

There were 59 out of 137 trials (43.1%) reporting adequate methods for blinding both participants and personnel to treatment allocation, and 29 trials (21.2%) were rated as being at a high risk of bias for blinding of participants and personnel. A further 49 trials (35.8%) did not provide enough information to assess the blinding of participants and personnel and the risk of bias was rated as being unclear.

Blinding of outcome assessment

For blinding the assessment of the primary outcomes, 56 out of 137 trials (40.9%) reported adequate methods, and 11 (8%) were rated as being at a high risk of bias for blinding the assessment of the primary outcomes. Seventy trials (51.1%) did not provide enough information for blinding the assessment of the primary outcomes and the risk of bias was rated as being unclear.

Incomplete outcome data

There were 94 out of 137 trials (68.6%) that were rated as being at a low risk of bias. In these trials, missing outcome data were < 10% and balanced in numbers across intervention groups, with similar reasons for missing data across groups. In 11 trials (8%), > 10% of patients dropped out or were not analysed as per the intention-to-treat principles following randomisation, indicating as being at a high risk of bias. Moreover, 32 trials (23.4%) did not provide enough information to be assessed, so it was uncertain whether or not the handling of incomplete data was appropriate, and the risk of bias was rated as being unclear in these trials.

Selective reporting

Only 14 out of 137 trials (10.2%) prespecified all outcomes in publicly available study protocols and were rated as being at a low risk of bias. Ten trials (7.3%) did not report all prespecified outcomes as reported in their published protocols or methodology within the main report and were rated as being at a high risk of bias for selective reporting. For most trials [i.e. 113 trials (82.5%)], it was not possible to trace a published protocol and the risk of bias was rated as being unclear.

Other bias (source of funding and conflicts of interest)

Several trials [i.e. 47 out of 137 (34.3%)] were conducted with either public or no funding and did not declare potential conflicts of interest. Eight trials (5.8%) were rated as being at a high risk of bias, as they were funded directly by the pharmaceutical industry. Eighty-two trials (59.9%) did not provide enough information to assess the source of funding or potential conflicts of interest and the risk of bias was rated as being unclear.

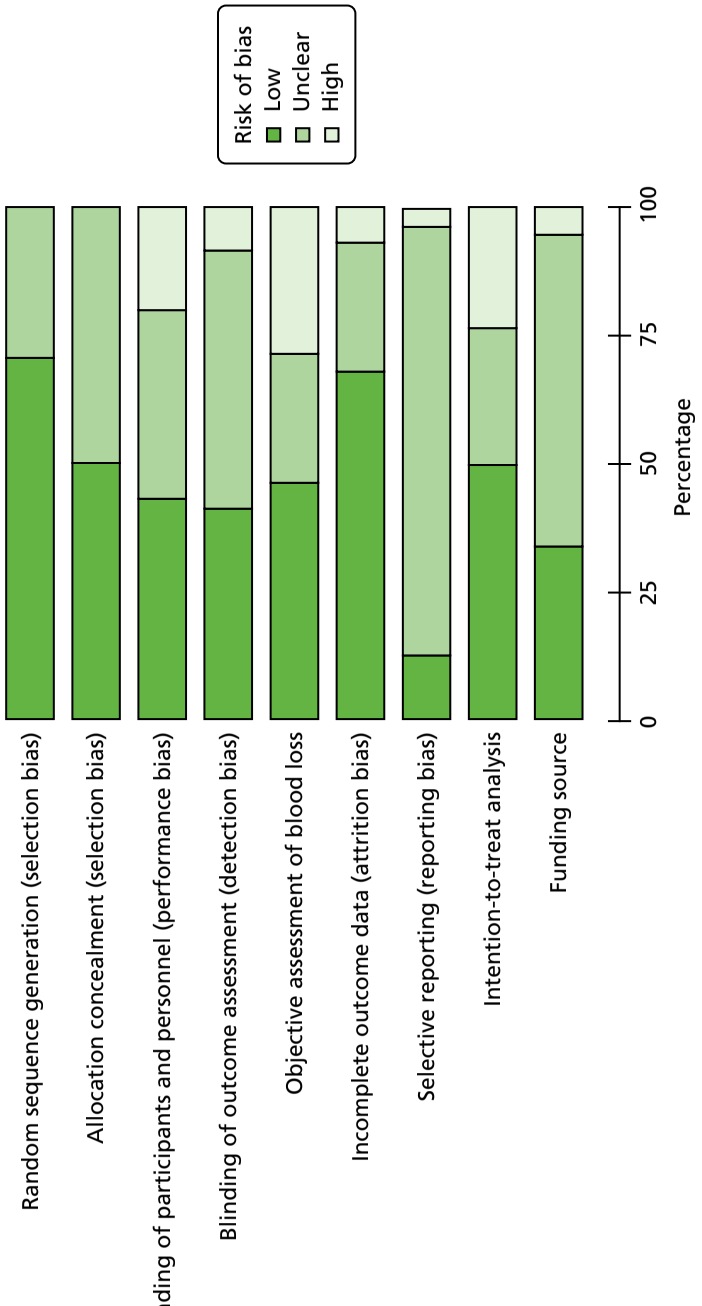

FIGURE 3 Risk-of-bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies.

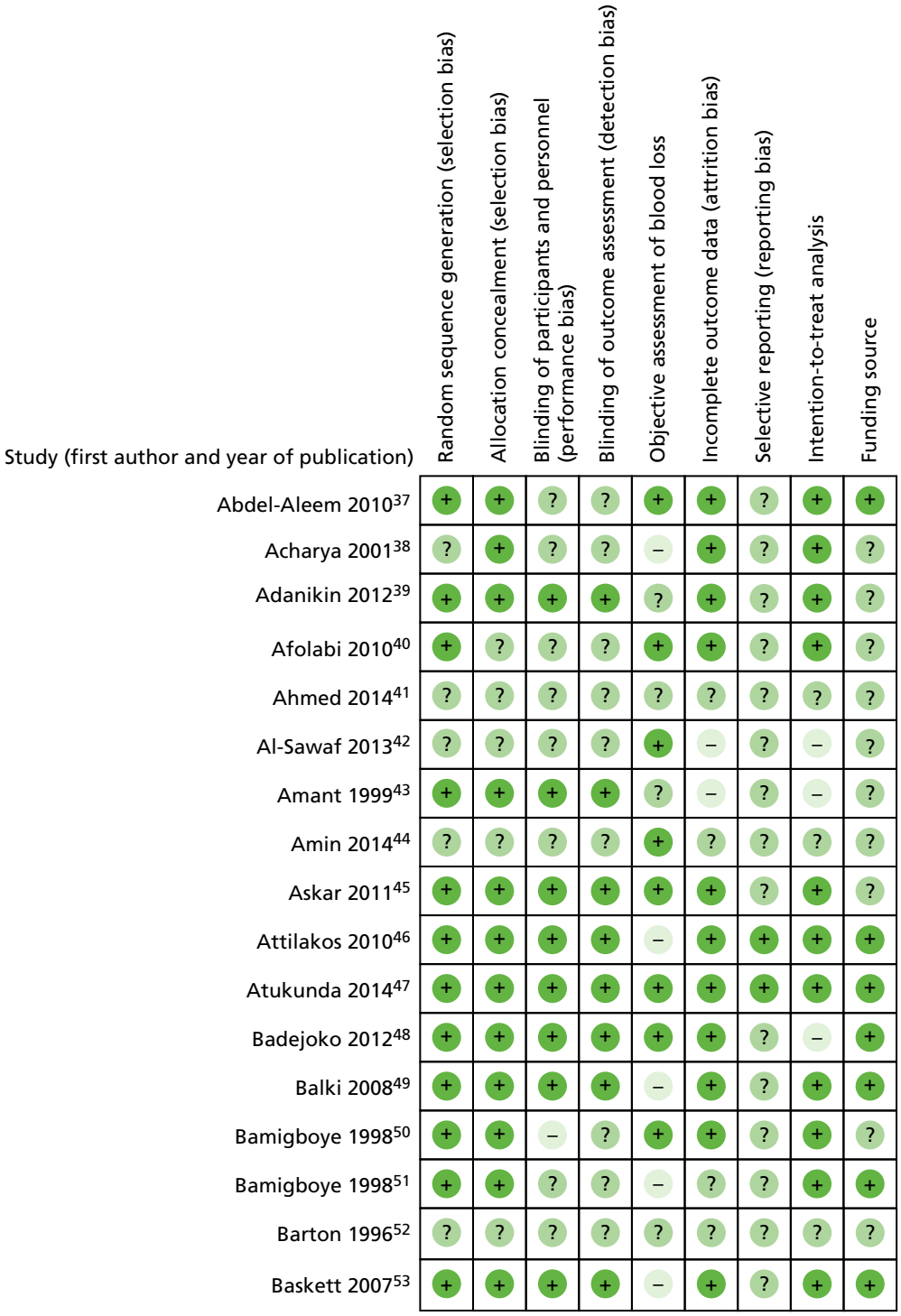

FIGURE 4 Risk-of-bias summary: review authors' judgements about each risk-of-bias item for each included study. +, low risk of bias; ?, uncertain risk of bias; –, high risk of bias. (*continued*)

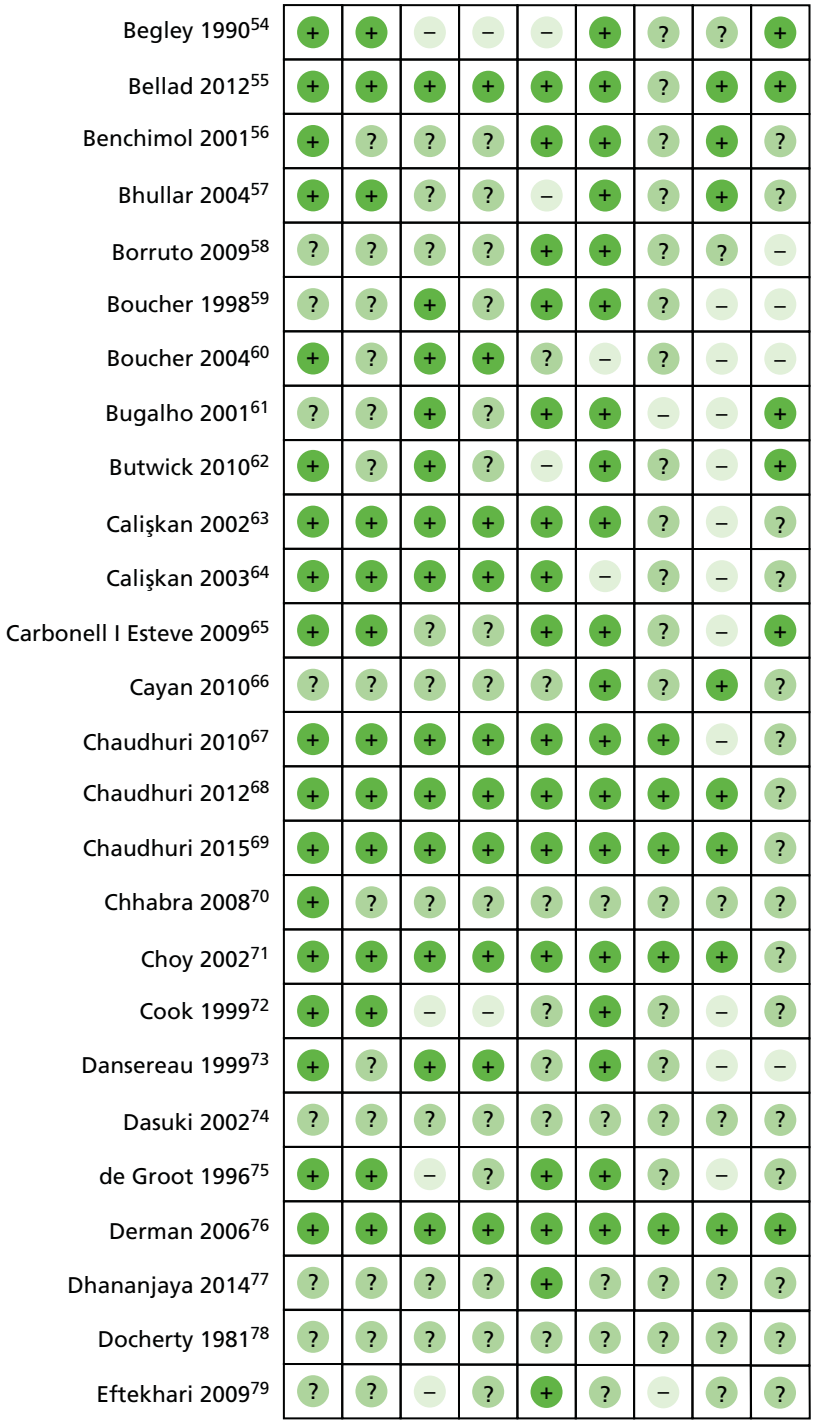

FIGURE 4 Risk-of-bias summary: review authors' judgements about each risk-of-bias item for each included study. +, low risk of bias; ?, uncertain risk of bias; –, high risk of bias. (*continued*)

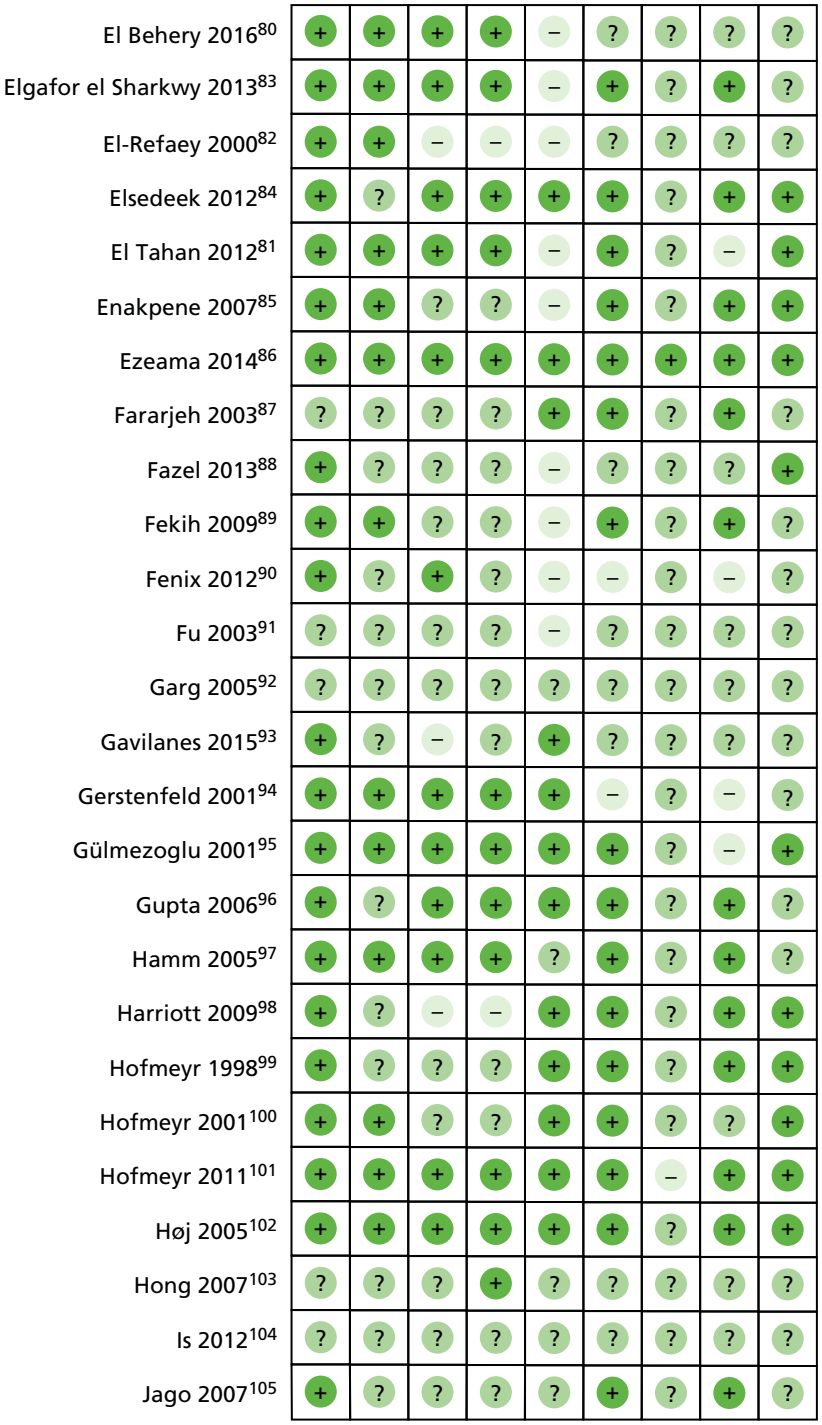

FIGURE 4 Risk-of-bias summary: review authors' judgements about each risk-of-bias item for each included study. +, low risk of bias; ?, uncertain risk of bias; –, high risk of bias. (*continued*)

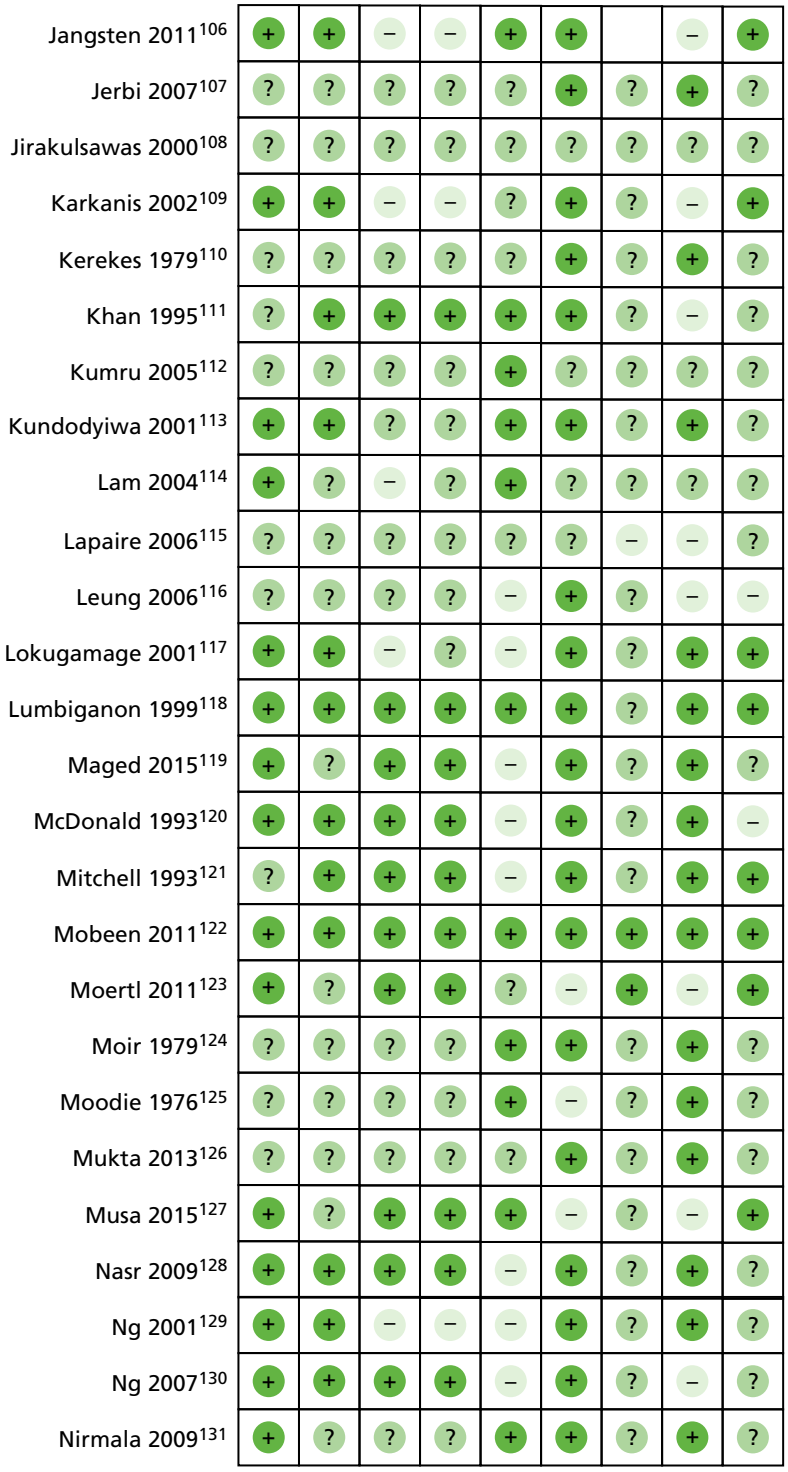

FIGURE 4 Risk-of-bias summary: review authors' judgements about each risk-of-bias item for each included study. +, low risk of bias; ?, uncertain risk of bias; –, high risk of bias. (*continued*)

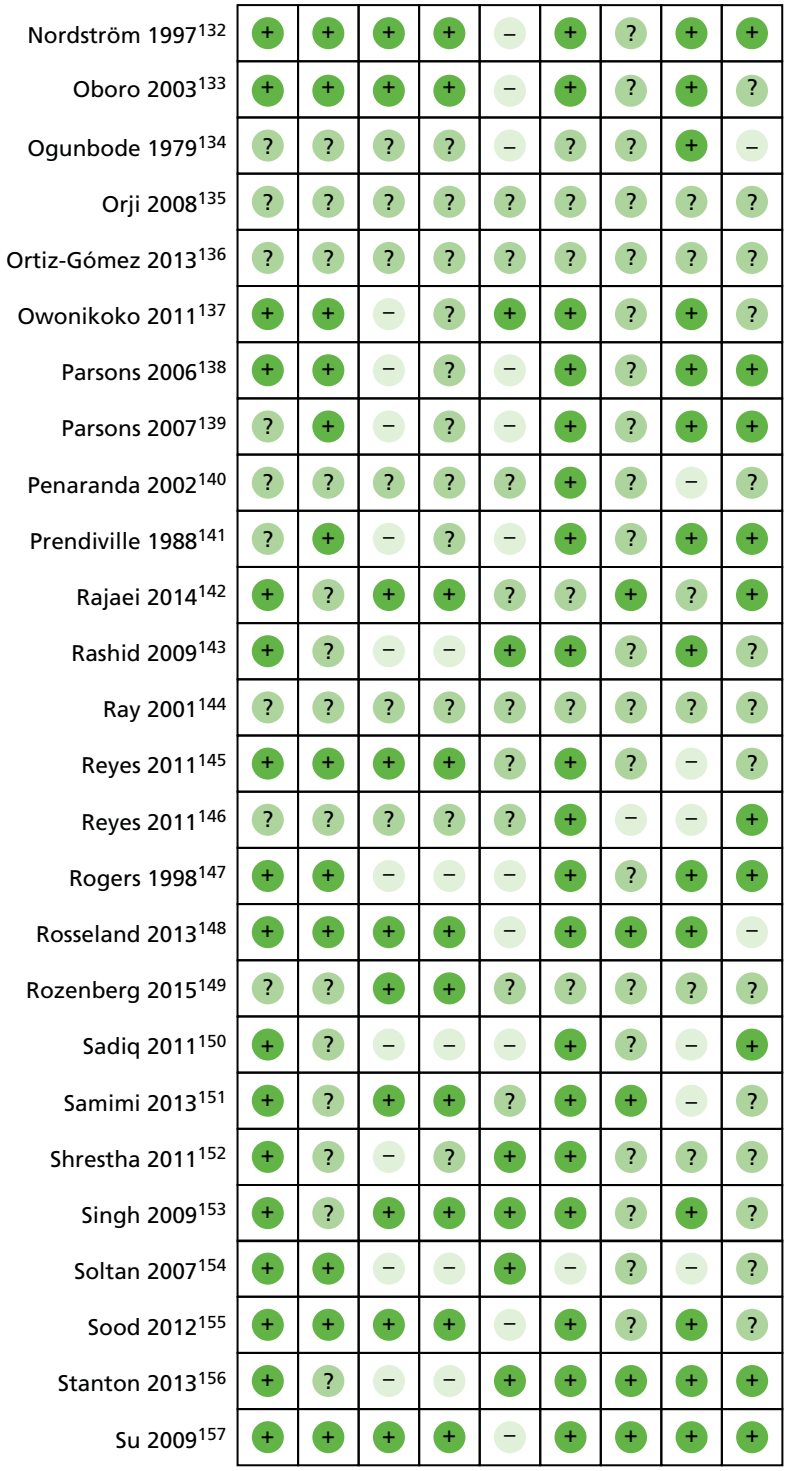

FIGURE 4 Risk-of-bias summary: review authors' judgements about each risk-of-bias item for each included study. +, low risk of bias; ?, uncertain risk of bias; –, high risk of bias. (*continued*)

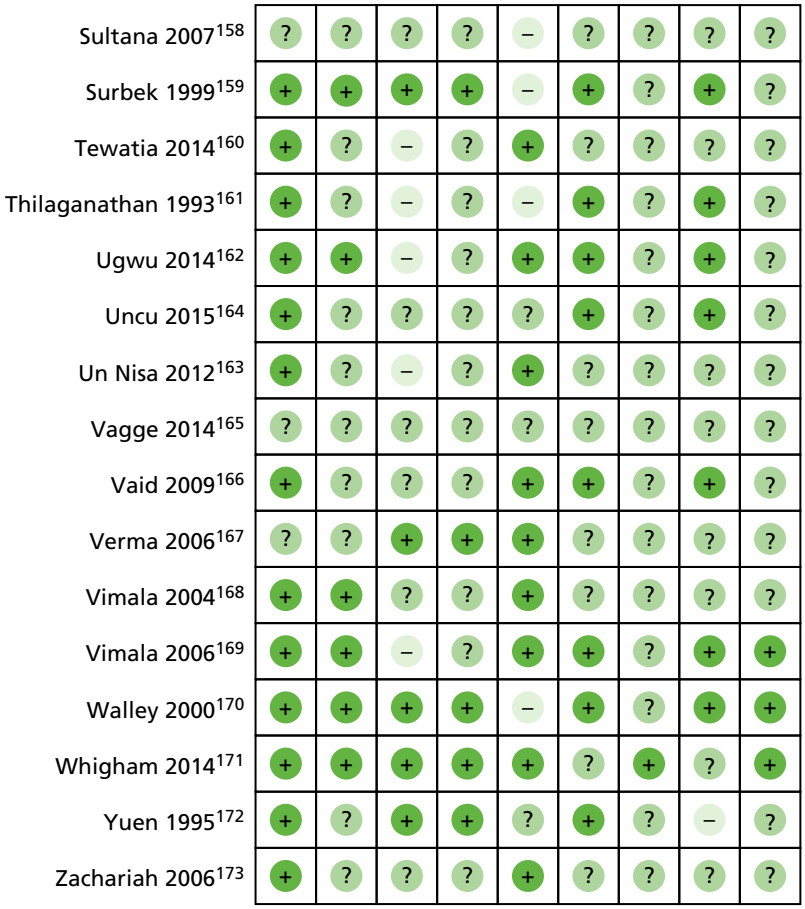

FIGURE 4 Risk-of-bias summary: review authors' judgements about each risk-of-bias item for each included study. +, low risk of bias; ?, uncertain risk of bias; –, high risk of bias.

Method of measuring blood loss

Only 14 out of 137 trials (10.2%) did not report blood loss outcomes or it was not possible to extract data for these outcomes from the published reports. From the studies that reported blood loss outcomes, 65 out of 123 trials (52.8%) reported relatively objective methods for measuring blood loss, such as weighing sponges, measurements in drapes or volumetric assessment, and were rated as being at a low risk of bias. In addition, 38 trials (30.9%) were rated as being at a high risk of bias for measuring blood loss, as the studies used subjective measurements, such as clinical or visual estimates, and 20 trials (16.3%) did not provide enough information to assess the method for measuring blood loss and the risk of bias was rated as being unclear.

Overall risk of bias

For the purpose of the sensitivity analysis, the number trials rated at a low, intermediate or high overall risk of bias have been assessed. For PPH blood loss of $\geq$ 500 ml, 29 out of 100 trials (29%) were rated as being at a low overall risk of bias, and 71 trials (71%) were rated as being at a high risk of bias as they were to be at either high risk or unclear risk of bias for at least one of the domains mentioned above. There were no trials that were rated as being at an intermediate risk of bias – see *Sensitivity analysis* for information about how this risk of bias impacted the results.

Effects of interventions

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml is presented in *Figure 5*. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention with any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. The numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is black when > 50% of the trials involved in the specific direct comparison are rated as being at a low risk of bias if they were double-blinded and had allocation concealment with little loss to follow-up (i.e. < 10%). The colour is blue when < 50% of the trials are rated as being at a low risk of bias. Multiarm trials contribute to more than one comparison. Oxytocin was the most frequently investigated intervention (i.e. in 82 trials), whereas carbetocin was investigated in only 13 trials (see *Figure 5*).

Pooled effect sizes from the NMA of 100 trials suggested that all interventions are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo (*Figure 6*). There is good statistical evidence that ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin are more effective than the standard intervention, oxytocin (ergometrine plus oxytocin vs. oxytocin: RR 0.69, 95% CI 0.57 to 0.83; carbetocin vs. oxytocin: RR 0.72, 95% CI 0.52 to 1.00; misoprostol plus oxytocin vs. oxytocin: RR 0.73, 95% CI 0.60 to 0.90; see *Figure 6*]. Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective than misoprostol and ergometrine when used alone. There was evidence of global inconsistency, in which the direct and indirect randomised evidence are not in agreement, in this analysis ($p = 0.046$). However, it is noted that the CIs for both the NMA and the direct evidence were overlapping across all comparisons, suggesting locally consistent results, except for ergometrine versus placebo or the control based on a single study.

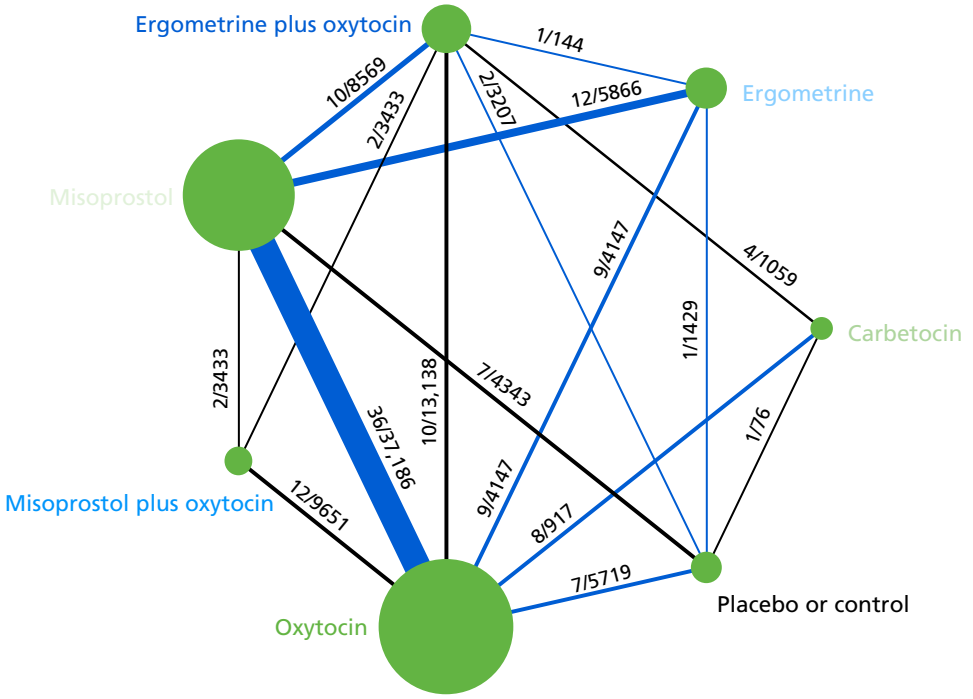

FIGURE 5 Network diagram for PPH blood loss of ≥ 500 ml.

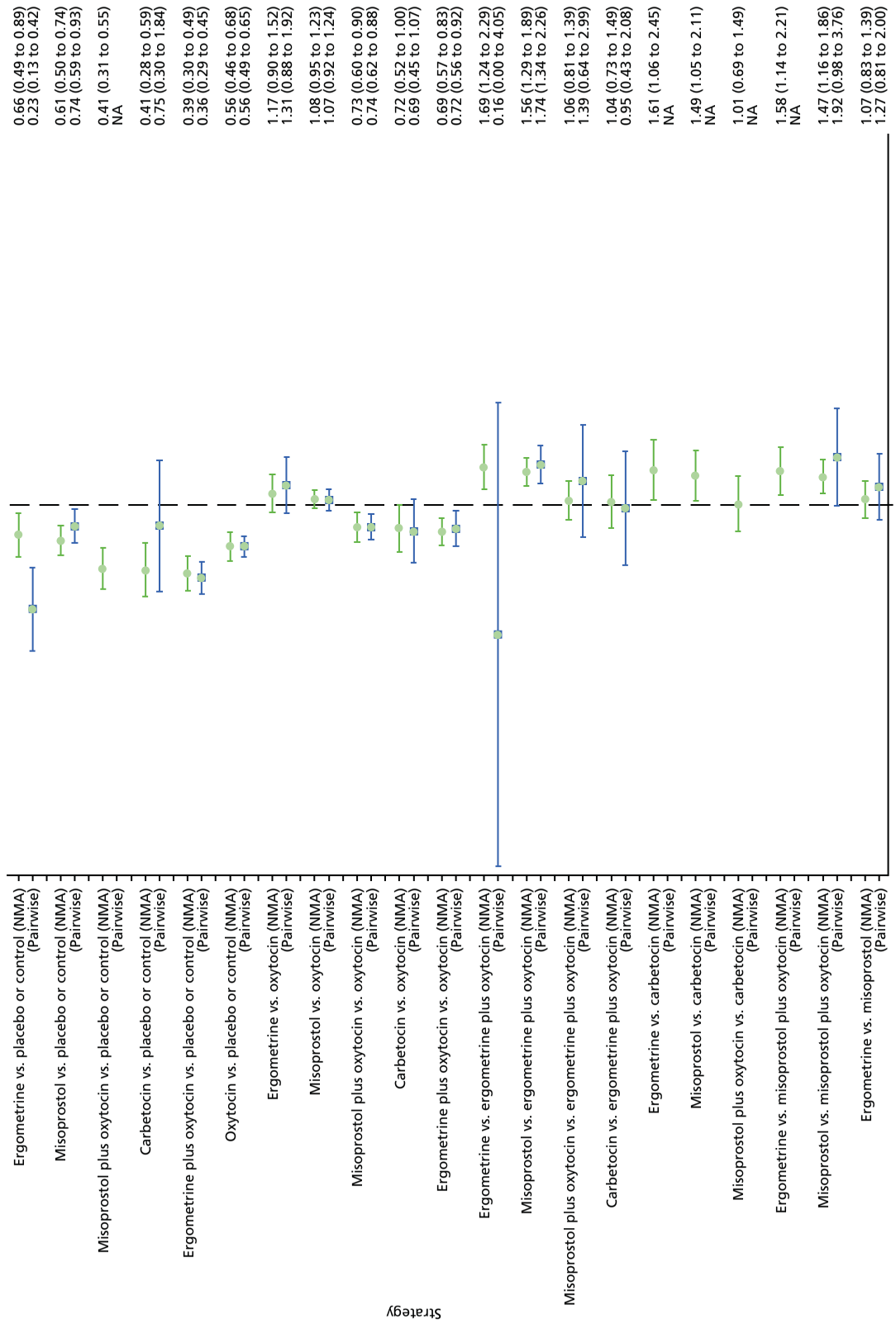

FIGURE 6 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml. NA, not applicable.

Figure 7 shows the cumulative probabilities, in the absence of bias, for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml. The *x*-axis reports each of the possible ranks, for which position 1 means that the intervention is ranked the highest and position 7 the lowest. The *y*-axis shows the cumulative probability with which each intervention has been ranked at each of the seven possible positions. To compare interventions the SUCRA was used. SUCRA can also be interpreted as the percentage of effectiveness or side effects of a treatment that would be ranked first without uncertainty. For example, ergometrine plus oxytocin has the highest probability (around 45%) of being the best drug. The probability of this intervention being either the best or the second-best drug is around 80% and being the best, the second best or the third best is 100%. The highest-ranked interventions are ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin, with an almost 100% probability of these three interventions being ranked first, second and third. Oxytocin is ranked fourth and its probability in being ranked in the top three interventions was close to 0%.

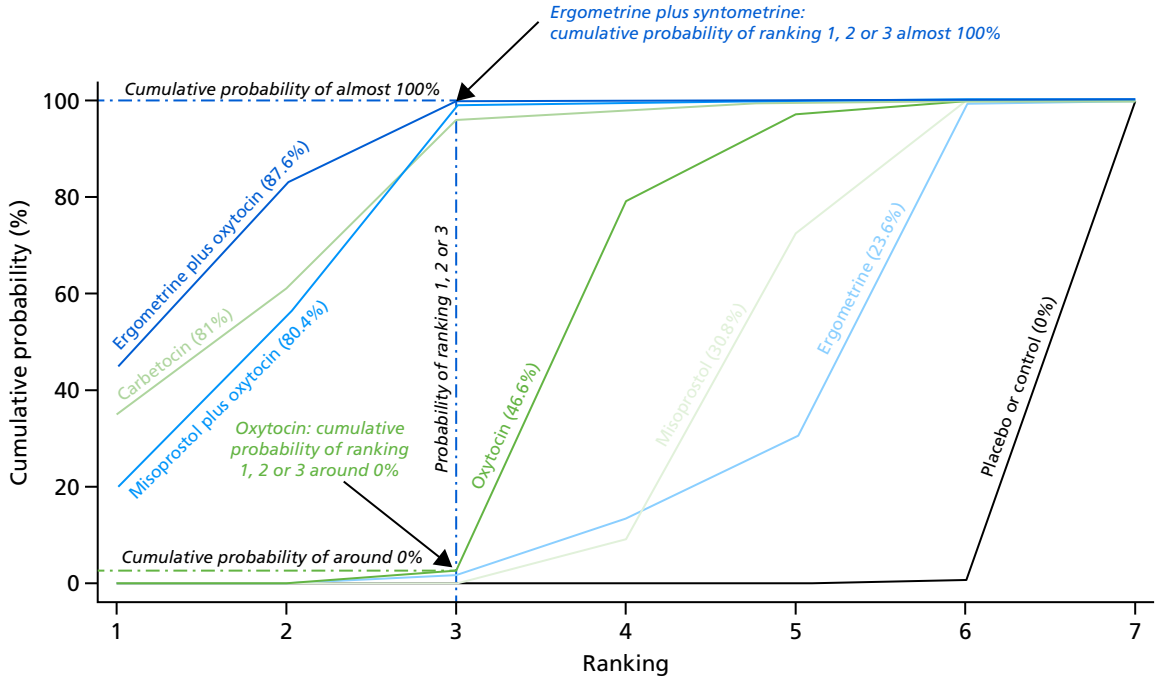

FIGURE 7 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml.

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

The network diagram for PPH blood loss of ≥ 1000 ml is presented in *Figure 8*. Oxytocin was the most frequently investigated intervention (i.e. in 77 trials), whereas carbetocin was investigated in only 11 trials (see *Figure 8*).

Pooled effect sizes from the NMA of 90 trials suggested that all interventions, except ergometrine, are effective for preventing PPH blood loss of ≥ 1000 ml when compared with placebo (*Figure 9*). Ergometrine plus oxytocin was the only intervention found to be more effective than the standard intervention, oxytocin, even though carbetocin and misoprostol plus oxytocin demonstrated a trend towards reduction of this outcome (see *Figure 9*). There was no evidence of global inconsistency in this analysis ($p = 0.345$).

Figure 10 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml. The highest-ranked interventions are ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin. Oxytocin is still ranked fourth and its probability in being ranked in the top three interventions was close to 20%.

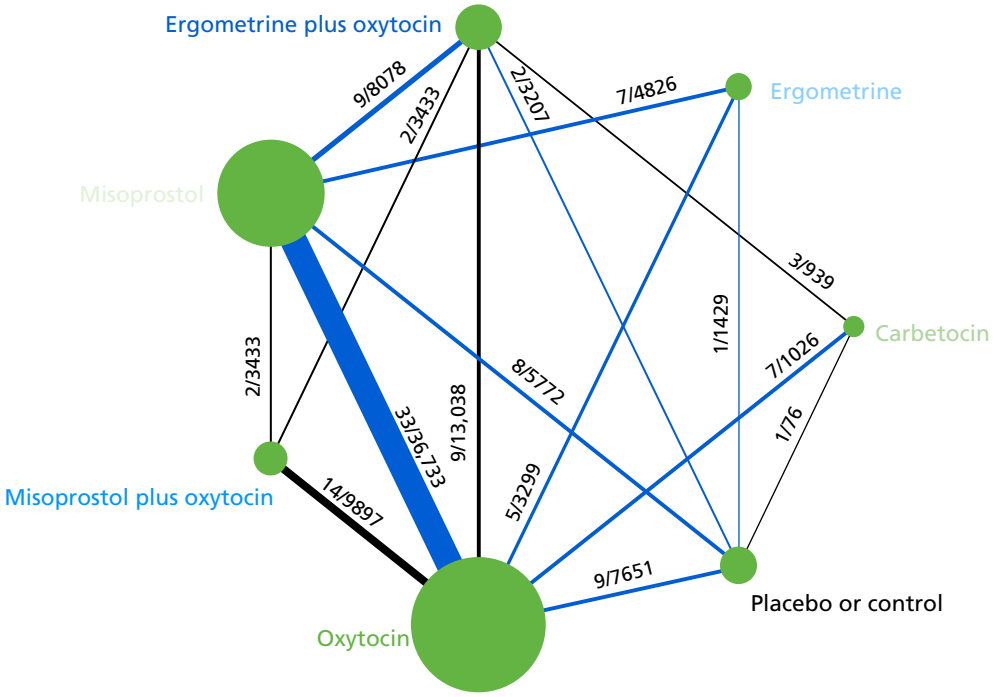

FIGURE 8 Network diagram for PPH blood loss of ≥ 1000 ml.

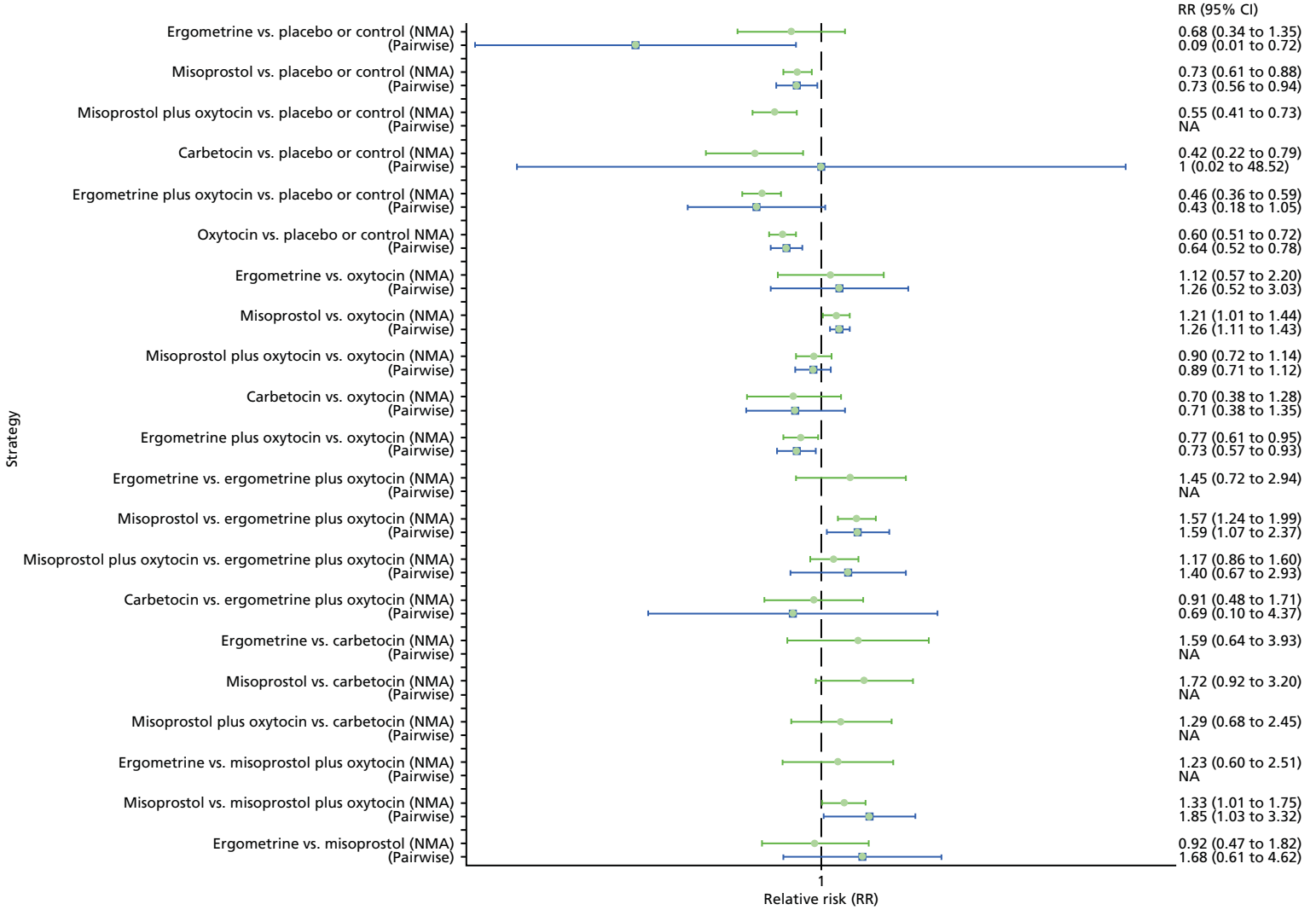

FIGURE 9 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml. NA, not applicable.

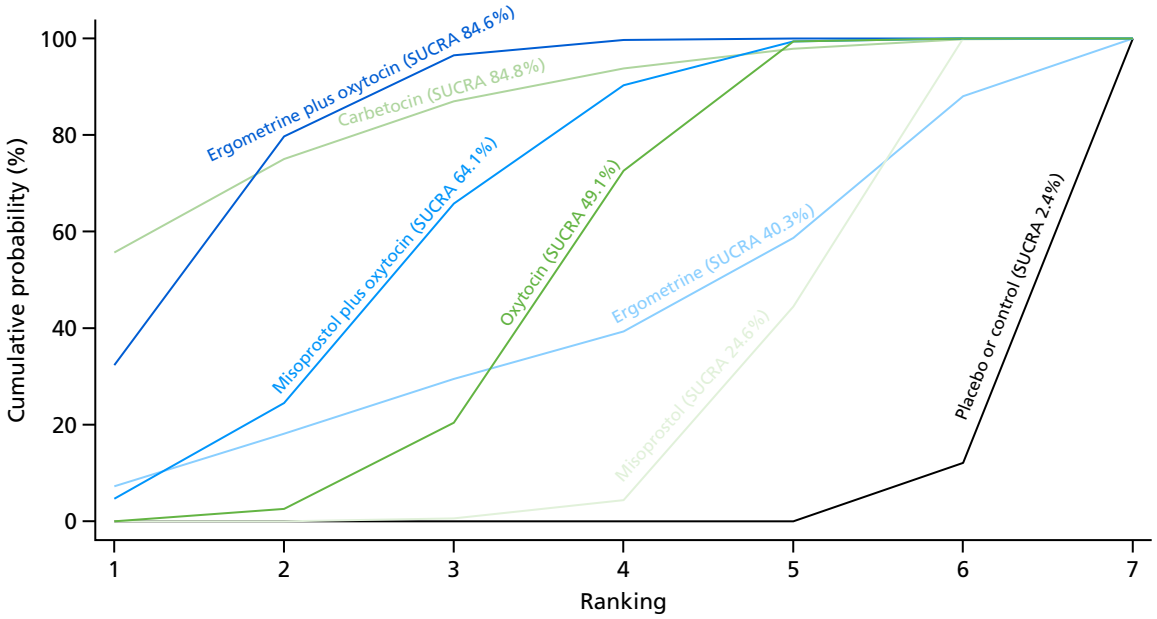

FIGURE 10 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml.

Maternal death

The network diagram for maternal death is presented in *Appendix 8*. Pooled effect sizes from the NMA of 50 trials suggested that there are no meaningful differences between all interventions for maternal death, as this outcome was so rare (*Figure 11*). There was no evidence of global inconsistency in this analysis ($p = 0.999$).

Figure 12 shows the cumulative probabilities for each intervention being at each possible rank for maternal death. No reliable ranking can be derived for this outcome.

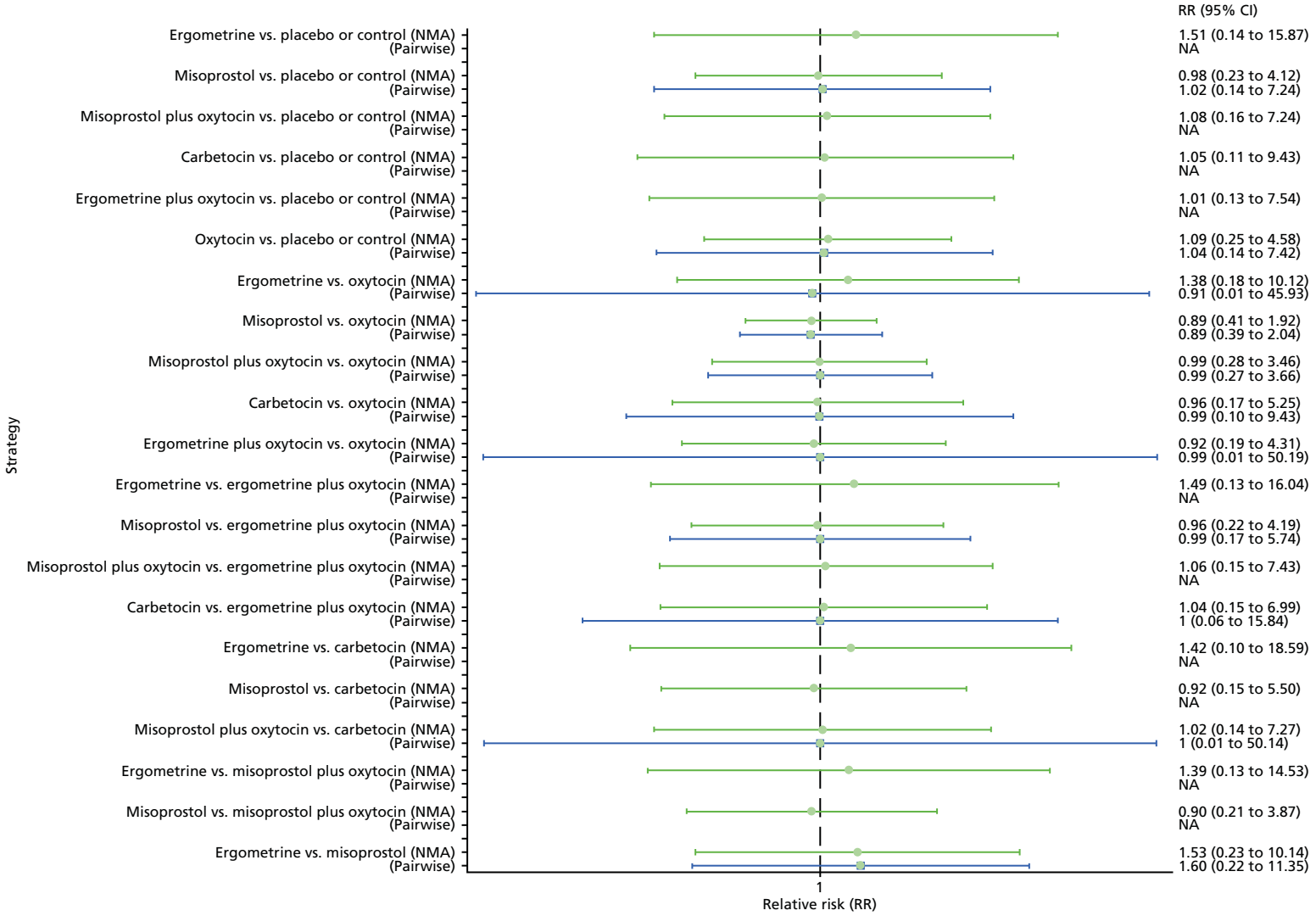

FIGURE 11 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for maternal death. NA, not applicable.

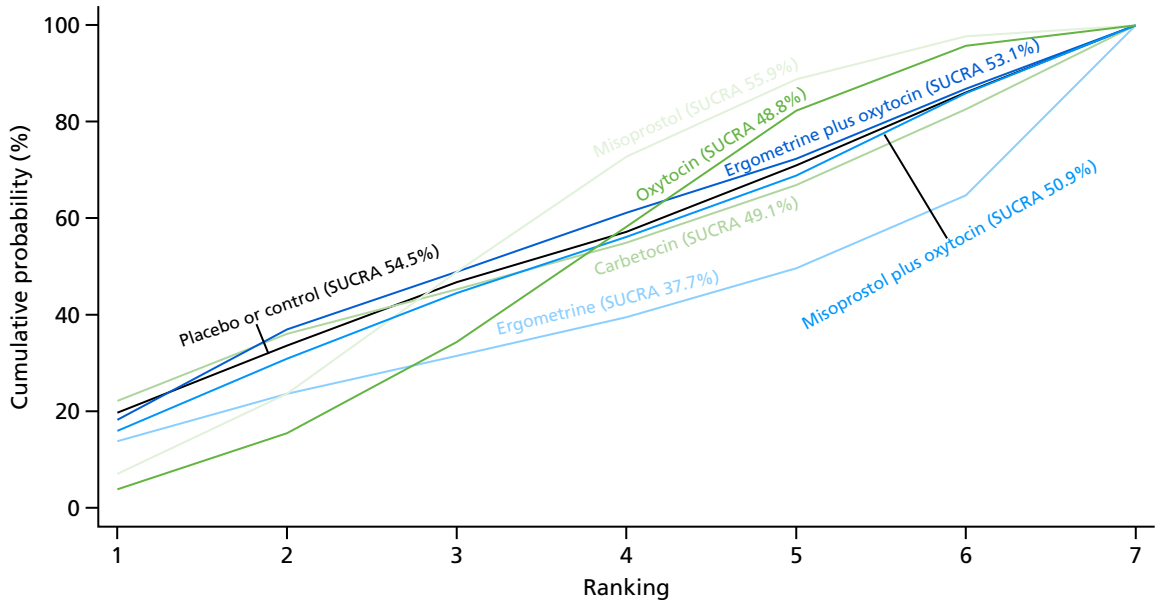

FIGURE 12 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for the prevention of maternal death.

Maternal deaths or severe morbidity

The network diagram for maternal death or severe morbidity is presented in *Appendix 8*. Pooled effect sizes from the NMA of 37 trials suggested that there are no detectable differences between all interventions for maternal deaths or severe morbidity, as this outcome was still so rare (*Figure 13*). There was no evidence of global inconsistency in this analysis ($p = 0.884$).

Figure 14 shows the cumulative probabilities for each intervention being at each possible rank for maternal death or severe morbidity. No sensible ranking can be derived for this outcome because of limited data.

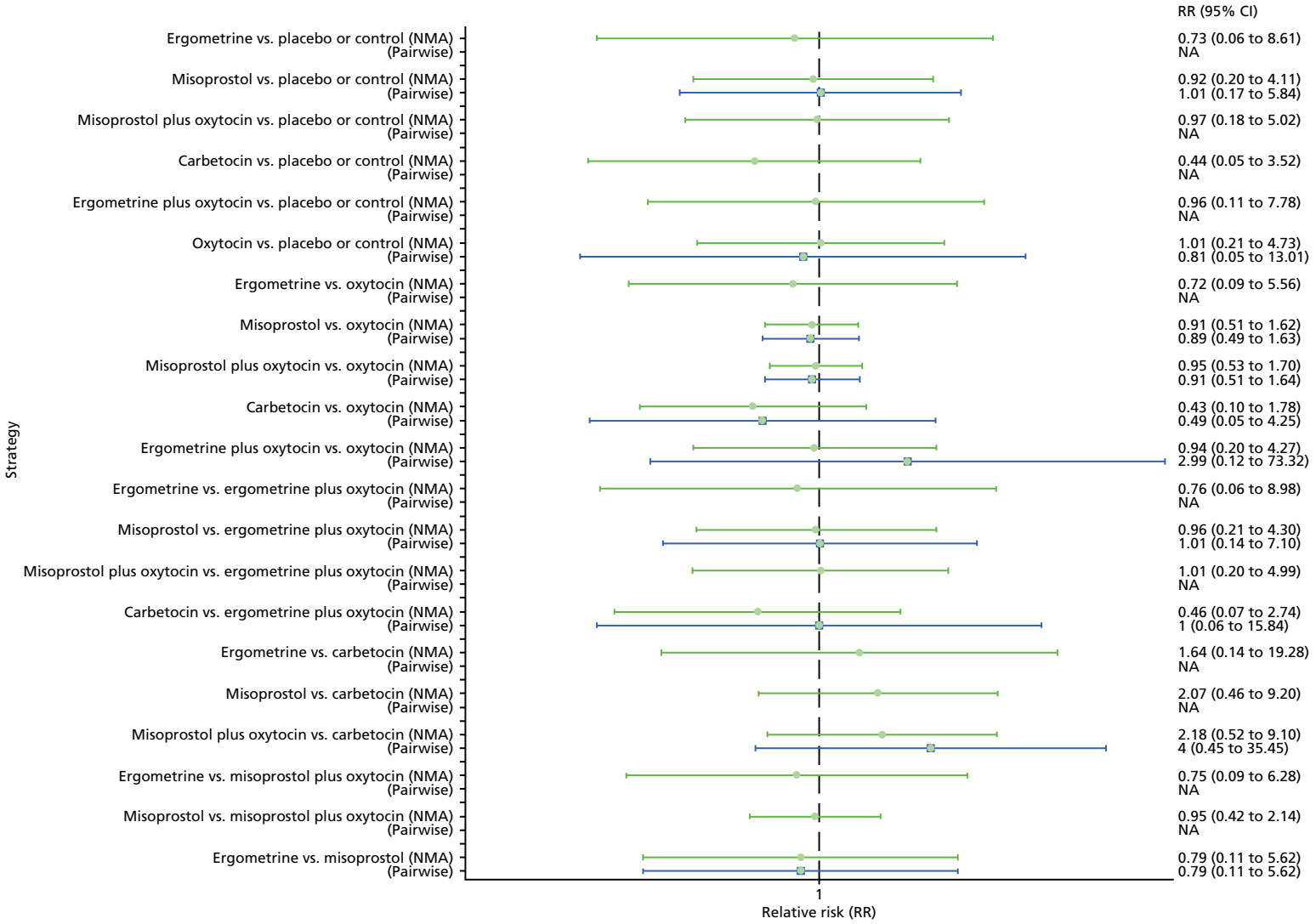

FIGURE 13 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for maternal death or severe morbidity. NA, not applicable.

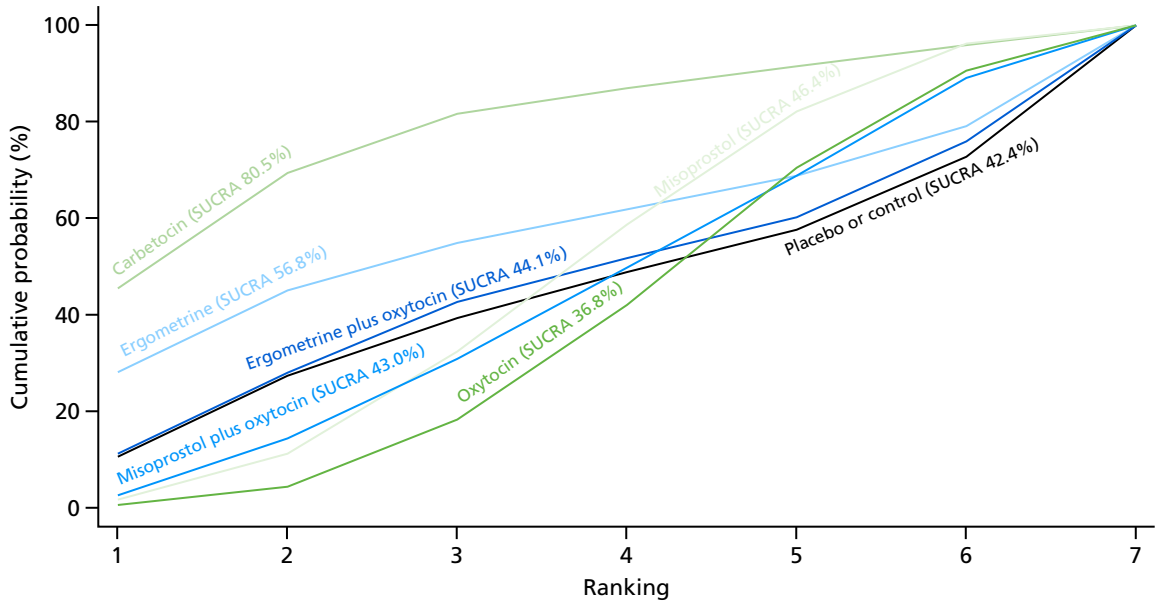

FIGURE 14 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for the prevention of maternal death or severe morbidity events.

Additional uterotonics

The network diagram for the requirement of additional uterotonics is presented in *Appendix 8*. Pooled effect sizes from the NMA of 107 trials suggested that all interventions are effective at reducing the requirement of additional uterotonics when compared with placebo (*Figure 15*). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were found to be more effective than the standard intervention, oxytocin (see *Figure 15*). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective than misoprostol and ergometrine when used alone. There was no evidence of global inconsistency in this analysis ($p = 0.275$).

Figure 16 shows the cumulative probabilities for each intervention being at each possible rank for the requirement of additional uterotonics. The highest-ranked interventions are ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin, with an almost 100% probability of these three interventions being ranked in the top three. Oxytocin is ranked fourth and its probability in being ranked in the top three interventions was close to 0%. The lowest-ranked interventions were misoprostol, ergometrine and placebo or the control.

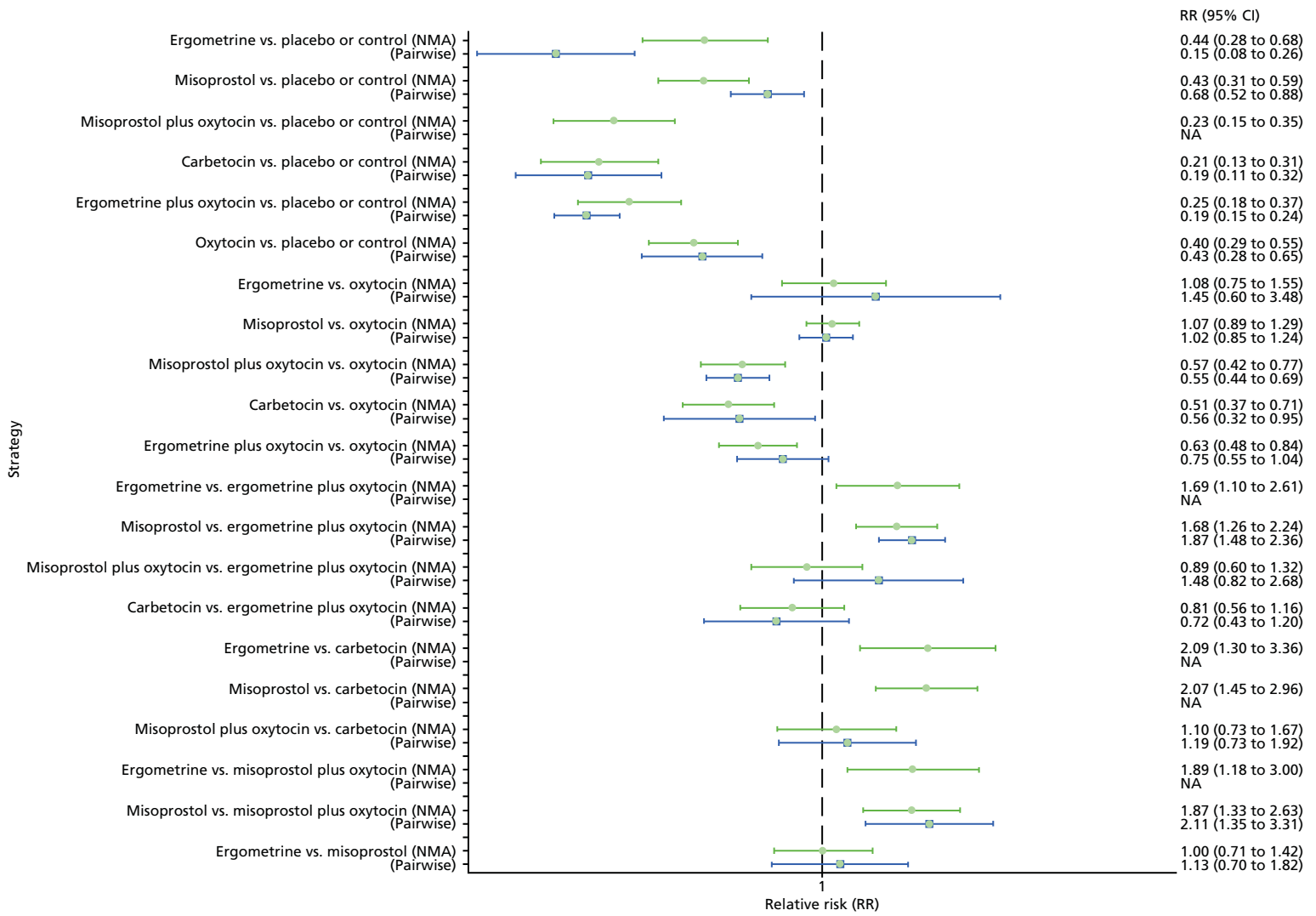

FIGURE 15 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the requirement of additional uterotonics. NA, not applicable.

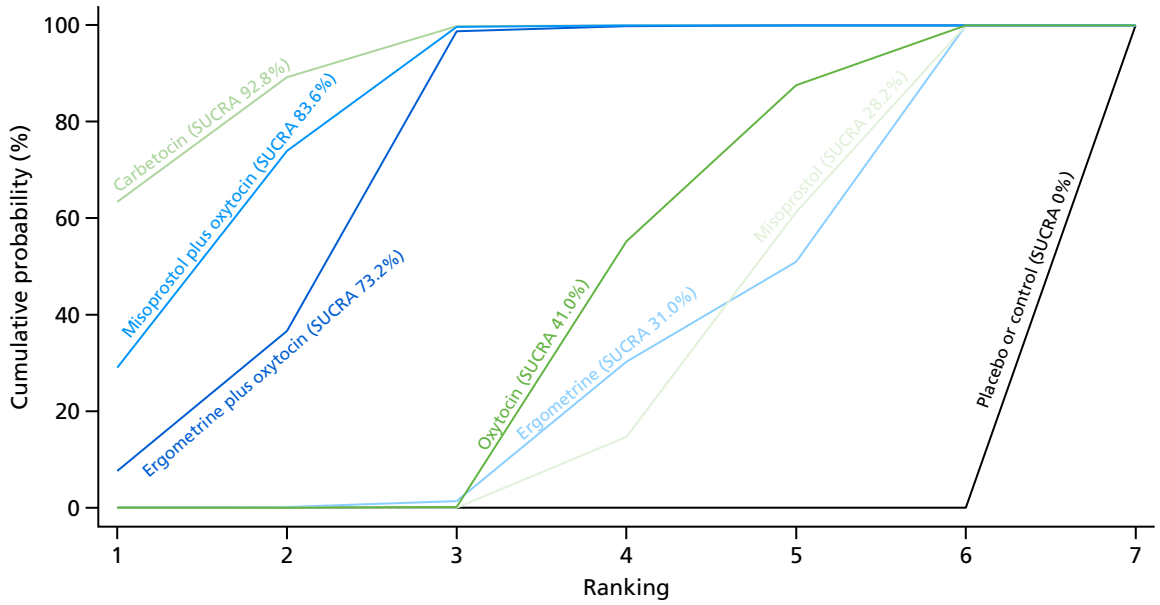

FIGURE 16 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for the requirement of additional uterotonics.

Transfusion

The network diagram for blood transfusion is presented in *Appendix 8*. Pooled effect sizes from the NMA of 92 trials suggests that all interventions, except ergometrine, are effective for preventing blood transfusion when compared with placebo (*Figure 17*). Misoprostol plus oxytocin was the only intervention found to be more effective than the standard intervention, oxytocin, even though carbetocin and ergometrine plus oxytocin demonstrated a trend towards reduction of this outcome (see *Figure 17*). There was no evidence of global inconsistency in this analysis ($p = 0.061$).

Figure 18 shows the cumulative probabilities for each intervention being at each possible rank for preventing blood transfusion. The highest-ranked interventions are misoprostol plus oxytocin, carbetocin and ergometrine plus oxytocin. Oxytocin is ranked fifth behind misoprostol and its probability of being ranked in the top three interventions was < 10%.

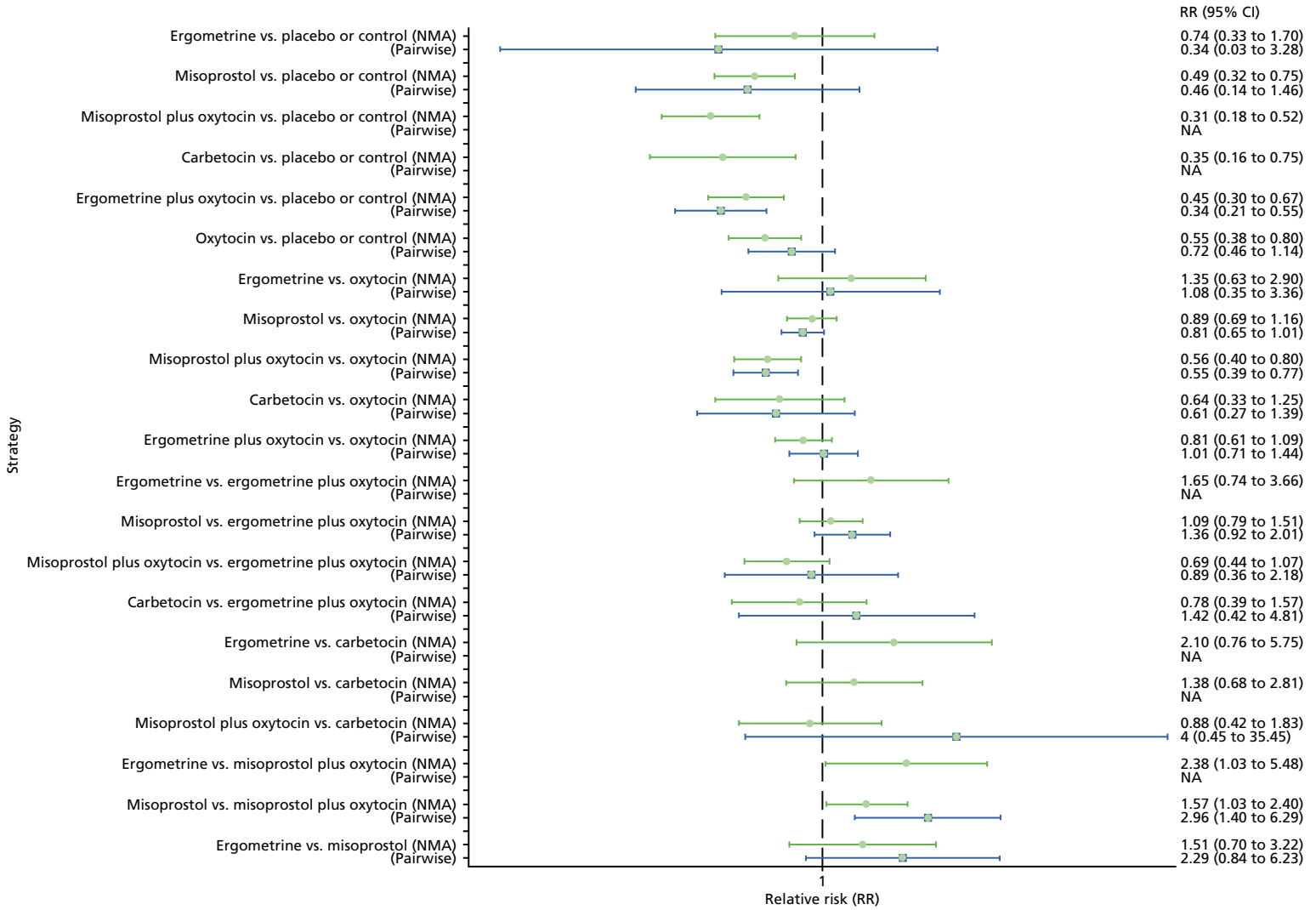

FIGURE 17 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the requirement of blood transfusion. NA, not applicable.

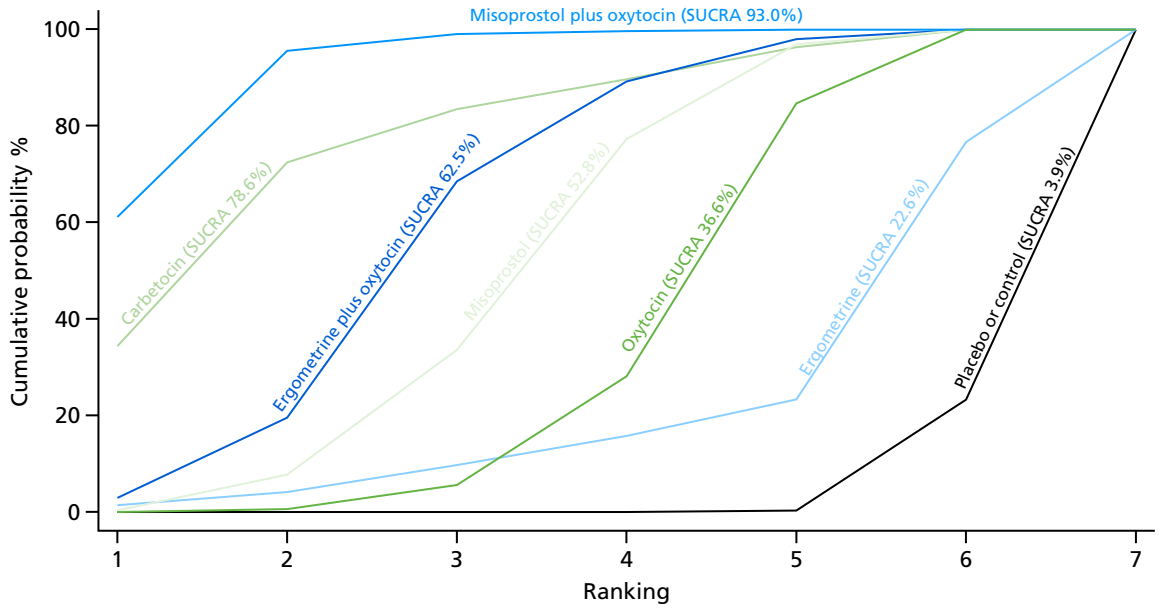

FIGURE 18 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for the requirement of blood transfusion.

Manual removal of the placenta

The network diagram for the requirement of manual removal of placenta is presented in *Appendix 8*. Pooled effect sizes from the NMA of 67 trials suggest that there are no significant differences between all interventions for this outcome (*Figure 19*). There was evidence of global inconsistency in this analysis ($p = 0.025$). However, it is noted that the CIs for both the NMA and the direct evidence were overlapping across all comparisons, suggesting locally consistent results except for ergometrine versus placebo or the control and carbetocin versus oxytocin based on single studies.

Figure 20 shows the cumulative probabilities for each intervention being at each possible rank for the prevention of blood transfusion. No clear ranking can be derived for this outcome, with all interventions being comparable except for carbetocin, as that drug appeared to have the highest probability being of the top-ranked intervention, with a probability close to 80%.

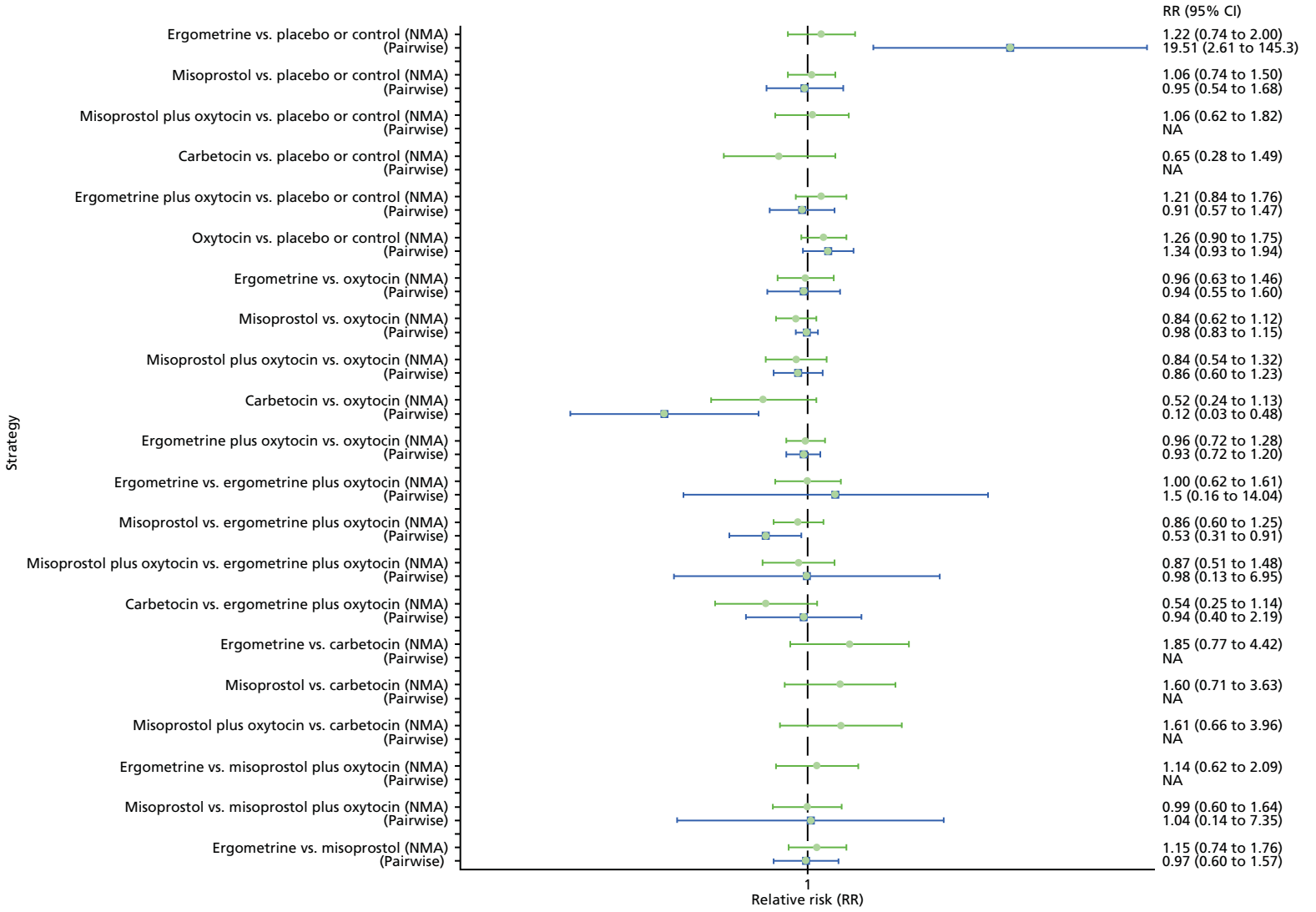

FIGURE 19 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the requirement of manual removal of placenta. NA, not applicable.

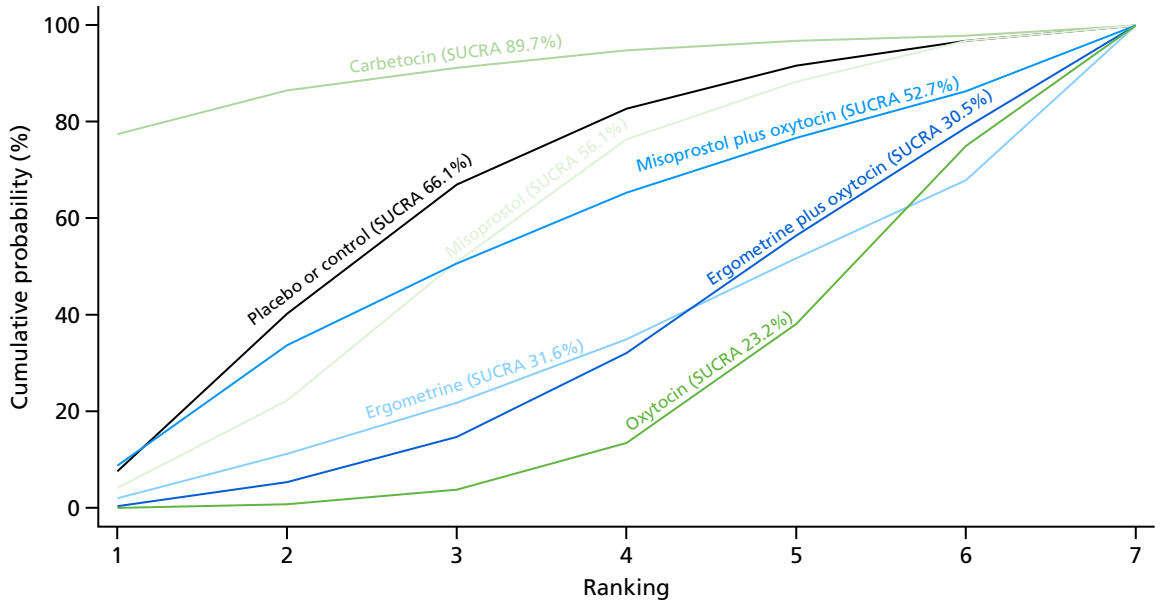

FIGURE 20 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for the requirement of manual removal of placenta.

Mean volumes of blood loss

The network diagram for blood loss (as reported in ml), as a continuous outcome, is presented in *Appendix 8*. Pooled effect sizes from the NMA of 102 trials suggested that all interventions are effective for reducing blood loss as a continuous outcome when compared with placebo (*Figure 21*). Carbetocin and misoprostol plus oxytocin were found to be more effective than the standard intervention, oxytocin, even though ergometrine plus oxytocin also demonstrated a trend towards reduction of this outcome (see *Figure 21*). Carbetocin and misoprostol plus oxytocin were more effective than ergometrine plus oxytocin in reducing blood loss. Carbetocin and misoprostol plus oxytocin were also found to be more effective in reducing blood loss than misoprostol and ergometrine when used alone. There was no evidence of global inconsistency in this analysis ($p = 0.111$).

Figure 22 shows the cumulative probabilities for each intervention being at each possible rank for preventing blood loss (as reported in ml) as a continuous outcome. The highest-ranked interventions are carbetocin, misoprostol plus oxytocin and ergometrine plus oxytocin. Oxytocin is ranked fourth and its probability in being ranked in the top three interventions was > 10%. The lowest-ranked interventions were misoprostol, ergometrine and placebo or the control.

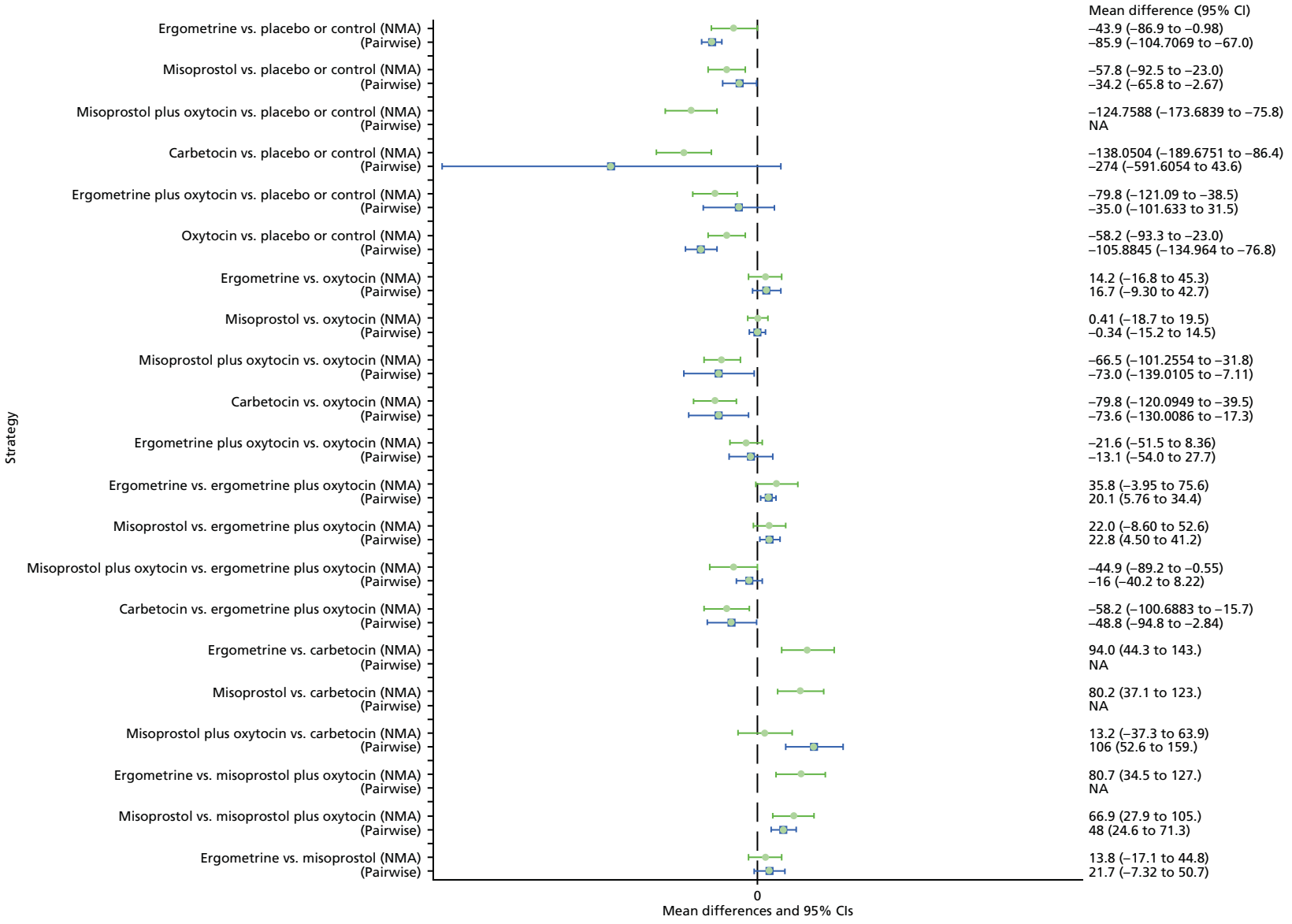

FIGURE 21 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for blood loss (ml). NA, not applicable.

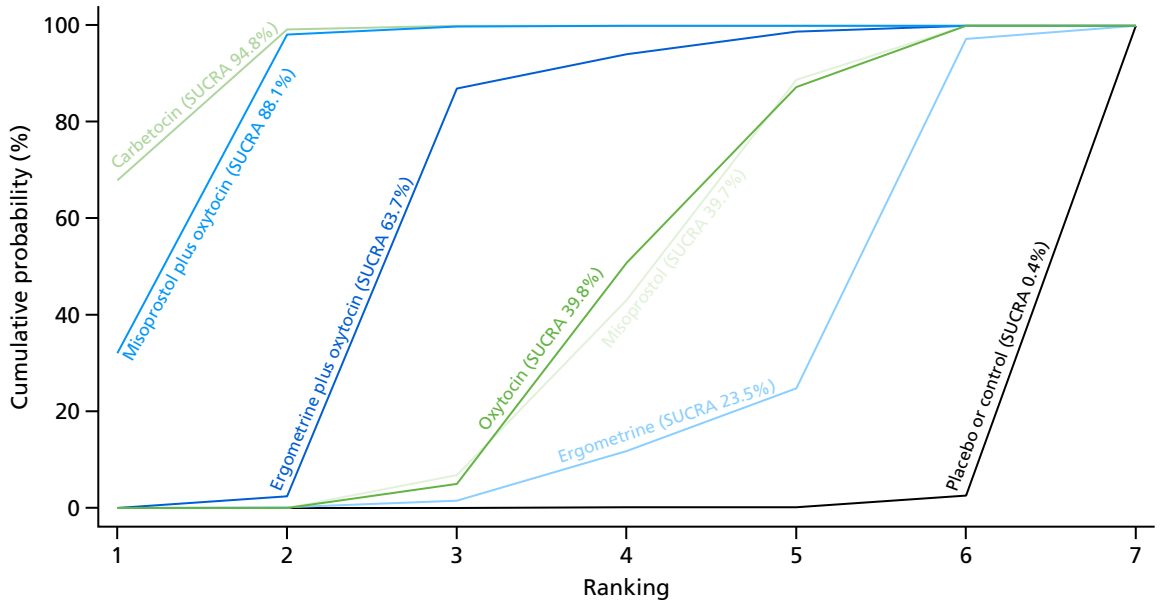

FIGURE 22 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for blood loss (ml).

Mean duration of the third stage of labour

The network diagram for the duration of the third stage (as reported in minutes), as a continuous outcome, is presented in *Appendix 8*. Pooled effect sizes from the NMA of 58 trials suggested that all interventions are effective for reducing the duration of the third stage as a continuous outcome when compared with placebo, except for carbetocin and misoprostol plus oxytocin, even though they demonstrated a similar trend towards reduction of this outcome (*Figure 23*). There were no significant differences between all active interventions for this outcome (see *Figure 23*). There was evidence of global inconsistency in this analysis ($p = 0.011$) and these results need to be interpreted with caution.

Figure 24 shows the cumulative probabilities for each intervention being at each possible rank for the reduction of the third stage as a continuous outcome. No sensible ranking can be derived for this outcome, with all interventions being comparable. The exception is ergometrine plus oxytocin as this intervention appeared to have the highest probability in being the top-ranked intervention, with a probability close to 60%, and the placebo or the control, which appeared to have the lowest ranking, with a probability of > 80%.

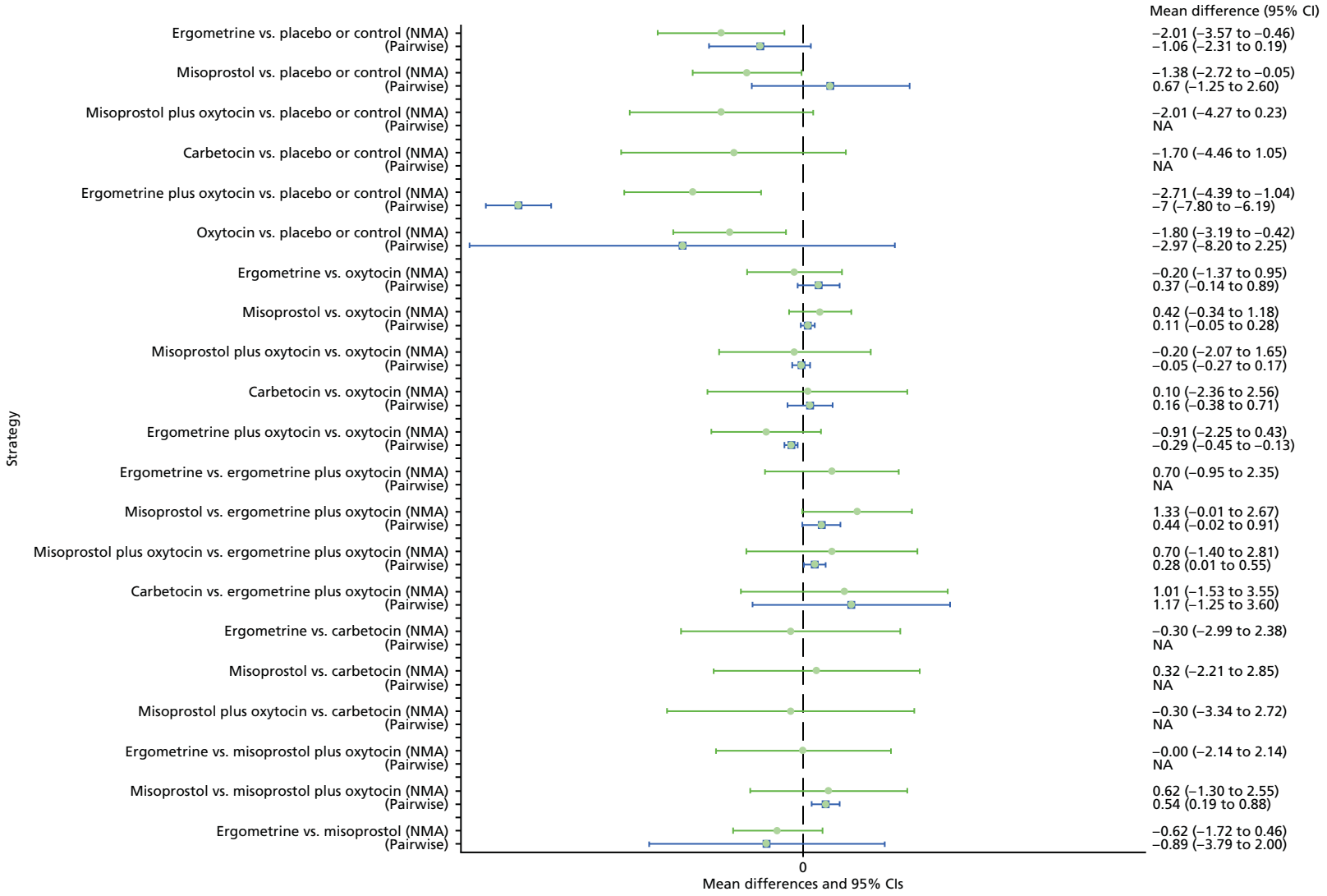

FIGURE 23 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for duration of third stage (minutes). NA, not applicable.

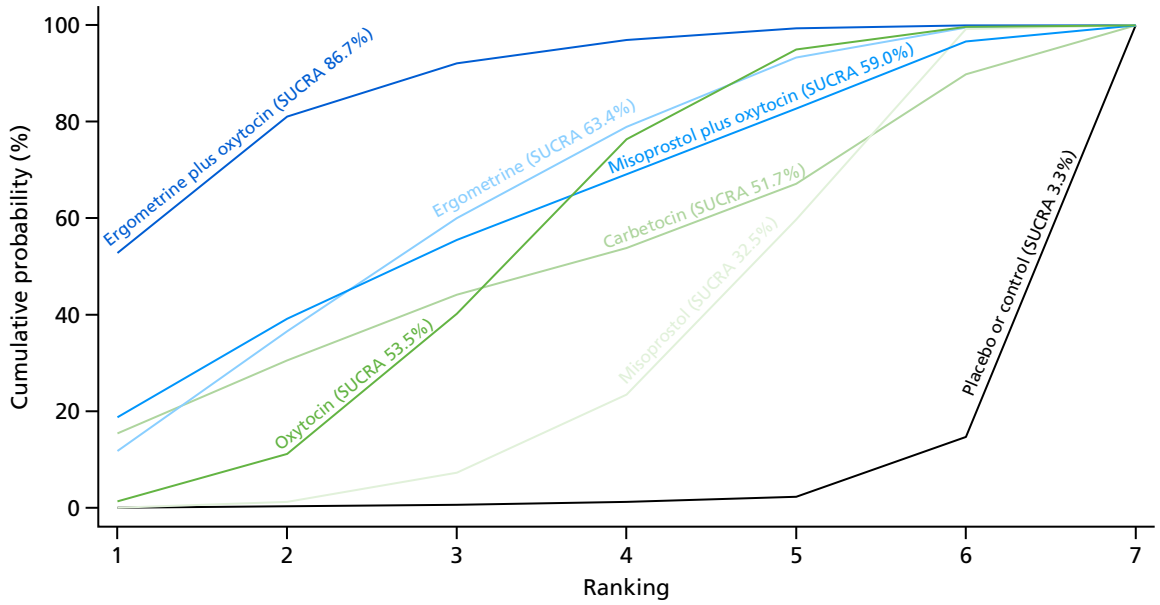

FIGURE 24 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for duration of third stage (minutes).

Change in haemoglobin levels

The network diagram for the change in Hb measurements before and after birth (as measured in g/l) is presented in *Appendix 8*. Pooled effect sizes from the NMA of 74 trials suggested that misoprostol plus oxytocin and carbetocin are effective for reducing the change in Hb measurements than placebo (*Figure 25*). Misoprostol plus oxytocin was the only intervention found to be more effective than the standard intervention, oxytocin (see *Figure 25*). Misoprostol plus oxytocin were also more effective than misoprostol and ergometrine when used alone. Carbetocin was more effective than ergometrine when used alone. However, there was evidence of substantial global inconsistency in this analysis ($p = 0.001$).

Figure 26 shows the cumulative probabilities for each intervention being at each possible rank for change in Hb measurements before and after birth. The highest-ranked interventions are misoprostol plus oxytocin, carbetocin and ergometrine plus oxytocin. Oxytocin is ranked fourth and its probability in being ranked in the top three interventions was just over 20%. The lowest-ranked interventions were misoprostol, ergometrine and placebo or the control.

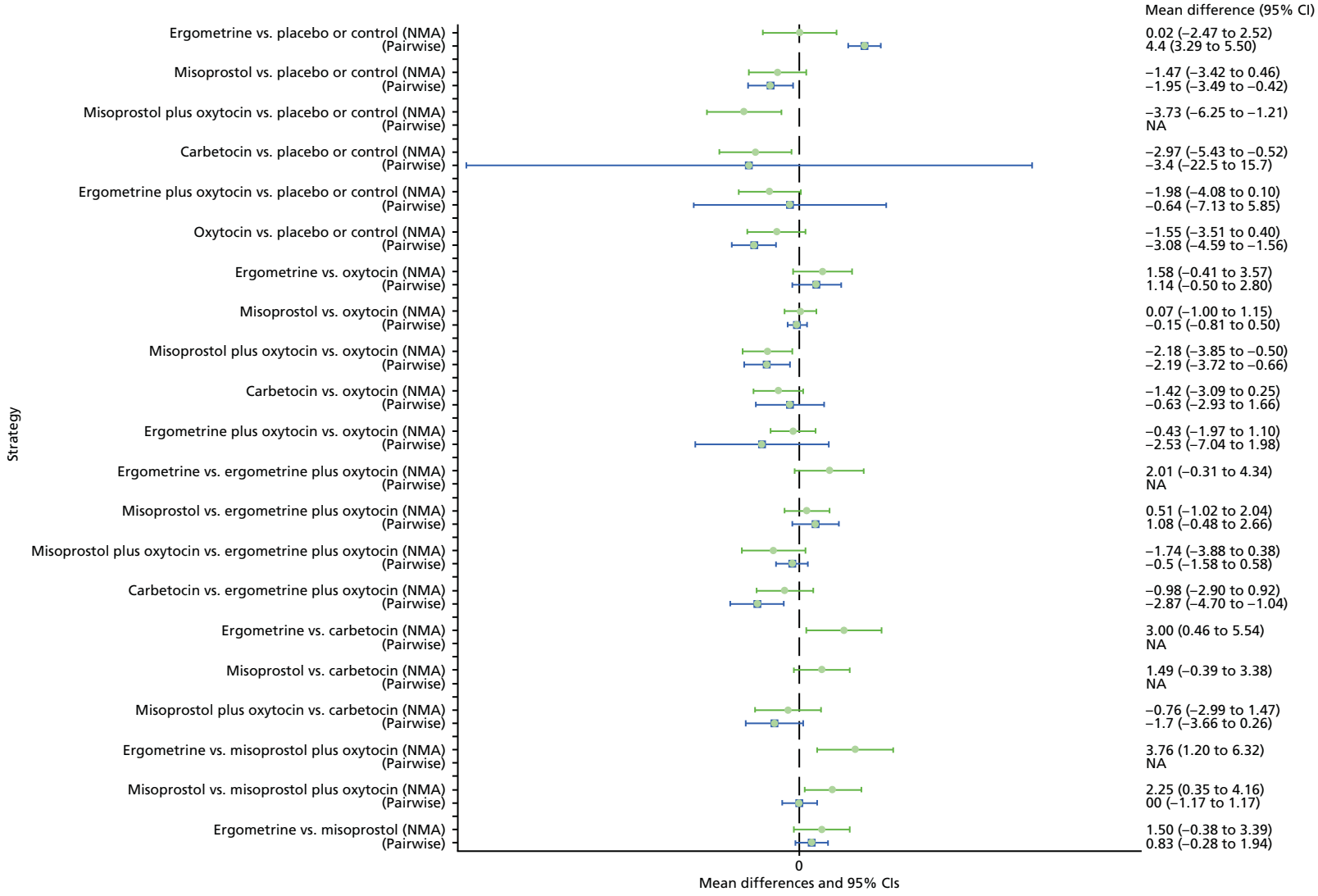

FIGURE 25 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for change in Hb measurements before and after birth (g/l). NA, not applicable.

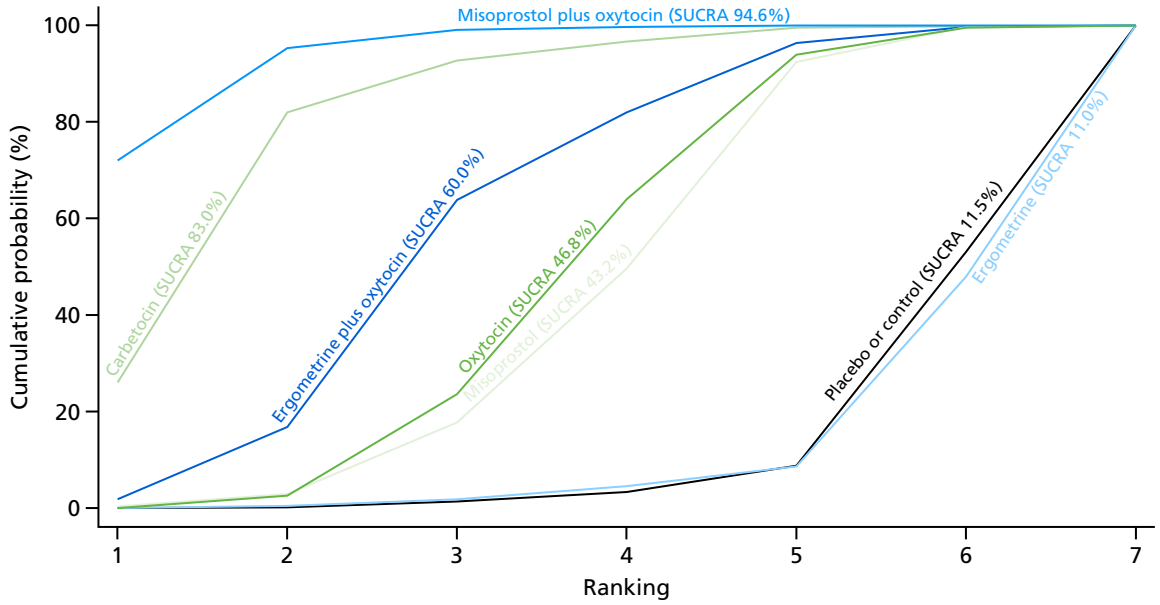

FIGURE 26 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for change in Hb measurements before and after birth (g/l).

Clinical signs of blood loss

There were no trials reporting clinical signs of acute blood loss.

Neonatal unit admission

The network diagram for neonatal unit admissions is presented in *Appendix 8*. Pooled effect sizes from the NMA of only six trials did not point towards any meaningful differences between all interventions for this outcome (*Figure 27*). There was no evidence of global inconsistency in this analysis ($p = 0.989$).

Figure 28 shows the cumulative probabilities for each intervention being at each possible rank for neonatal unit admissions. No sensible ranking can be derived for this outcome because of too few studies.

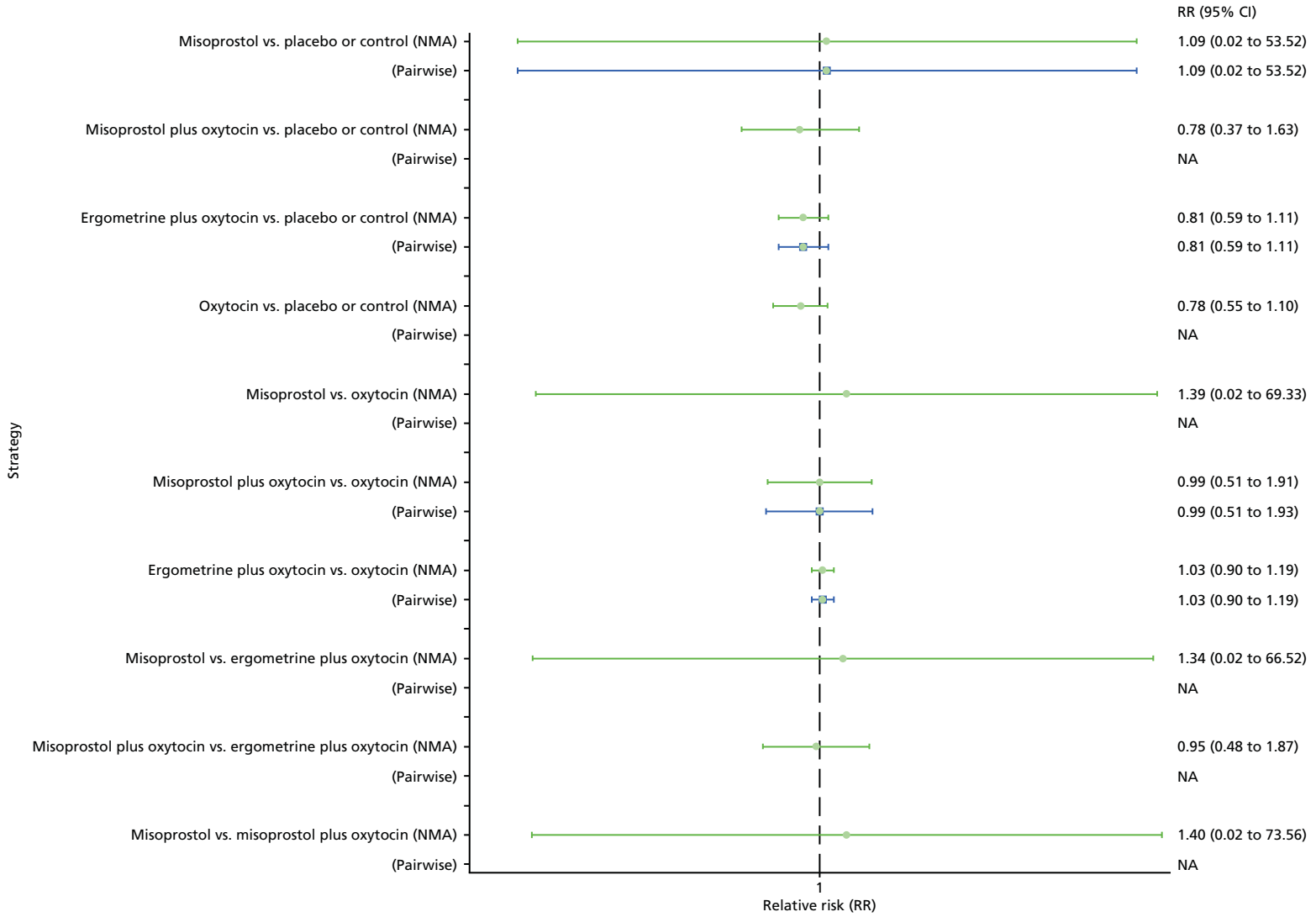

FIGURE 27 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for neonatal unit admissions. NA, not applicable.

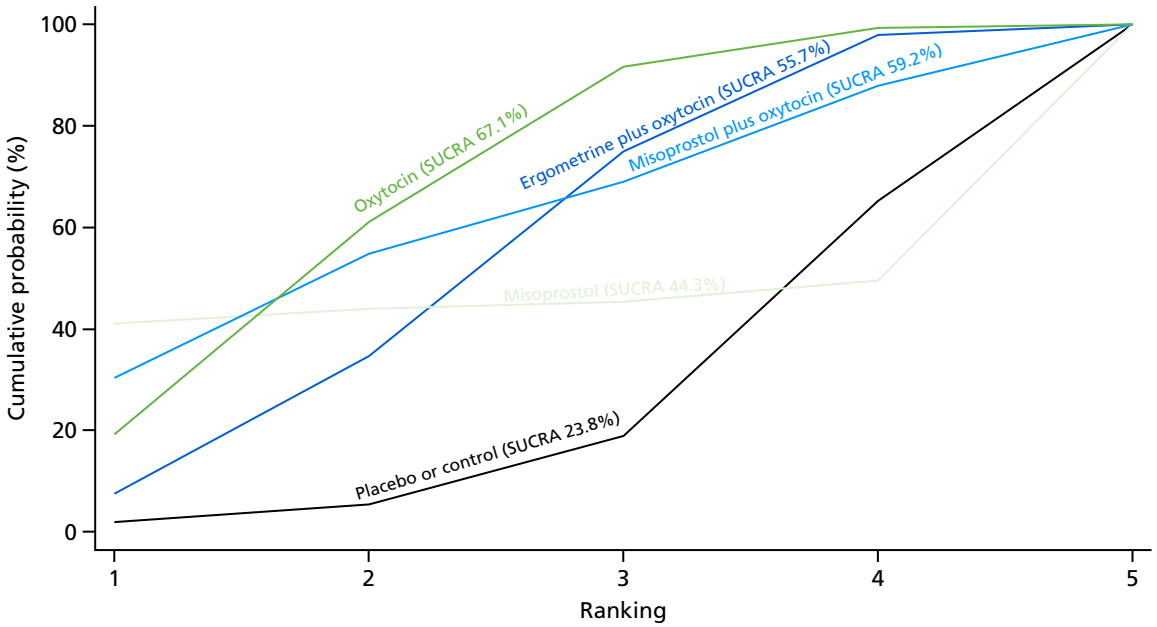

FIGURE 28 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for neonatal unit admissions.

Breastfeeding at discharge

The network diagram for breastfeeding at discharge is presented in *Appendix 8*. Pooled effect sizes from the NMA of only five trials did not point towards any meaningful differences between interventions for this outcome (*Figure 29*). There was no evidence of global inconsistency in this analysis ($p = 0.167$).

Figure 30 shows the cumulative probabilities for each intervention being at each possible rank for breastfeeding at discharge. No clear ranking can be derived for this outcome, with all interventions being comparable again because of too few studies.

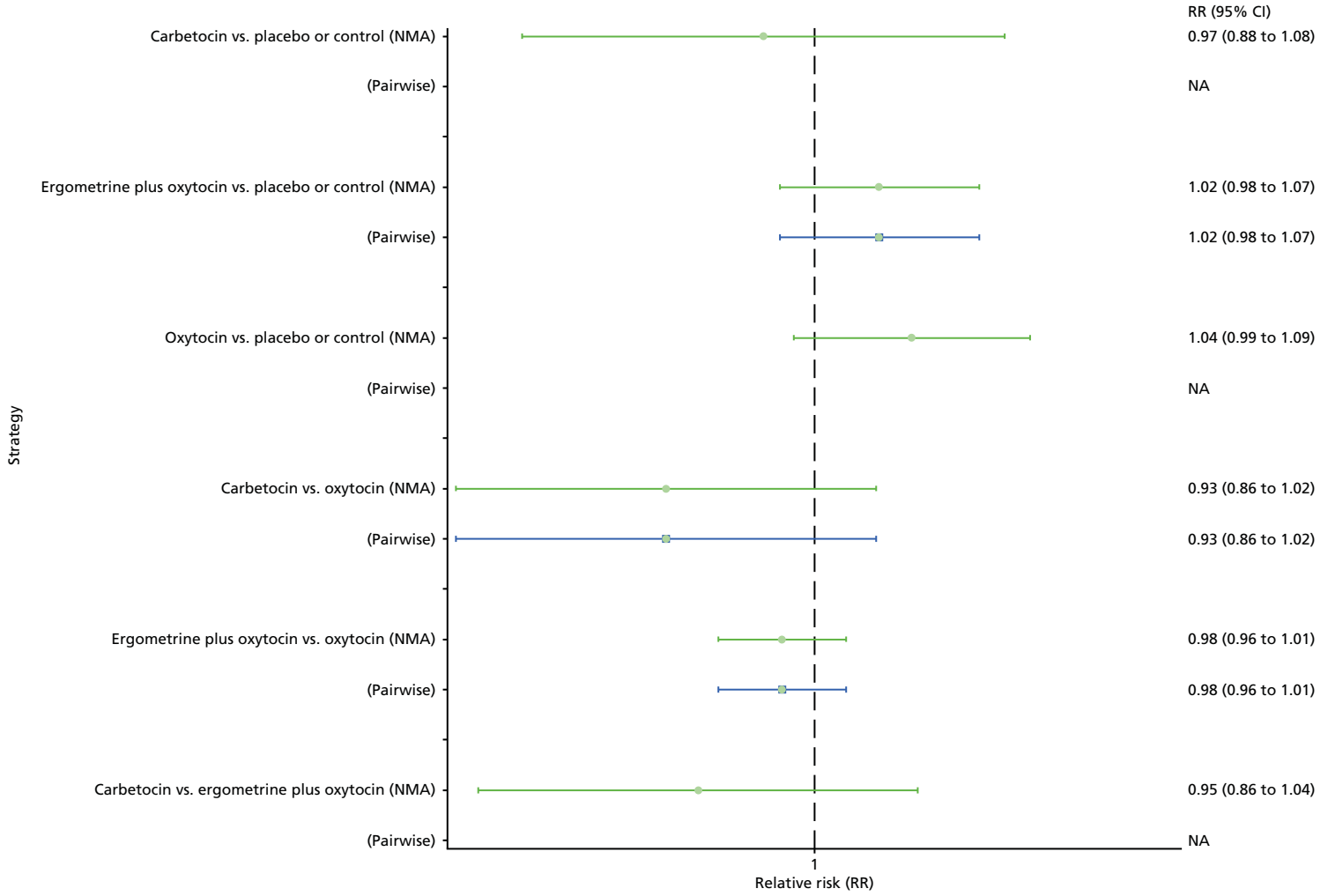

FIGURE 29 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for breastfeeding at discharge. NA, not applicable.

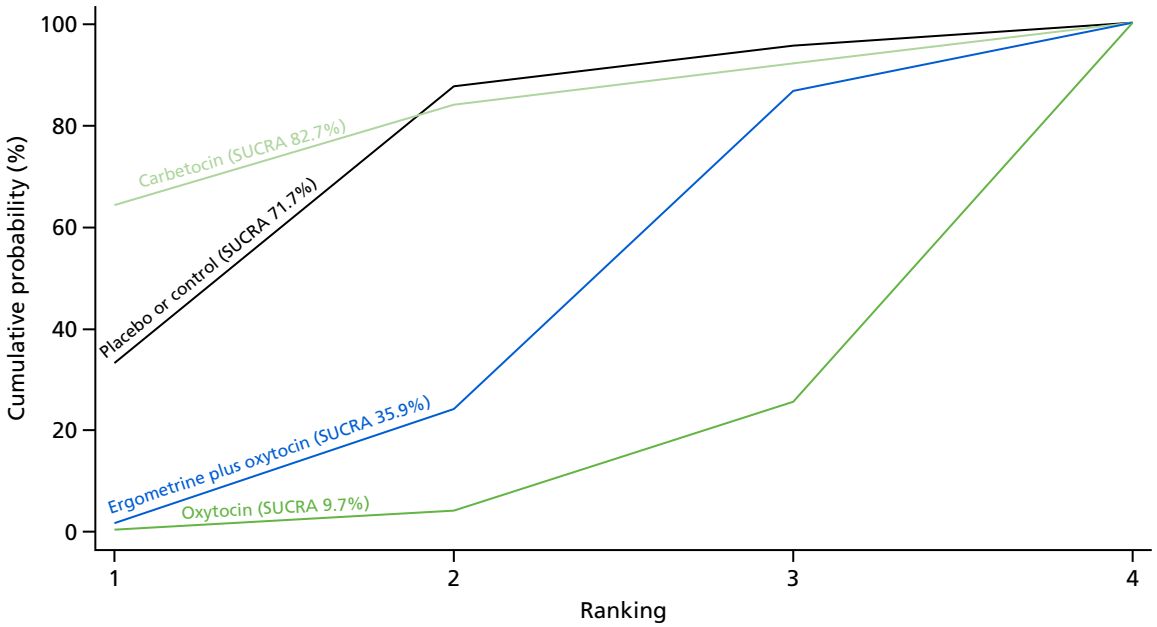

FIGURE 30 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for breastfeeding at discharge.

Side effects

Nausea

The network diagram for nausea is presented in *Appendix 8*. Pooled effect sizes from the NMA of 74 trials suggested that ergometrine and ergometrine plus oxytocin are worse than the placebo or the control in causing nausea (*Figure 31*). Ergometrine, ergometrine plus oxytocin, misoprostol and misoprostol plus oxytocin were found to be worse in causing nausea than the standard intervention, oxytocin (see *Figure 31*). Ergometrine, ergometrine plus oxytocin and misoprostol plus oxytocin were significantly worse in causing nausea than carbetocin. There was evidence of global inconsistency in this analysis ($p = 0.005$). However, it is noted that the CIs for both the NMA and the direct evidence were overlapping across all comparisons, suggesting locally consistent results except for ergometrine versus placebo or the control based on a single study.

Figure 32 shows the cumulative probabilities for each intervention being at each possible rank for causing nausea. The highest-ranked and least likely interventions to cause nausea are carbetocin, oxytocin and placebo or the control. The lowest-ranked and most likely interventions to cause nausea are ergometrine plus oxytocin and ergometrine.

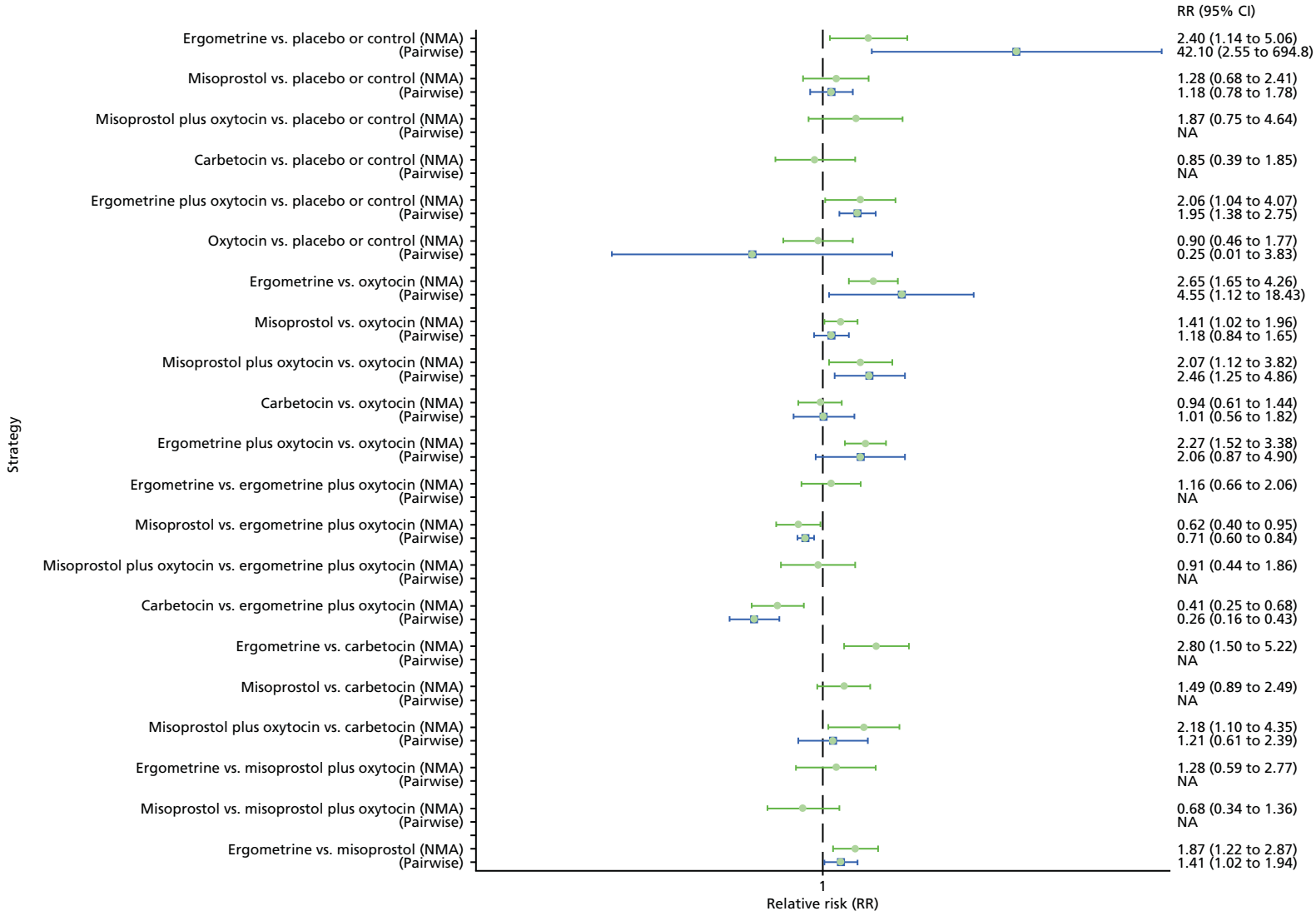

FIGURE 31 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for nausea. NA, not applicable.

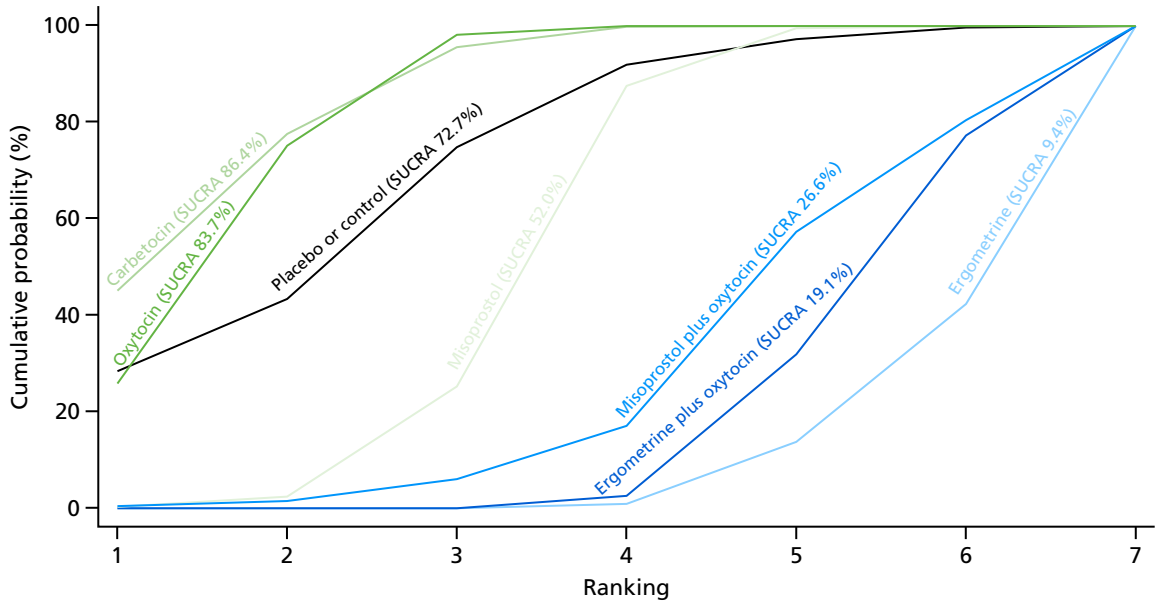

FIGURE 32 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for nausea.

Vomiting

The network diagram for vomiting is presented in *Appendix 8*. Pooled effect sizes from the NMA of 83 trials suggested that ergometrine and ergometrine plus oxytocin are worse than the placebo or the control in causing vomiting (*Figure 33*). Ergometrine, ergometrine plus oxytocin, misoprostol and misoprostol plus oxytocin were found to be worse in causing vomiting than the standard intervention, oxytocin (see *Figure 33*). Ergometrine, ergometrine plus oxytocin, misoprostol and misoprostol plus oxytocin were significantly worse in causing vomiting than carbetocin. There was no evidence of global inconsistency in this analysis ($p = 0.06$).

Figure 34 shows the cumulative probabilities for each intervention being at each possible rank for causing vomiting. The highest-ranked interventions are carbetocin, oxytocin and placebo or the control, with an almost 100% probability of these three interventions being ranked in the top three. The lowest-ranked interventions were ergometrine plus oxytocin and ergometrine.

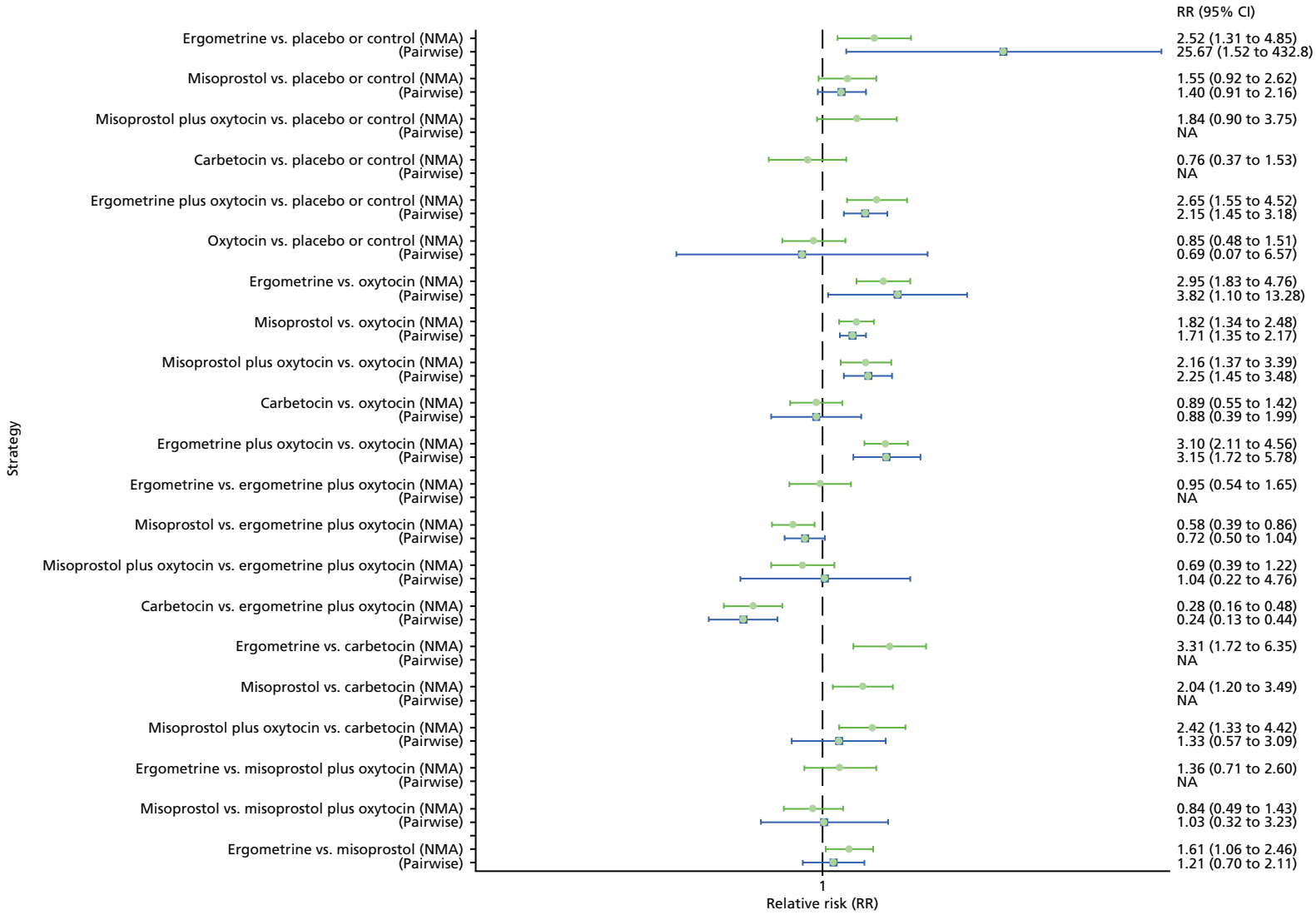

FIGURE 33 Forest plot with relative RRs and 95% CIs from the NMAs and pairwise analyses for vomiting. NA, not applicable.

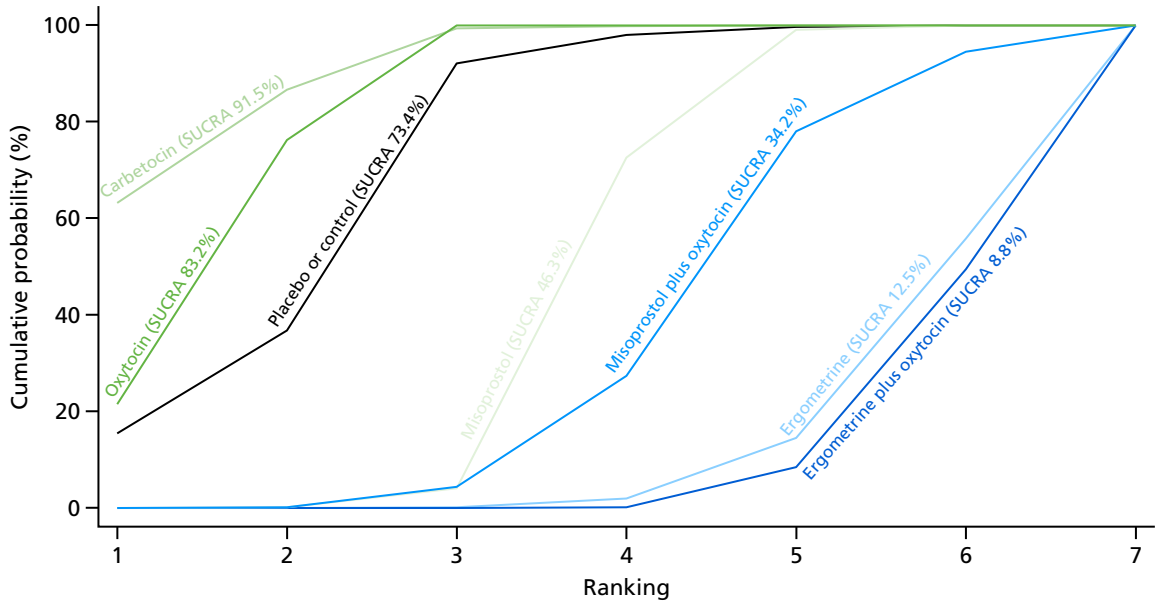

FIGURE 34 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for vomiting.

Hypertension

The network diagram for hypertension is presented in *Appendix 8*. Pooled effect sizes from the NMA of 15 trials suggested that ergometrine is worse than the placebo or the control in causing hypertension (*Figure 35*). Ergometrine was found to be worse in causing hypertension than the standard intervention, oxytocin (see *Figure 35*). Ergometrine is also significantly worse in causing hypertension than carbetocin and misoprostol. There was no evidence of global inconsistency in this analysis ($p = 0.481$).

Figure 36 shows the cumulative probabilities for each intervention being at each possible rank for causing hypertension. The lowest-ranked interventions were ergometrine and ergometrine plus oxytocin. However, not all interventions could be ranked because of the lack of studies in this analysis.

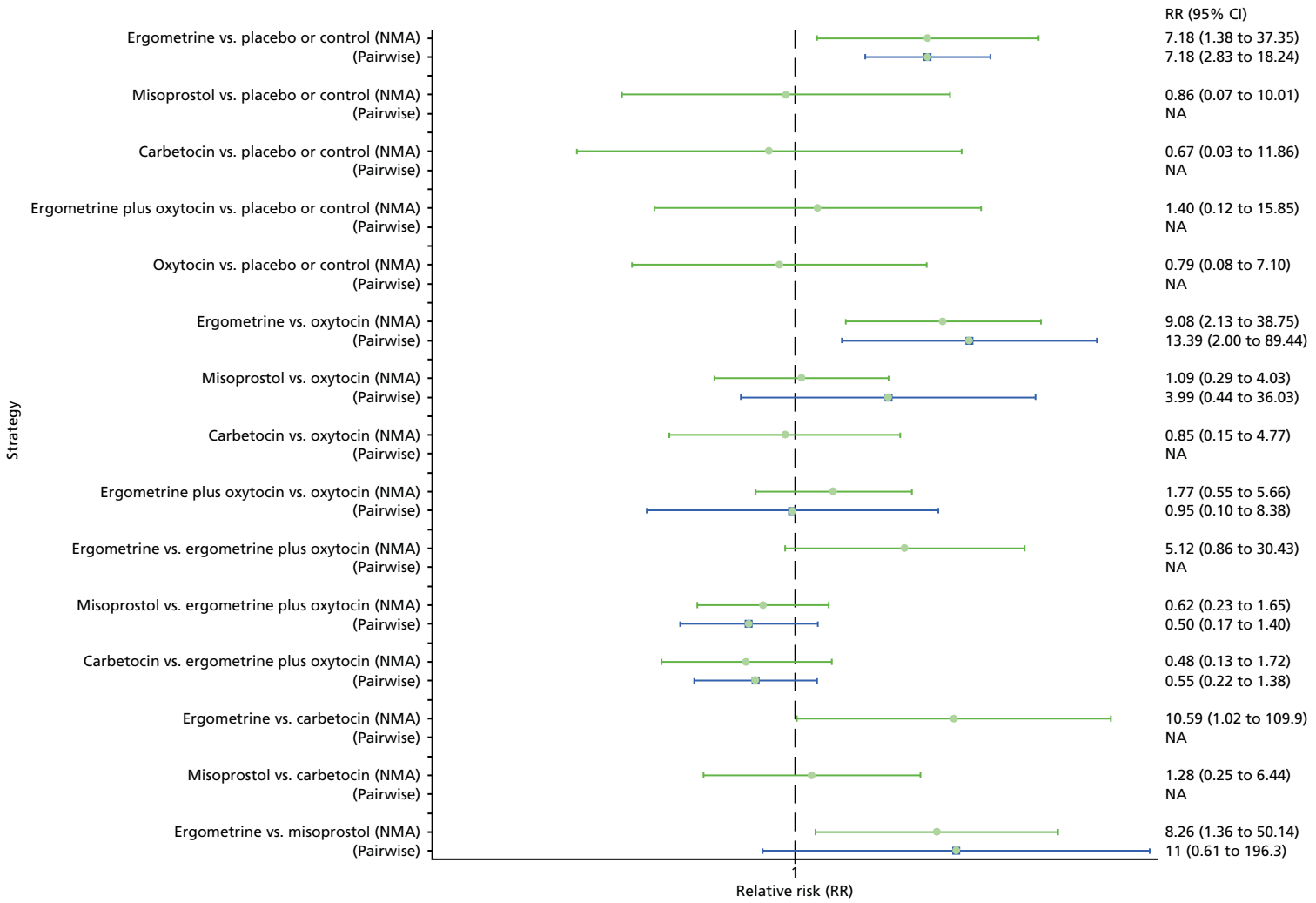

FIGURE 35 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for hypertension. NA, not applicable.

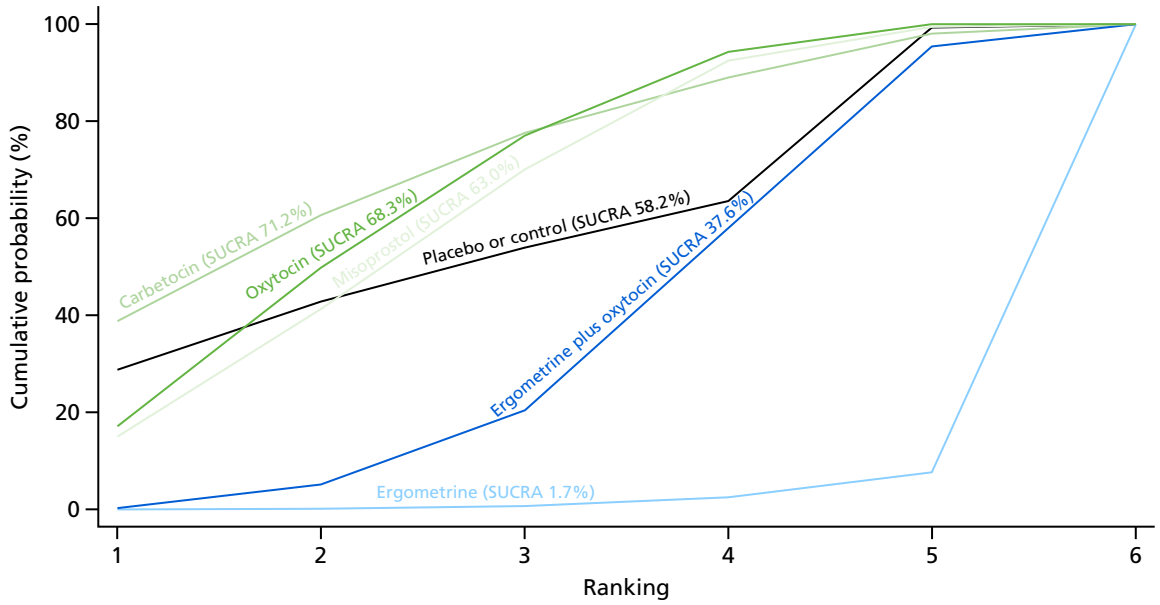

FIGURE 36 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for hypertension.

Headache

The network diagram for headache is presented in *Appendix 8*. Pooled effect sizes from the NMA of 45 trials suggested that ergometrine is worse than the placebo or the control in causing headaches (*Figure 37*). Ergometrine was found to be worse in causing headache than the standard intervention, oxytocin (see *Figure 37*). Ergometrine is also significantly worse in causing headaches than carbetocin and misoprostol. There was no evidence of global inconsistency in this analysis ($p = 0.826$).

Figure 38 shows the cumulative probabilities for each intervention being at each possible rank for causing headache. The lowest-ranked interventions were ergometrine, misoprostol plus oxytocin and ergometrine plus oxytocin. The highest-ranked interventions are placebo or the control, carbetocin and oxytocin.

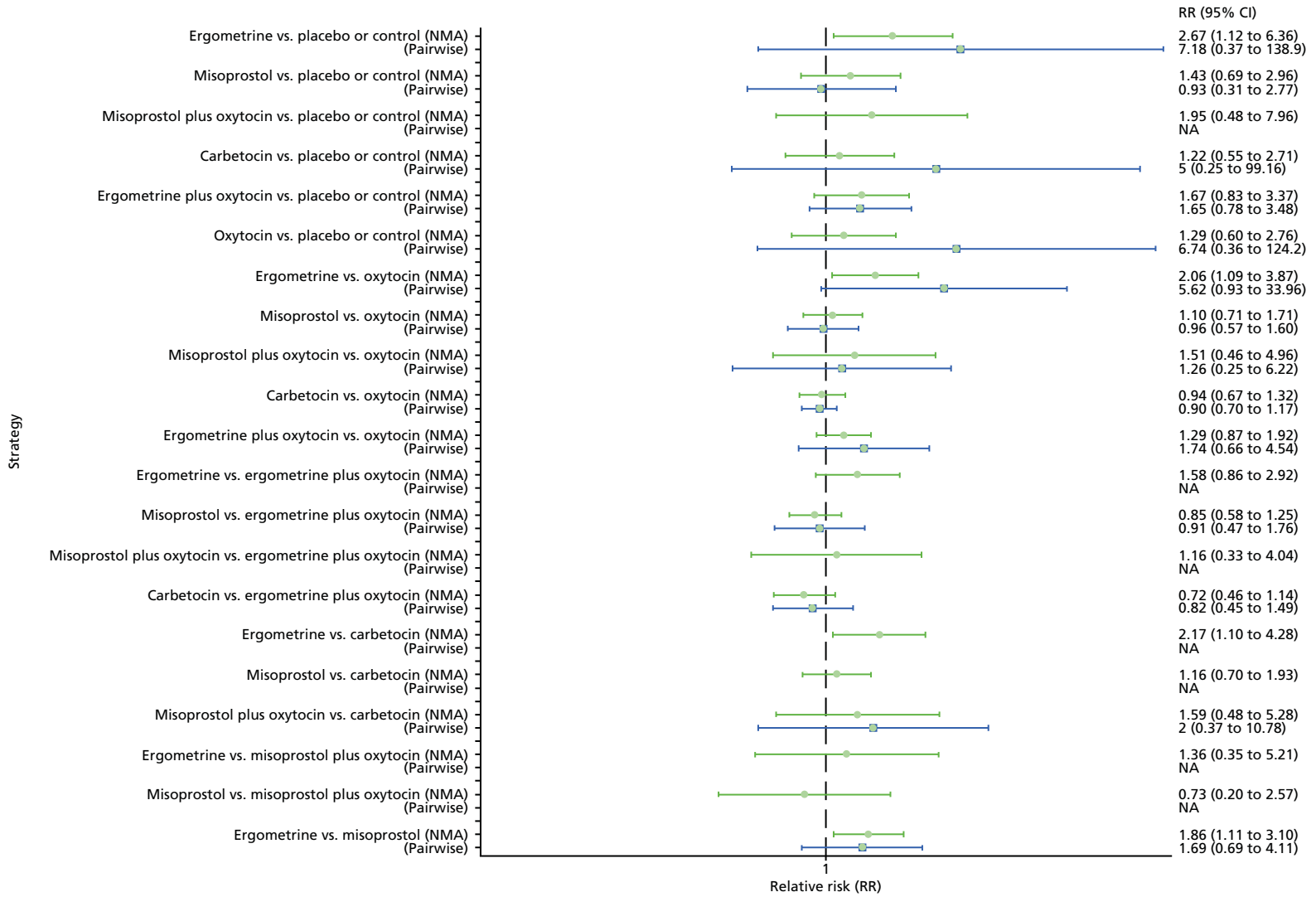

FIGURE 37 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for headaches. NA, not applicable.

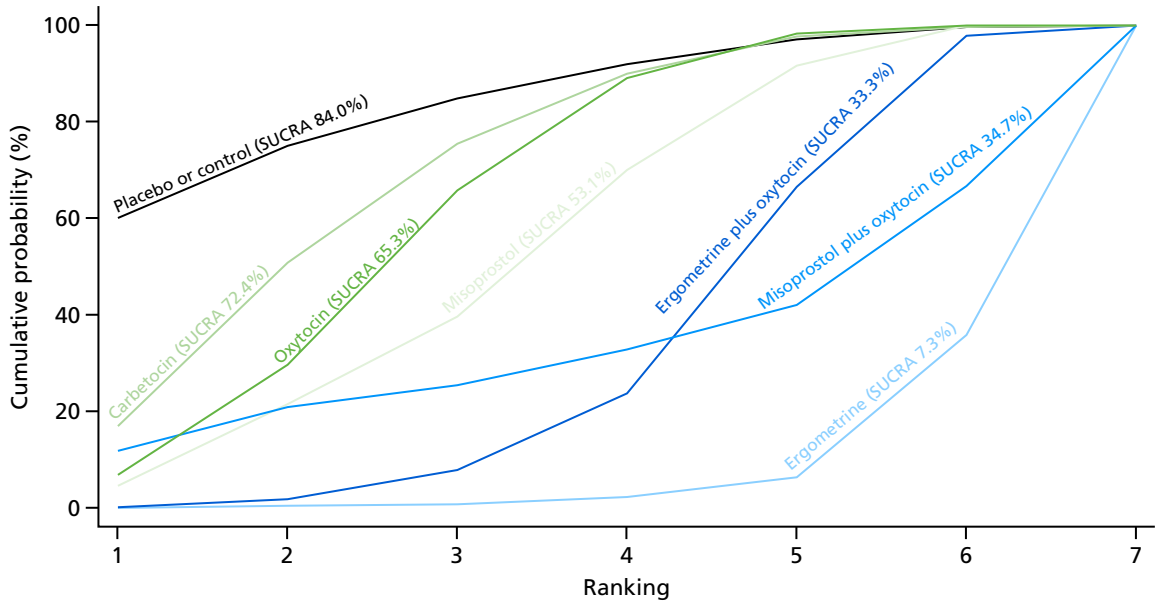

FIGURE 38 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for headaches.

Fever

The network diagram for fever is presented in *Appendix 8*. Pooled effect sizes from the NMA of 64 trials suggested that misoprostol and misoprostol plus oxytocin are worse than the placebo or the control in causing fever (*Figure 39*). Misoprostol and misoprostol plus oxytocin were found to be worse in causing fever than the standard intervention, oxytocin (see *Figure 39*). Misoprostol and misoprostol plus oxytocin were also significantly worse in causing fever than carbetocin, ergometrine and ergometrine plus oxytocin, with the exception of the comparison carbetocin versus misoprostol plus oxytocin, which fell just short of being statistically significant. There was no evidence of global inconsistency in this analysis ($p = 0.352$).

Figure 40 shows the cumulative probabilities for each intervention being at each possible rank for causing fever. The highest-ranked interventions are carbetocin, oxytocin and placebo or the control. The lowest-ranked interventions were misoprostol and misoprostol plus oxytocin. The rest of the interventions were similar in ranking to the placebo or the control group.

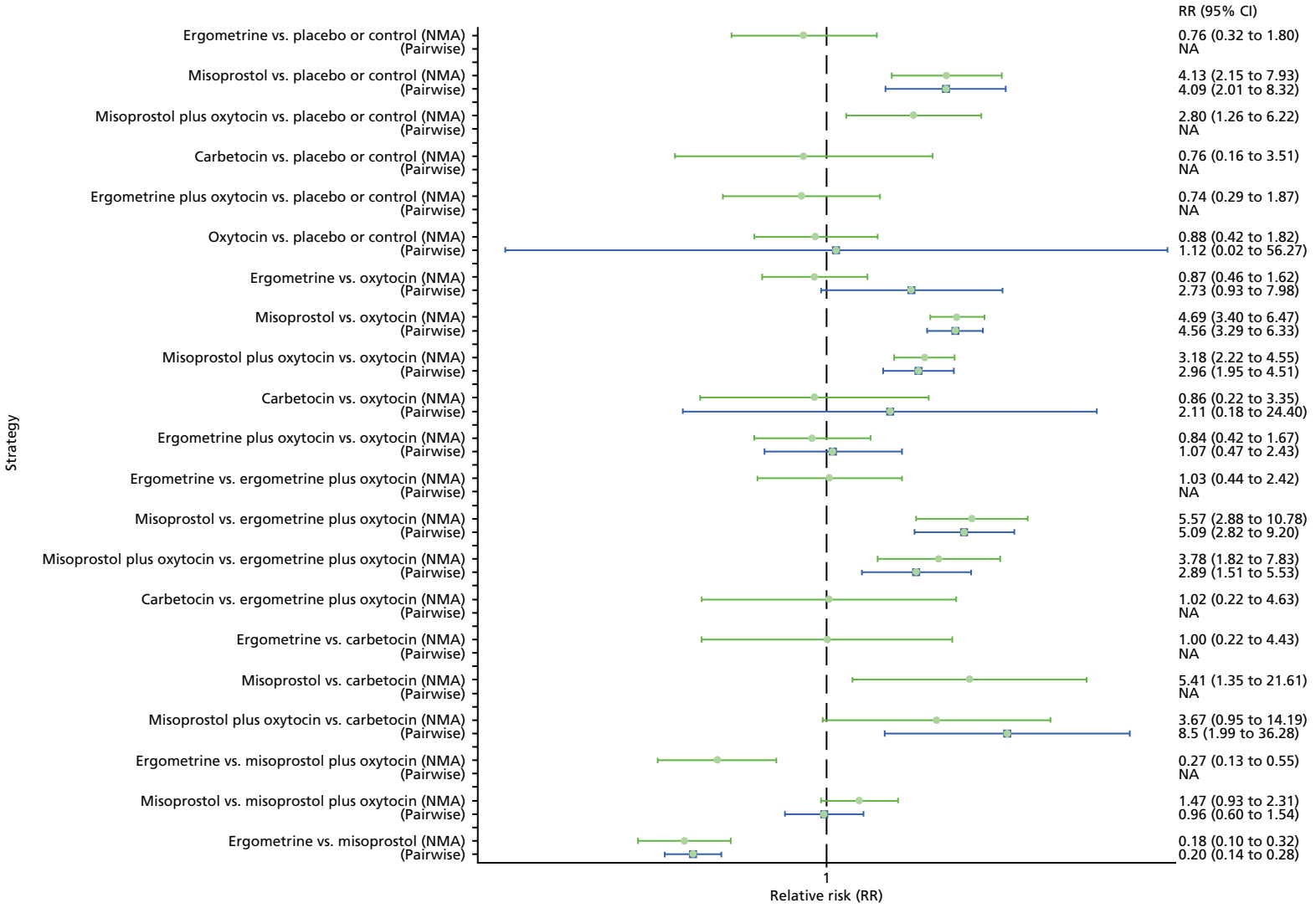

FIGURE 39 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for fever. NA, not applicable.

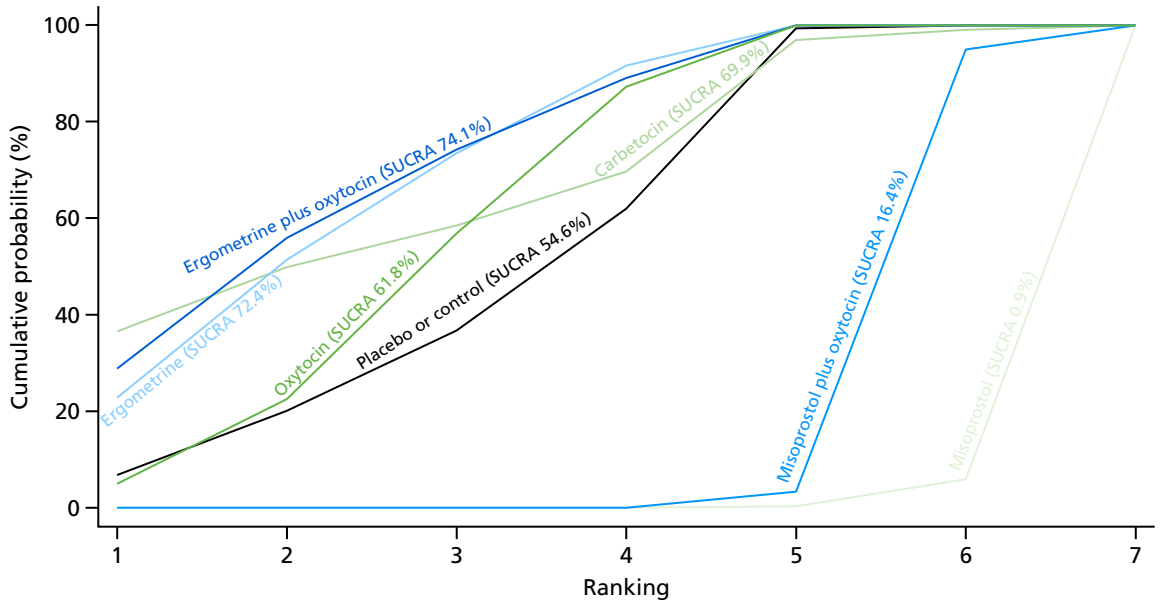

FIGURE 40 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof and combinations thereof for fever.

Shivering

The network diagram for shivering is presented in *Appendix 8*. Pooled effect sizes from the NMA of 87 trials suggested that misoprostol and misoprostol plus oxytocin are worse than the placebo or the control in causing shivering (*Figure 41*). Misoprostol and misoprostol plus oxytocin were found to be worse in causing shivering than the standard intervention, oxytocin (see *Figure 41*). Misoprostol and misoprostol plus oxytocin were also significantly worse in causing shivering than carbetocin, ergometrine and ergometrine plus oxytocin. There was no evidence of global inconsistency in this analysis ($p = 0.923$).

Figure 42 shows the cumulative probabilities for each intervention being at each possible rank for causing shivering. The highest-ranked interventions are carbetocin and oxytocin. The lowest-ranked interventions were misoprostol and misoprostol plus oxytocin. Ergometrine and ergometrine plus oxytocin were similar in ranking to the placebo or the control group.

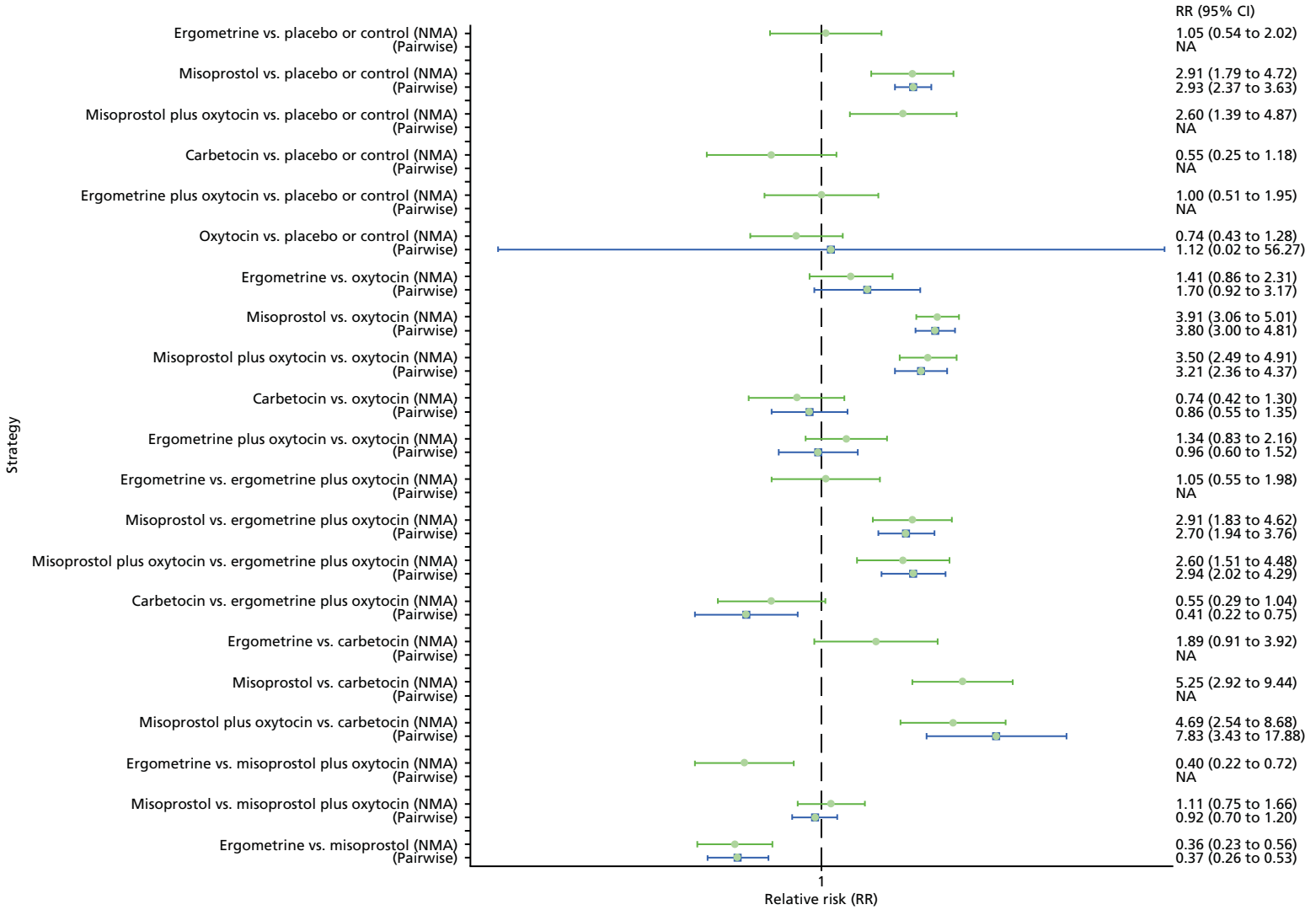

FIGURE 41 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for shivering. NA, not applicable.

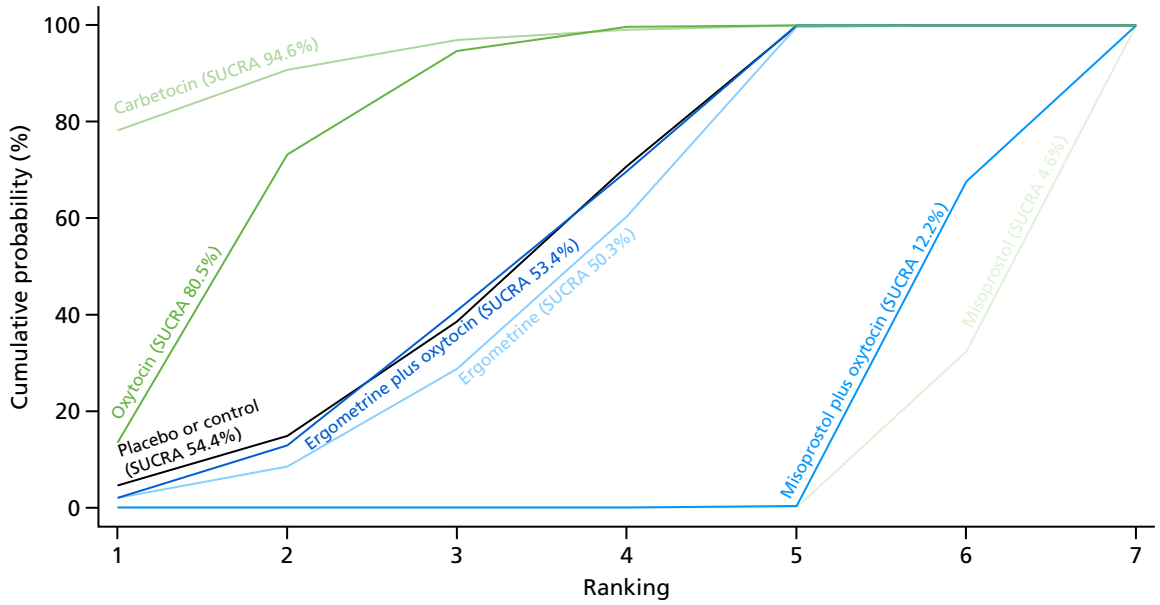

FIGURE 42 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for shivering.

Tachycardia

The network diagram for tachycardia is presented in *Appendix 8*. Pooled effect sizes from the NMA of seven trials suggested that only carbetocin is worse than oxytocin and ergometrine plus oxytocin in causing tachycardia, but most of the comparisons were based on single studies (*Figure 43*). There was no evidence of global inconsistency in this analysis ($p = 0.361$).

Figure 44 shows the cumulative probabilities for each intervention being at each possible rank for causing tachycardia. No clear ranking emerges and not all interventions could be ranked because of the lack of studies in this analysis.

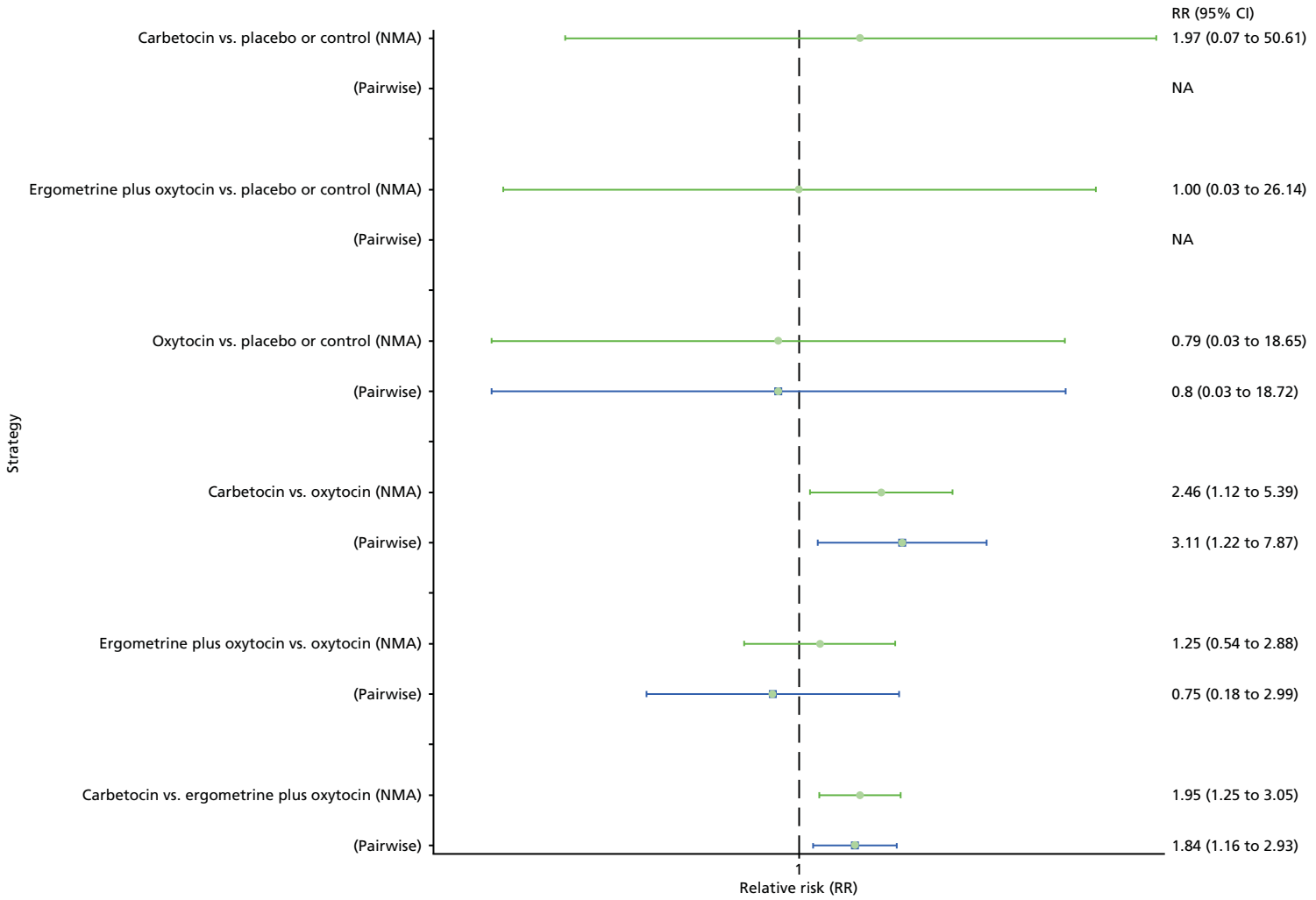

FIGURE 43 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for tachycardia. NA, not applicable.

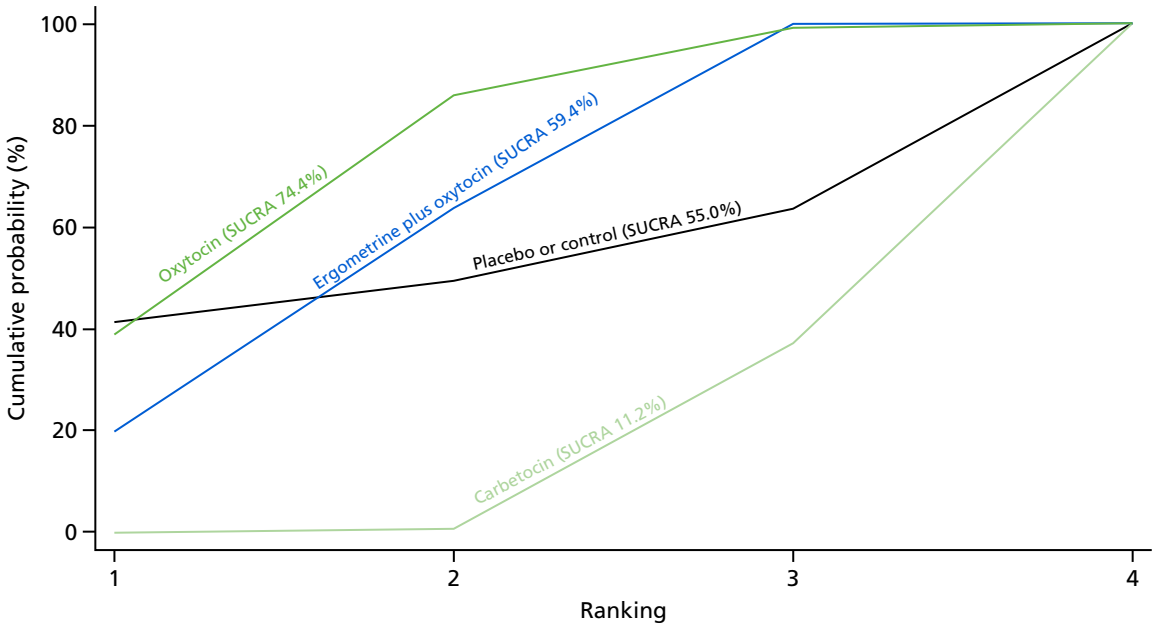

FIGURE 44 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for tachycardia.

Hypotension

The network diagram for hypotension is presented in *Appendix 8*. Pooled effect sizes from the NMA of eight trials suggested a lack of evidence that any intervention is worse or better than any other, but most of the comparisons were based on single studies (*Figure 45*). There was no evidence of global inconsistency in this analysis ($p = 0.304$).

Figure 46 shows the cumulative probabilities for each intervention being at each possible rank for causing hypotension. The highest-ranked interventions were misoprostol and placebo or the control. For the rest of the interventions no clear ranking emerges and not all interventions could be ranked because of the lack of studies in this analysis.

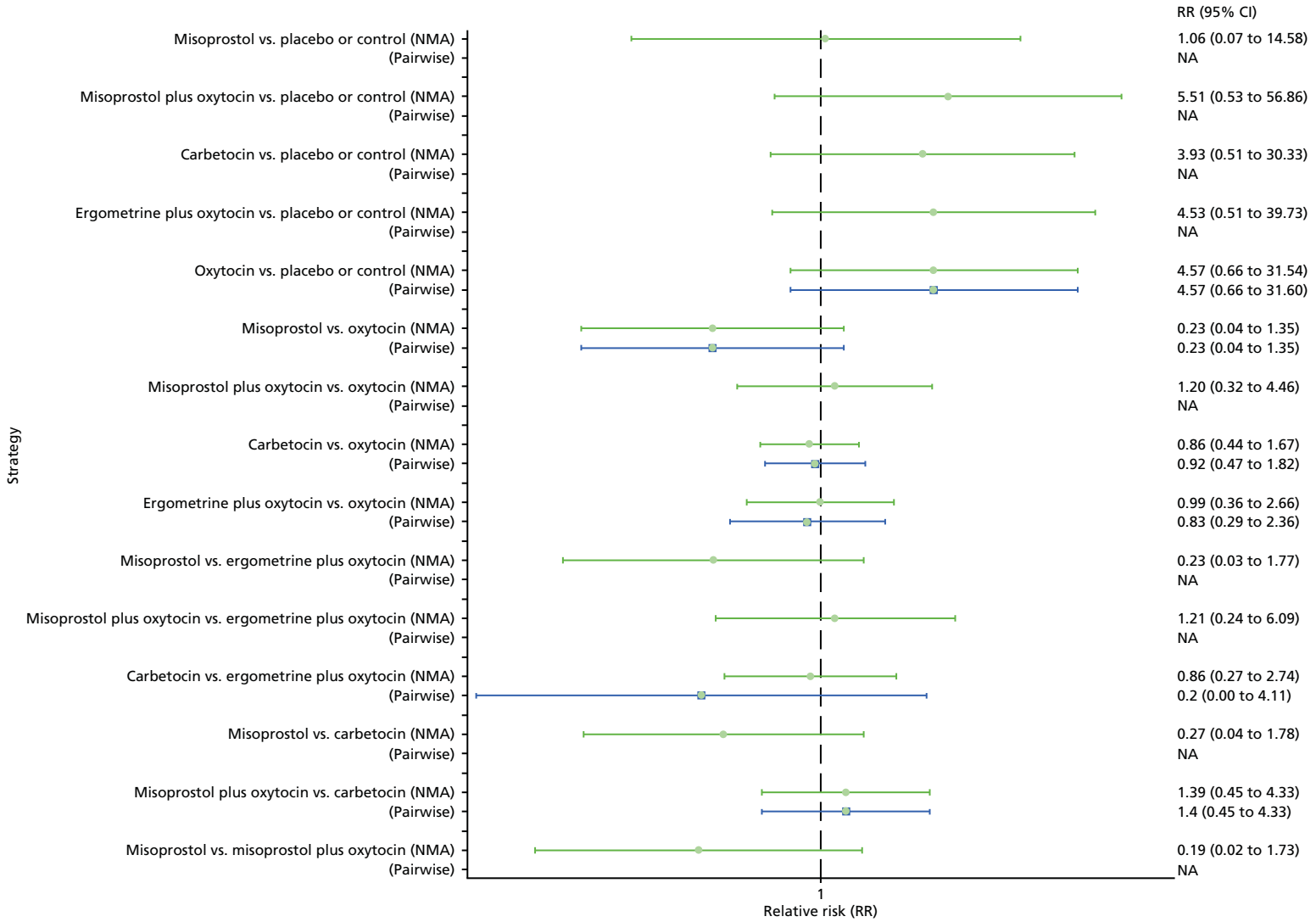

FIGURE 45 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for hypotension. NA, not applicable.

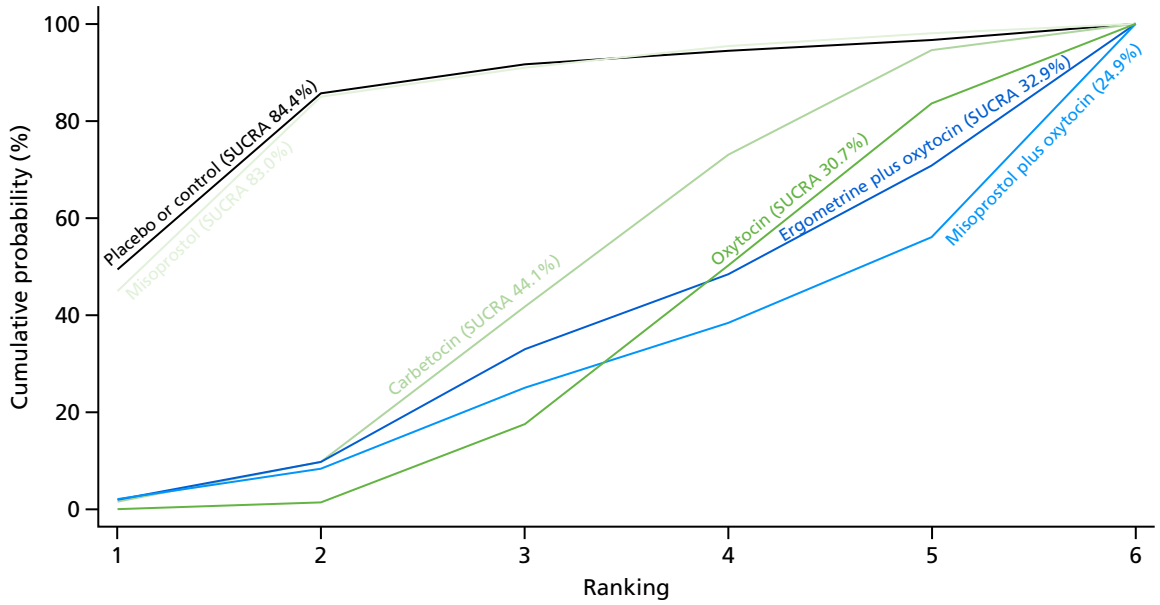

FIGURE 46 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for hypotension.

Abdominal pain

The network diagram for abdominal pain is presented in *Appendix 8*. Pooled effect sizes from the NMA of 25 trials suggested that misoprostol plus oxytocin is worse than the placebo or the control in causing abdominal pain (*Figure 47*). No active intervention was found to be worse or better than any other. There was evidence of global inconsistency in this analysis ($p = 0.035$). However, it is noted that the CIs for both the NMA and the direct evidence were overlapping across all comparisons, suggesting locally fairly consistent results.

Figure 48 shows the cumulative probabilities for each intervention being at each possible rank for causing abdominal pain. The highest-ranked intervention was placebo or the control. For the rest of the interventions no clear ranking emerges because of the lack of studies in this analysis.

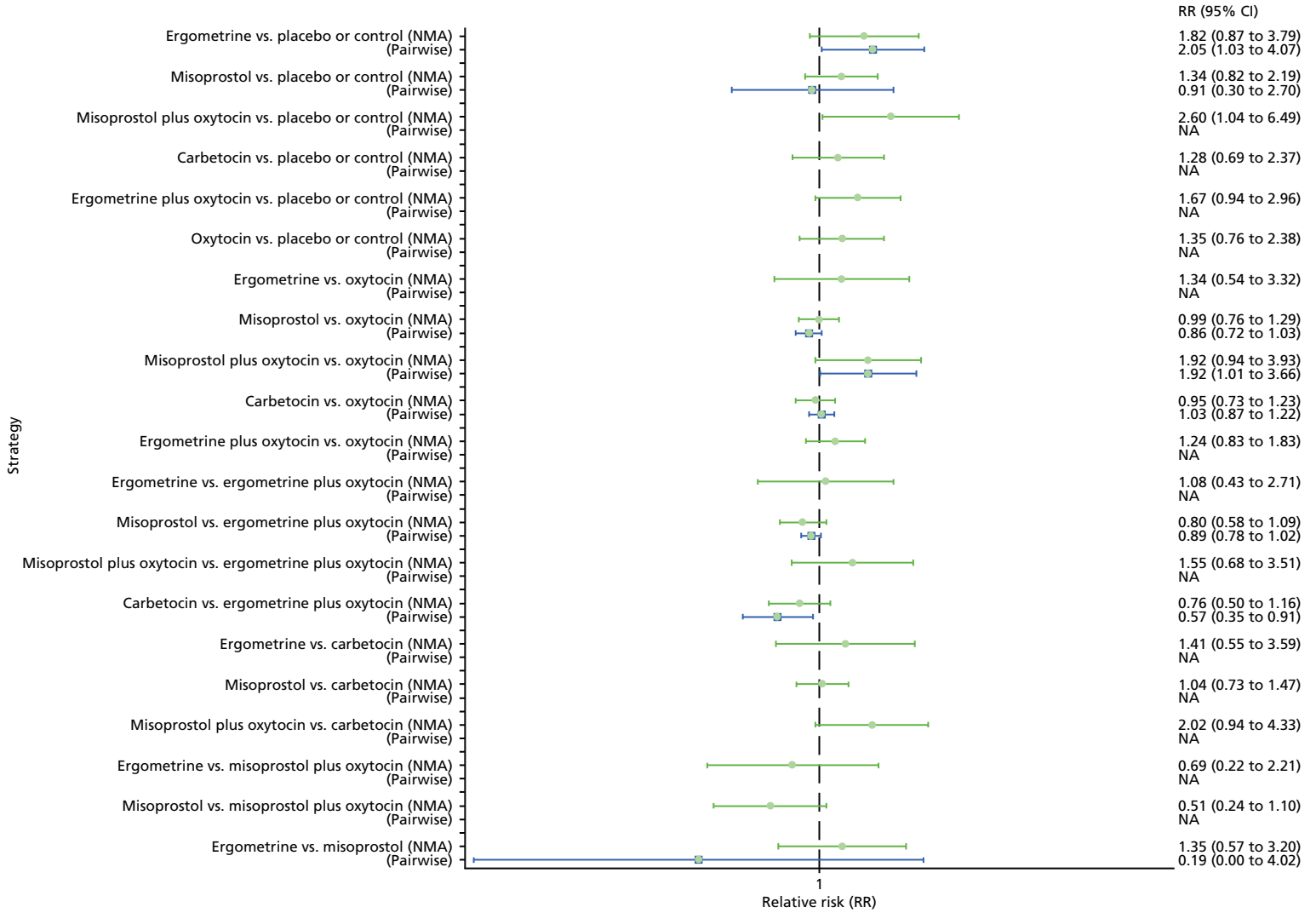

FIGURE 47 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for abdominal pain. NA, not applicable.

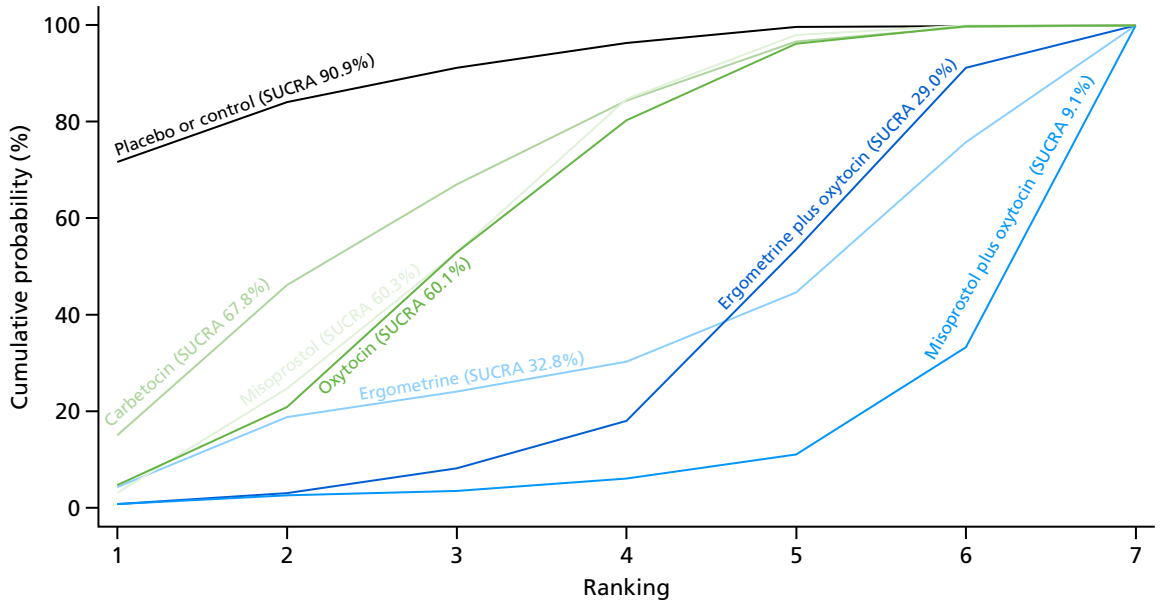

FIGURE 48 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for abdominal pain.

Subgroup analyses

Mode of birth

Vaginal birth

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml for the subgroup, including only vaginal births, is presented in *Appendix 8*. Pooled effect sizes from the NMA of 85 trials suggested that all interventions are effective for preventing PPH blood loss of ≥ 500 ml when compared with the placebo (*Figure 49*). Ergometrine plus oxytocin and misoprostol plus oxytocin were found to be more effective than the standard intervention, oxytocin, even though carbetocin also demonstrated a trend towards reduction of this outcome (see *Figure 49*). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective than misoprostol and ergometrine when used alone. There was no evidence of global inconsistency in this analysis ($p = 0.06$).

Figure 50 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the subgroup including only vaginal births. The highest-ranked interventions are ergometrine plus oxytocin, carbetocin, and misoprostol plus oxytocin, with an almost 100% probability of these three interventions being ranked first, second or third. Oxytocin is ranked fourth and its probability of being ranked in the top three interventions was close to 0%.

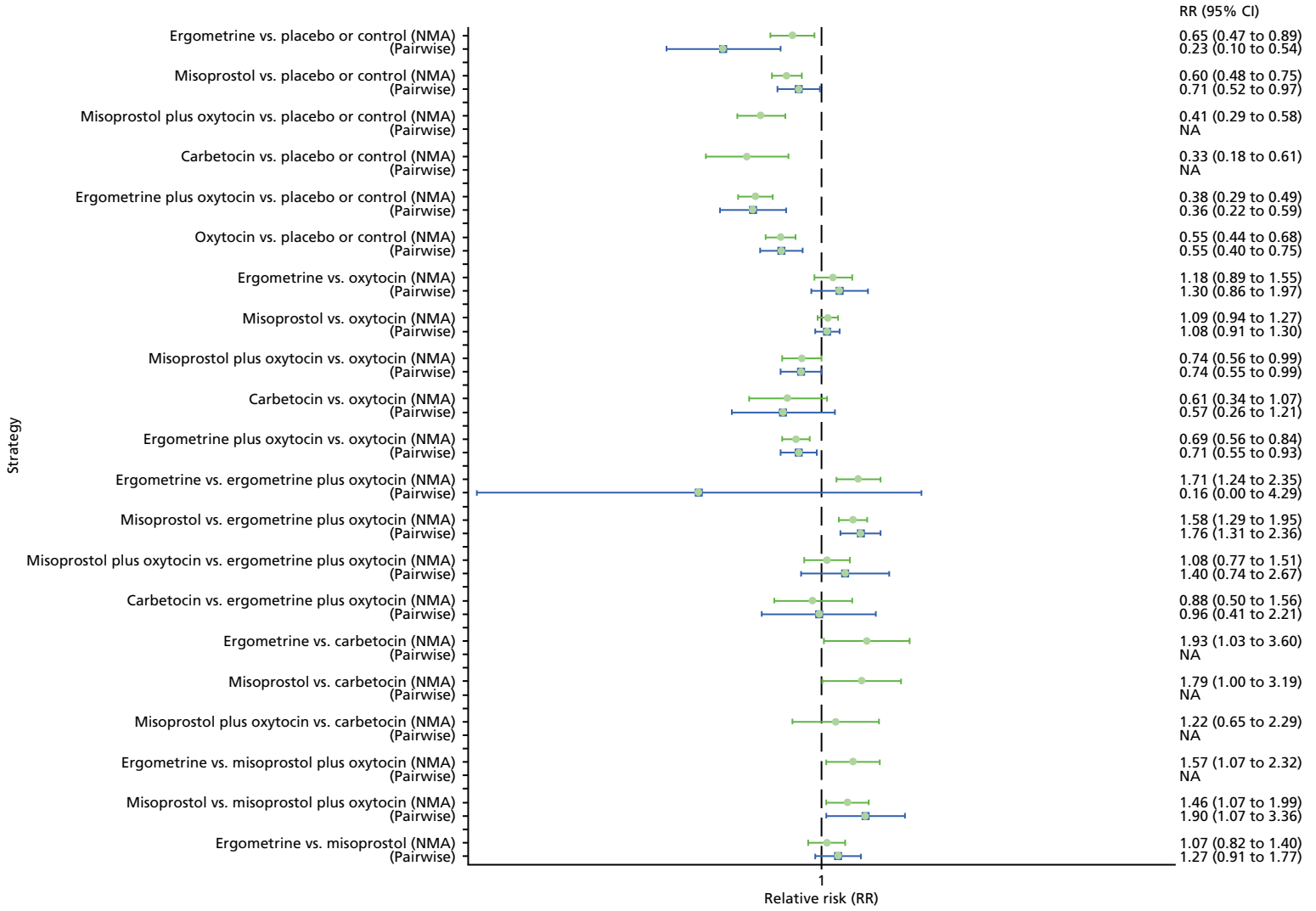

FIGURE 49 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, by mode of birth (vaginal birth). NA, not applicable.

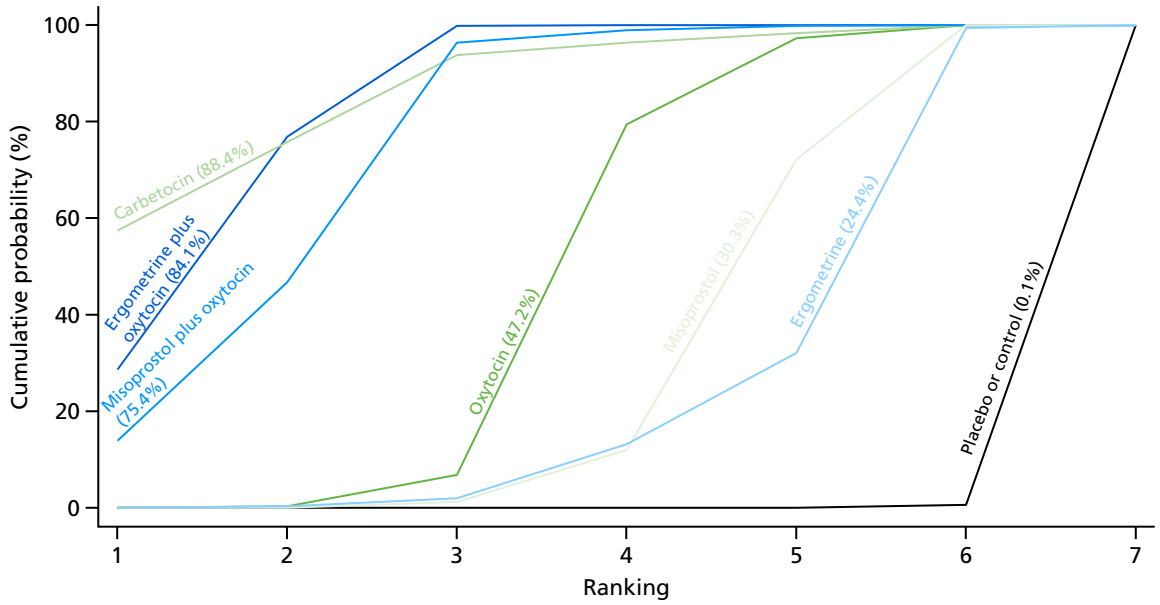

FIGURE 50 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, by mode of birth (vaginal birth).

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

Pooled effect sizes from the NMA of 71 trials suggested that all interventions except carbetocin and ergometrine are effective for preventing PPH blood loss of ≥ 1000 ml when compared with placebo (*Figure 51*). Ergometrine plus oxytocin was the only intervention found to be more effective than the standard intervention, oxytocin, even though carbetocin and misoprostol plus oxytocin demonstrated a trend towards reduction of this outcome (see *Figure 51*). There was no evidence of global inconsistency in this analysis ($p = 0.206$).

Figure 52 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the subgroup including only vaginal births. The highest-ranked interventions are carbetocin, ergometrine plus oxytocin, and misoprostol plus oxytocin. Oxytocin is ranked fourth and its probability of being ranked in the top two interventions was close to 0%.

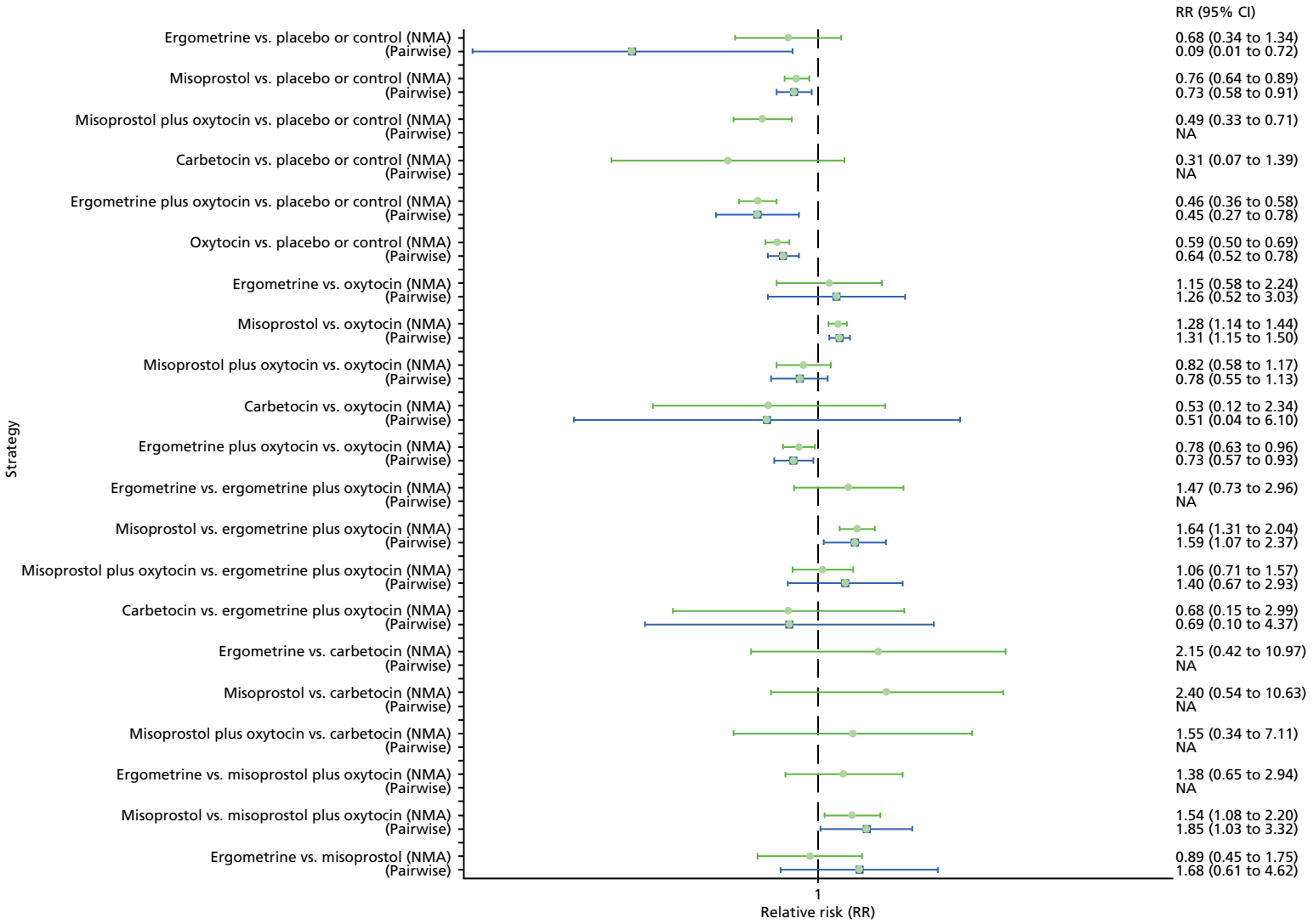

FIGURE 51 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, by mode of birth (vaginal birth). NA, not applicable.

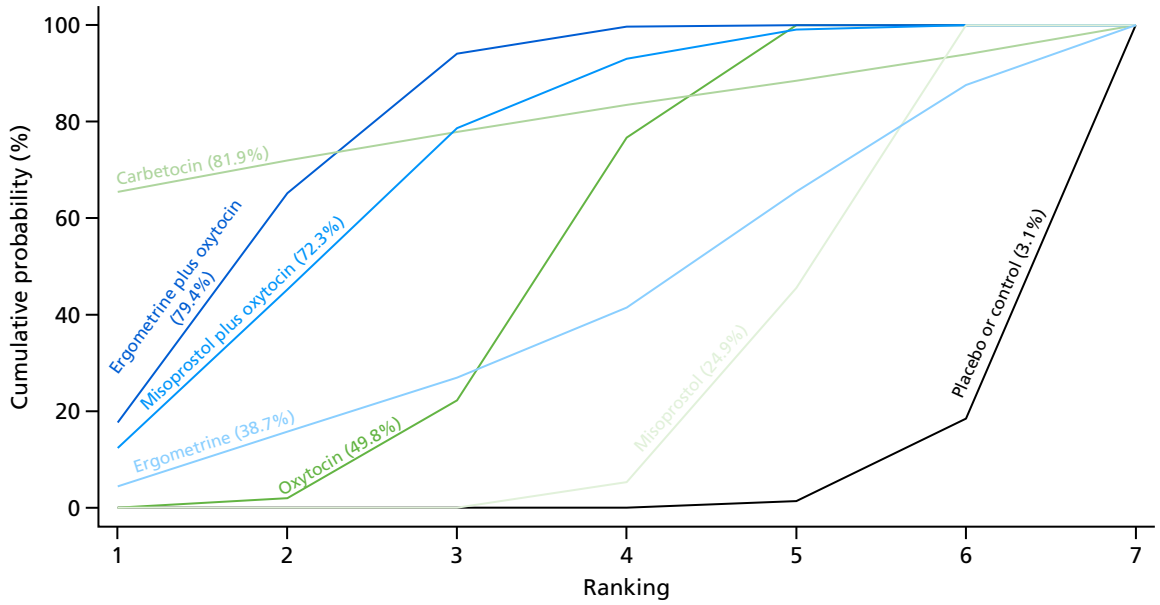

FIGURE 52 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml by mode of birth (vaginal birth).

Caesarean section

Primary postpartum haemorrhage blood loss of ≥ 500 ml

Pooled effect sizes from the NMA of 15 trials suggested that only misoprostol plus oxytocin is better than oxytocin alone in preventing PPH blood loss of ≥ 500 ml in women undergoing caesareans, but most of the comparisons were based on single studies (*Figure 53*). There was no evidence of global inconsistency in this analysis ($p = 0.249$).

Figure 54 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the subgroup including only caesareans. The highest-ranked interventions are misoprostol plus oxytocin and carbetocin. Oxytocin is ranked third and its probability in being ranked in the top two interventions was close to 5%. Ergometrine and ergometrine plus oxytocin could not be ranked, as there were no studies found comparing those drugs with any other interventions in the network.

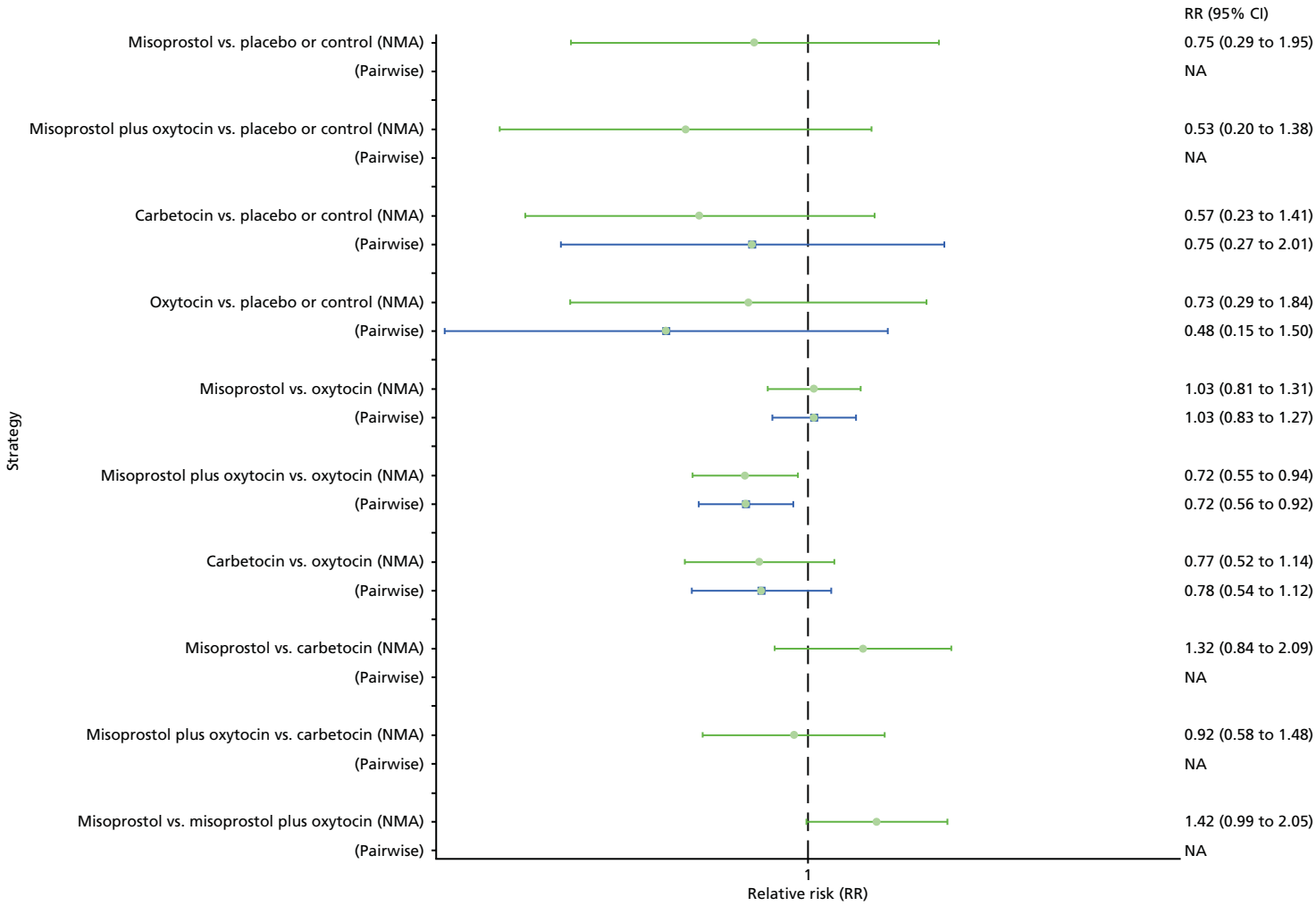

FIGURE 53 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml by mode of birth (caesarean). NA, not applicable.

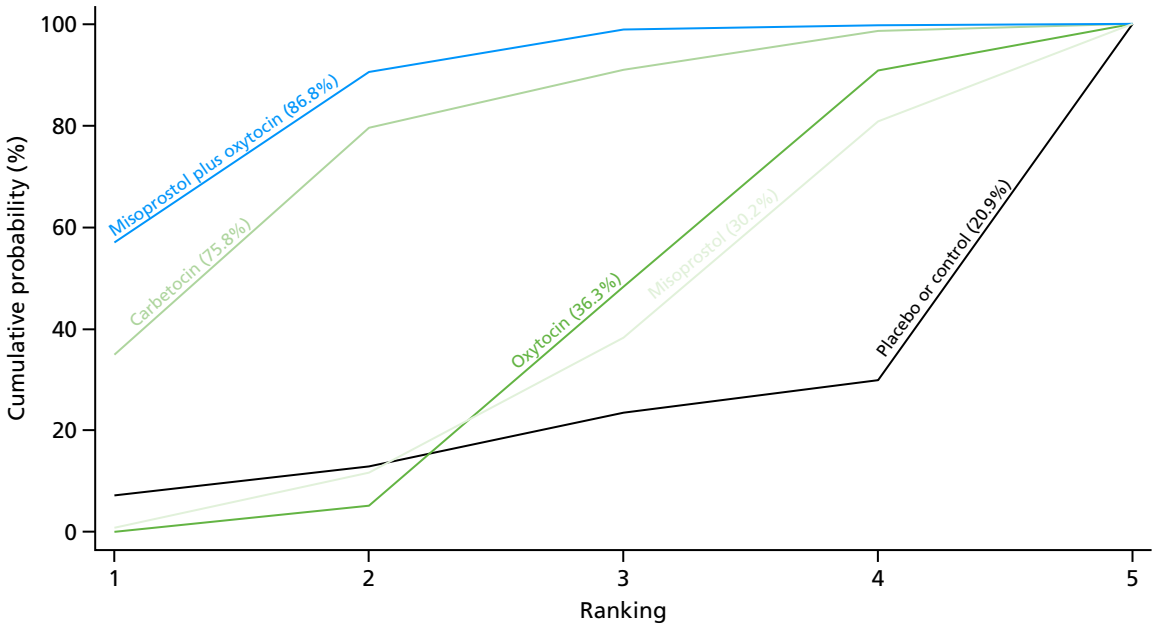

FIGURE 54 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, by mode of birth (caesarean).

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

Pooled effect sizes from the NMA of 19 trials suggested a lack of evidence that any intervention is worse or better than any other in preventing PPH blood loss of ≥ 1000 ml in women undergoing caesareans, but many of the comparisons were based on single studies (*Figure 55*). There was no evidence of global inconsistency in this analysis ($p = 0.86$).

Figure 56 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the subgroup including only caesareans. No clear ranking emerges in this analysis. Ergometrine and ergometrine plus oxytocin could not be ranked, as there were no studies found comparing those drugs with any other interventions in the network.

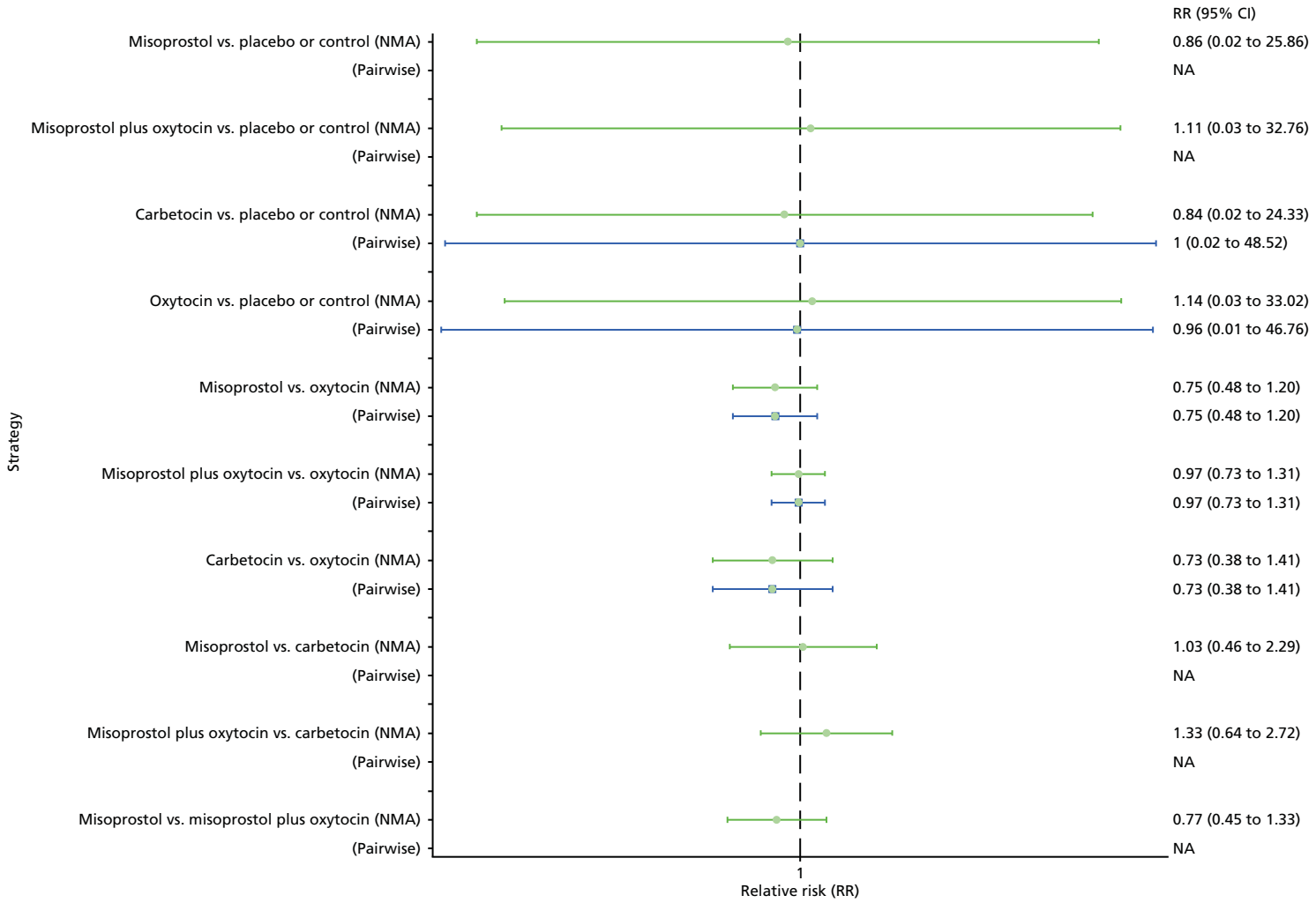

FIGURE 55 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, by mode of birth (caesarean). NA, not applicable.

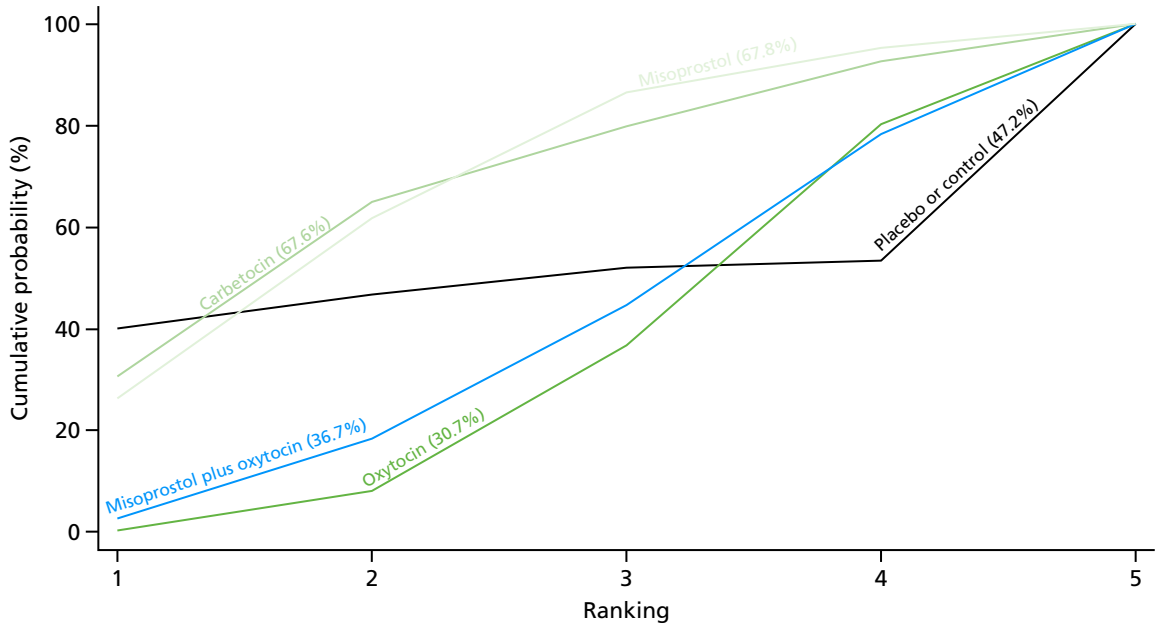

FIGURE 56 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, by mode of birth (caesarean).

Prior risk of postpartum haemorrhage

Low risk for postpartum haemorrhage

Primary postpartum haemorrhage blood loss of ≥ 500 ml

Pooled effect sizes from the NMA of 35 trials suggested that only ergometrine plus oxytocin and misoprostol are better than the placebo in preventing PPH blood loss of ≥ 500 ml in women at low risk for PPH, but most of the comparisons were based on single studies (*Figure 57*). There was no evidence of global inconsistency in this analysis ($p = 0.236$).

Figure 58 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the subgroup including trials with only women at low risk for PPH. The highest-ranked interventions are ergometrine plus oxytocin and carbetocin. Oxytocin is ranked fourth behind misoprostol and its probability in being ranked in the top two interventions was close to 10%. Misoprostol plus oxytocin could not be ranked, as there were no studies found comparing this intervention with any other interventions in the network.

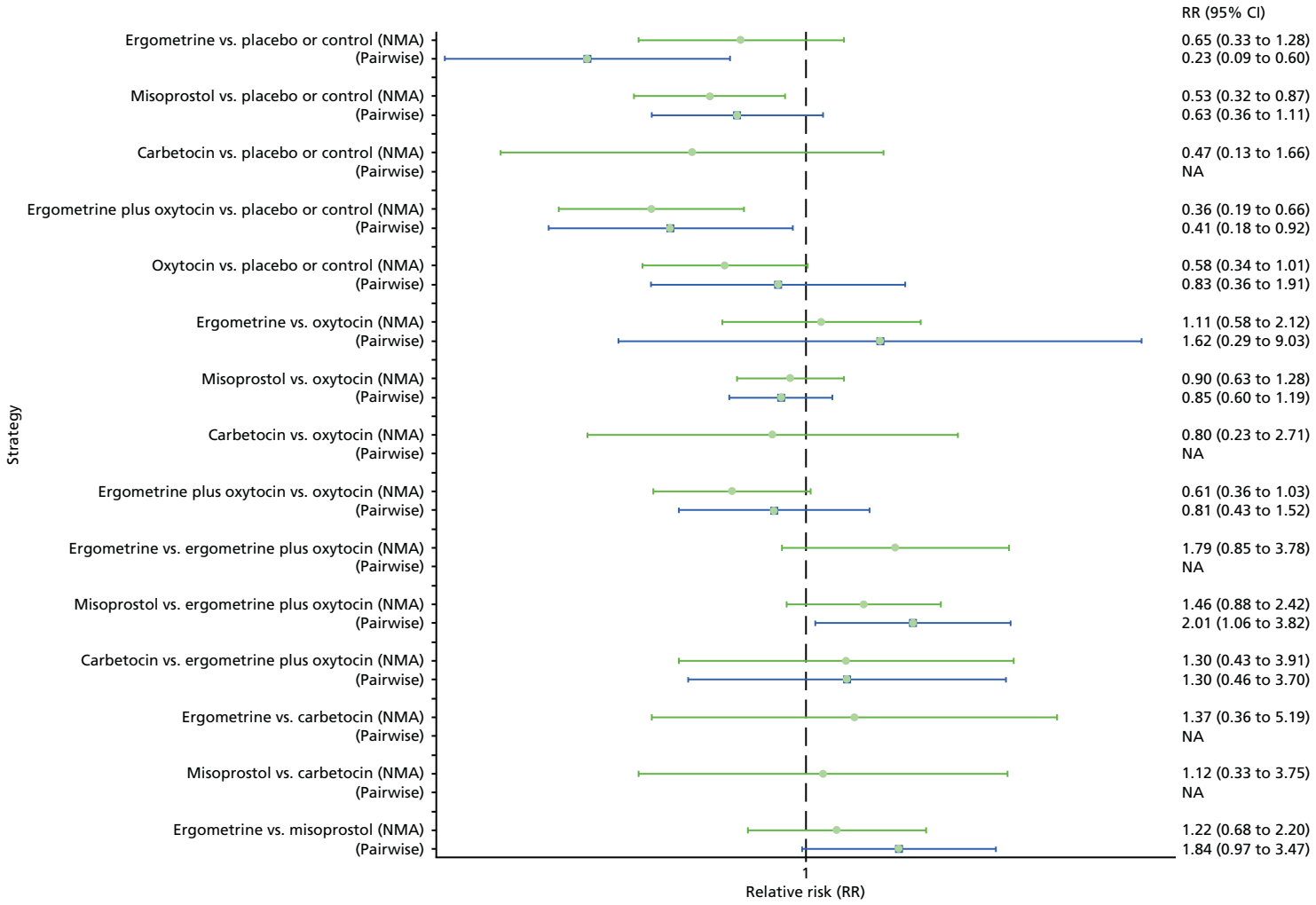

FIGURE 57 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, by prior risk for PPH (low risk). NA, not applicable.

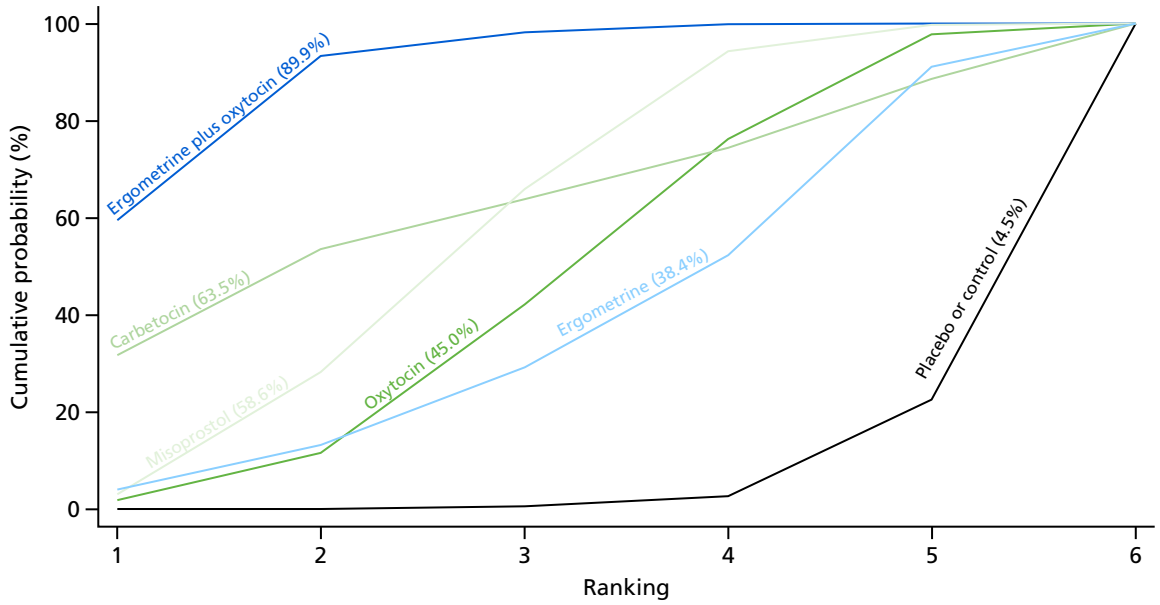

FIGURE 58 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, by prior risk for PPH (low risk).

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

Pooled effect sizes from the NMA of 32 trials suggested that ergometrine plus oxytocin, oxytocin, ergometrine and misoprostol are better than placebo in preventing PPH blood loss of ≥ 1000 ml in women at low risk for PPH (*Figure 59*). The comparisons between active interventions appeared to be underpowered to detect differences between them. There was no evidence of global inconsistency in this analysis ($p = 0.477$).

Figure 60 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the subgroup including trials with only women at low risk for PPH. No clear ranking emerges in this analysis. Ergometrine could not be ranked, as there were no studies found comparing those drugs with any other interventions in the network.

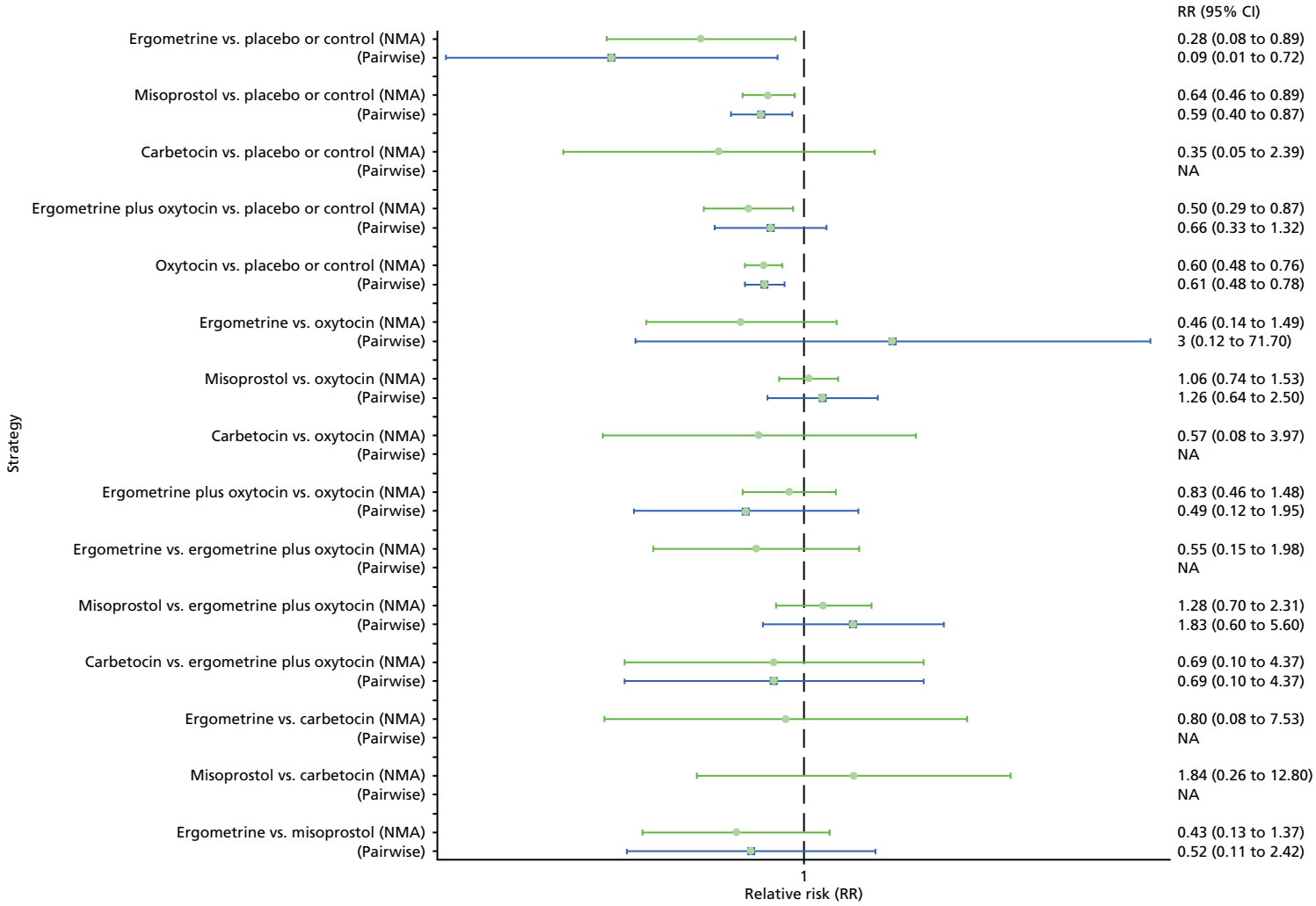

FIGURE 59 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, by prior risk for PPH (low risk). NA, not applicable.

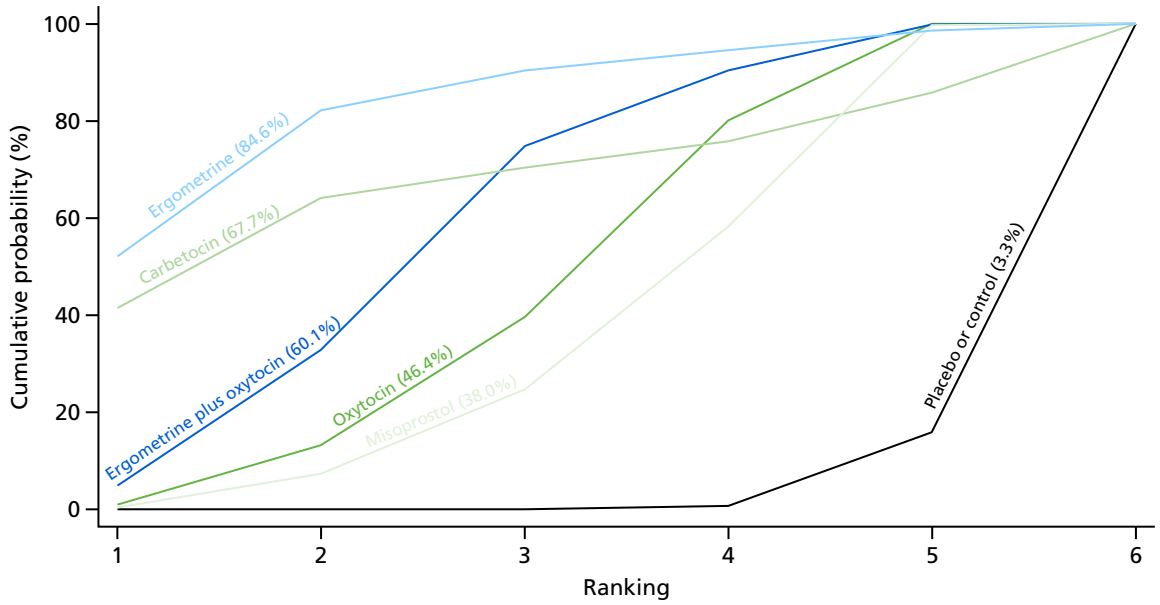

FIGURE 60 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, by prior risk for PPH (low risk).

High risk for postpartum haemorrhage

Primary postpartum haemorrhage blood loss of ≥ 500 ml

Pooled effect sizes from the NMA of 21 trials suggested that only misoprostol plus oxytocin is better than oxytocin in preventing PPH blood loss of ≥ 500 ml and carbetocin showed a similar trend towards prevention of this outcome for women at high risk for PPH, but most of the comparisons were based on single studies (*Figure 61*). There was no evidence of global inconsistency in this analysis ($p = 0.211$).

Figure 62 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the subgroup including trials with only women at high risk for PPH. The highest-ranked interventions are misoprostol plus oxytocin and carbetocin. Oxytocin is ranked third closely followed by misoprostol and its probability in being ranked in the top two interventions was close to 0%.

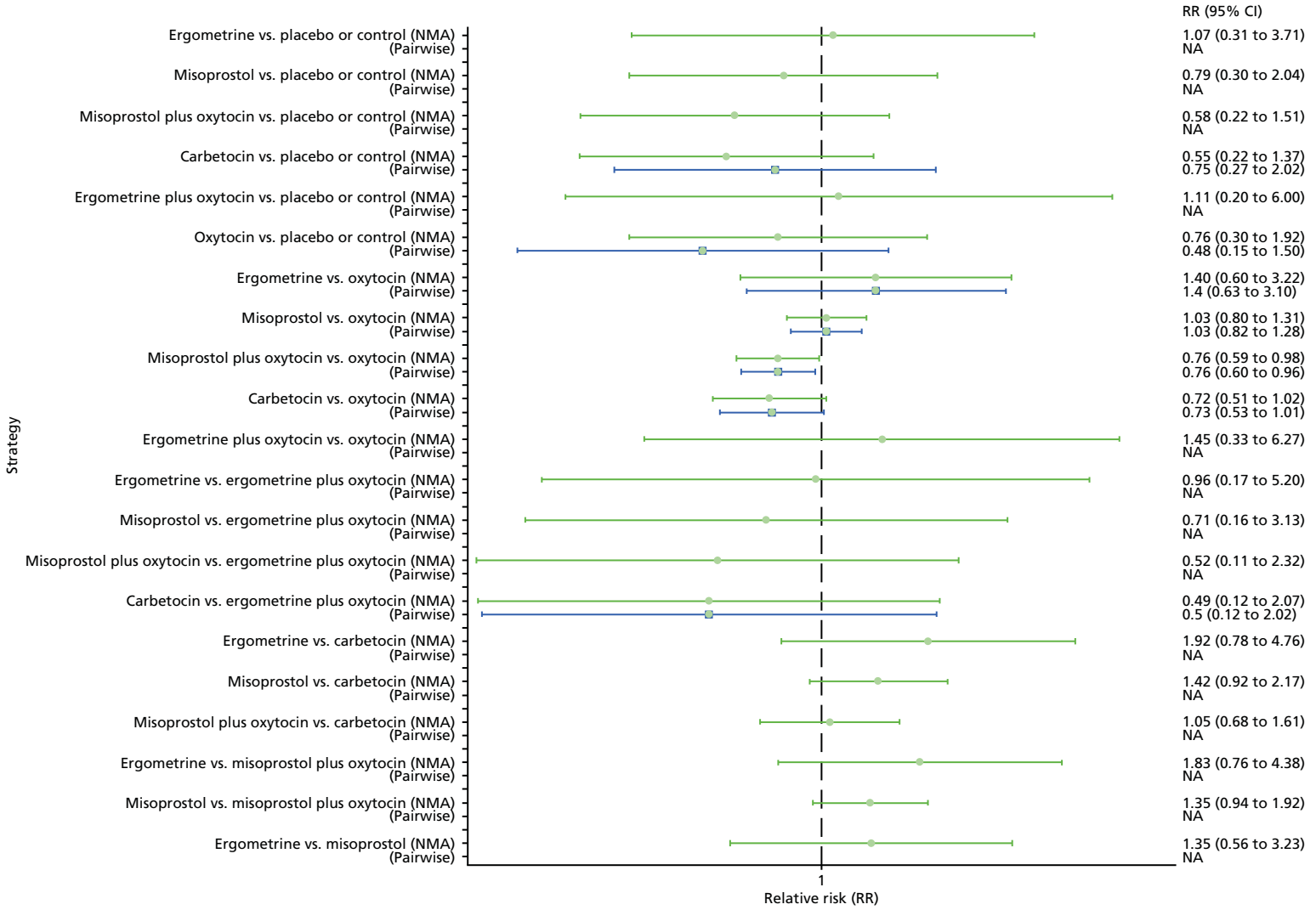

FIGURE 61 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml by prior risk for PPH (high risk). NA, not applicable.

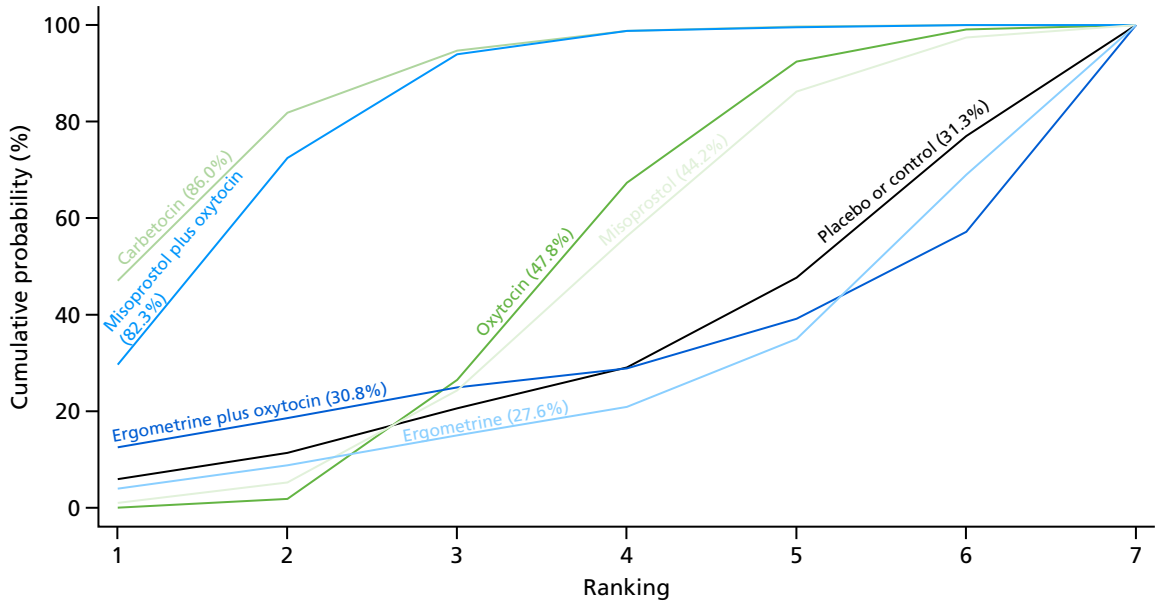

FIGURE 62 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, by prior risk for PPH (high risk).

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

Pooled effect sizes from the NMA of 22 trials suggested a lack of evidence that any intervention is worse or better than any other in preventing PPH blood loss of ≥ 1000 ml in women at high risk for PPH, and many of the comparisons were based on single studies (*Figure 63*). There was no evidence of global inconsistency in this analysis ($p = 0.851$).

Figure 64 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the subgroup including trials with only women at high risk for PPH. No clear ranking emerges in this analysis. Ergometrine and ergometrine plus oxytocin could not be ranked as there were no studies found comparing those drugs with any other interventions in the network.

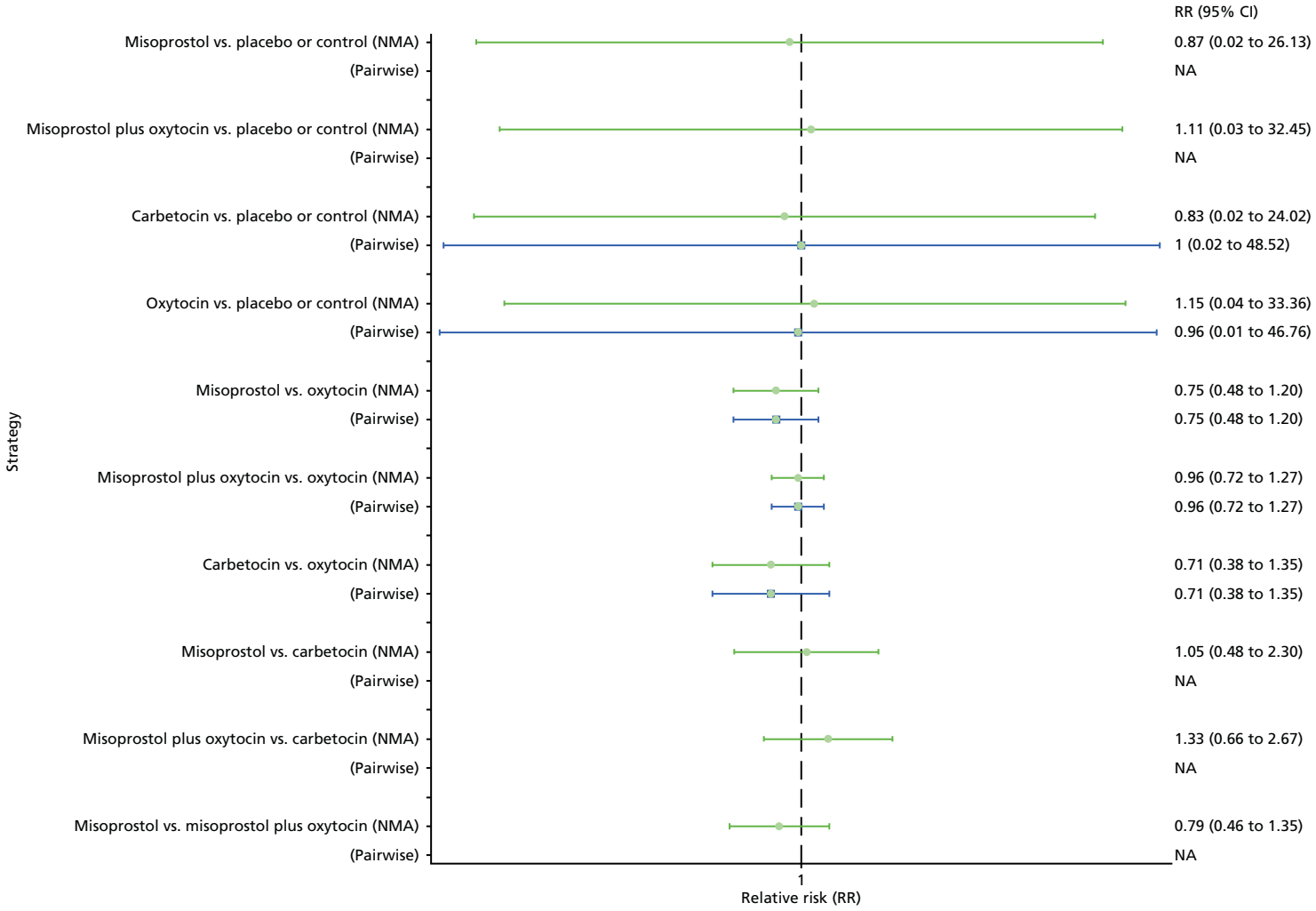

FIGURE 63 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, by prior risk for PPH (high risk). NA, not applicable.

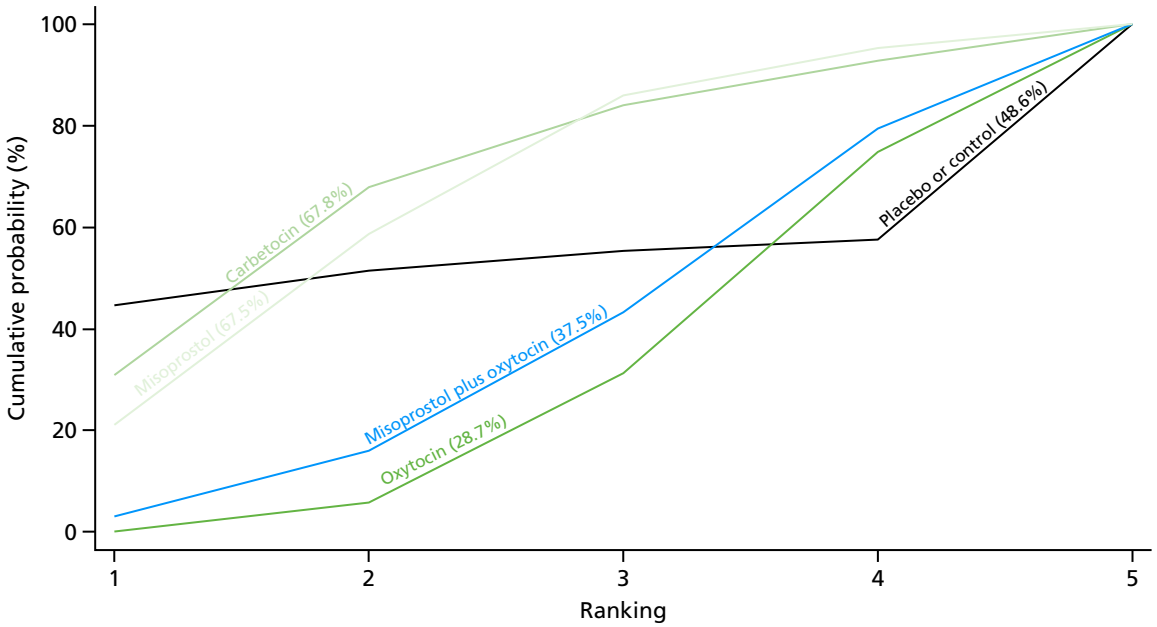

FIGURE 64 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, by prior risk for PPH (high risk).

Health-care setting

Hospital setting

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml for the subgroup including trials carried out in the hospital setting is presented in *Appendix 8*. Pooled effect sizes from the NMA of 95 trials suggested that all interventions are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo (*Figure 65*). Ergometrine plus oxytocin, and misoprostol plus oxytocin were found to be more effective than the standard intervention, oxytocin, even though carbetocin also demonstrated a trend towards reduction of this outcome (*Figure 65*). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective than misoprostol and ergometrine when used alone. There was evidence of global inconsistency in this analysis ($p = 0.0448$). However, it is noted that the CIs for both the NMA and the direct evidence were overlapping across all comparisons, suggesting locally consistent results except for ergometrine versus placebo or the control based on a single study.

Figure 66 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the subgroup including trials carried out in the hospital setting. The highest-ranked interventions are ergometrine plus oxytocin, carbetocin, and misoprostol plus oxytocin, with an almost 100% probability of these three interventions being ranked first, second or third. Oxytocin is ranked fourth and its probability of being ranked in the top three interventions was close to 0%.

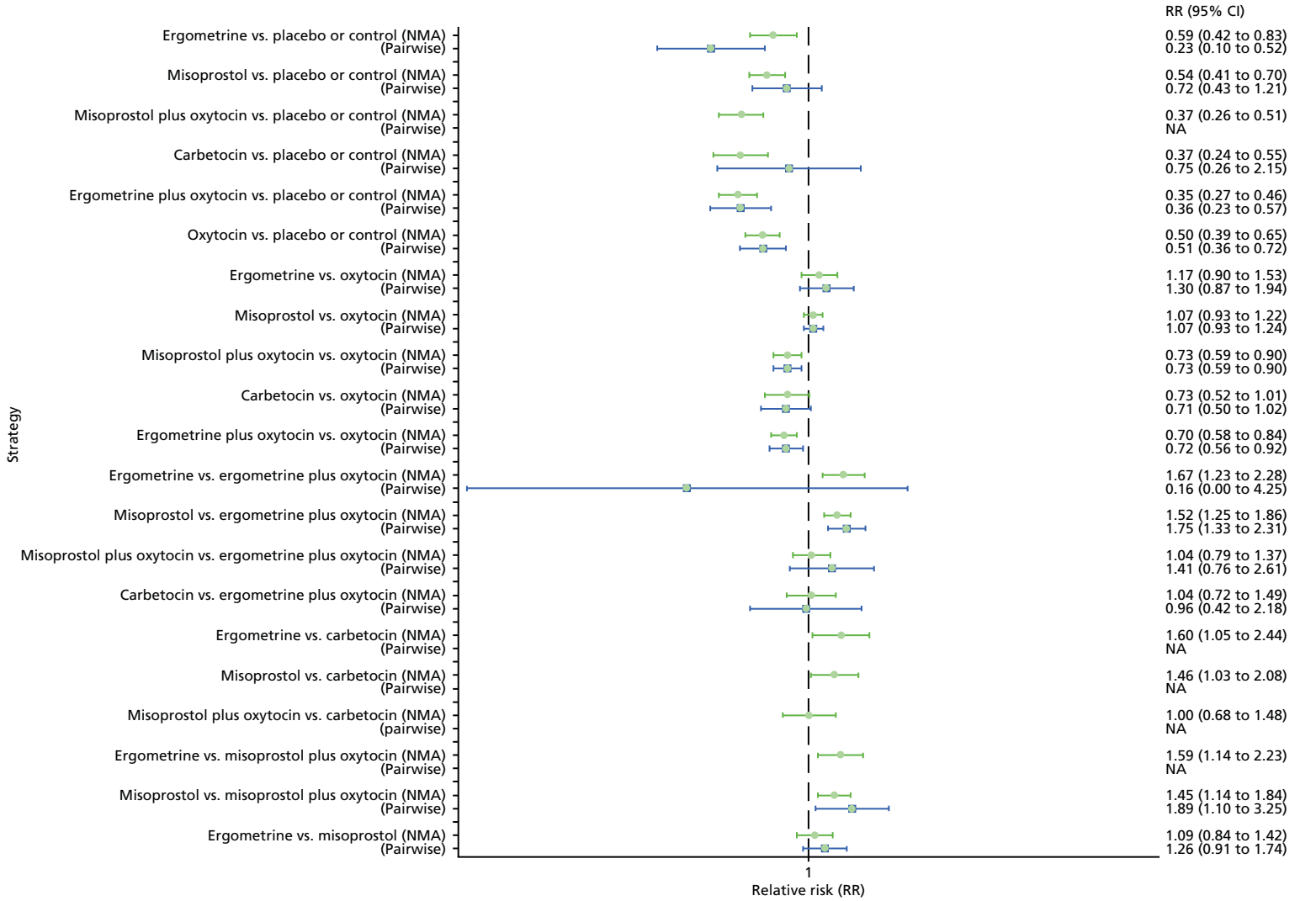

FIGURE 65 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, by health-care setting (hospital setting). NA, not applicable.

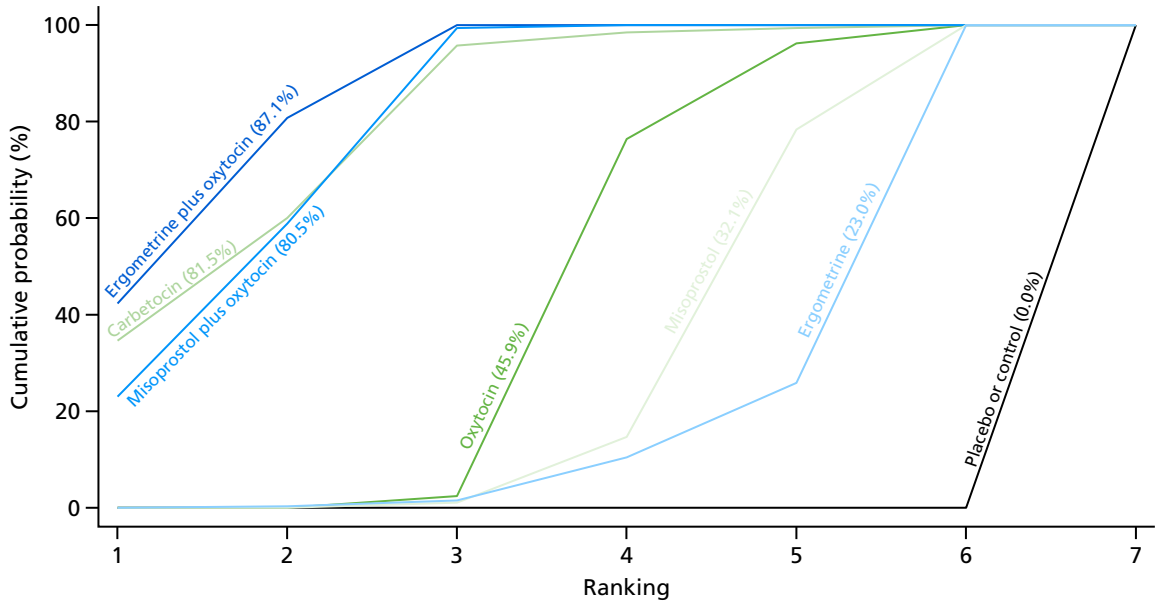

FIGURE 66 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, by health-care setting (hospital setting).

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

Pooled effect sizes from the NMA of 85 trials suggested that all interventions, except ergometrine, are effective for preventing PPH blood loss of ≥ 1000 ml when compared with the placebo for the subgroup including trials carried out in the hospital setting (*Figure 67*). Ergometrine plus oxytocin was the only intervention found to be more effective than the standard intervention, oxytocin, even though carbetocin and misoprostol plus oxytocin demonstrated a trend towards reduction of this outcome (*Figure 67*). There was no evidence of global inconsistency in this analysis ($p = 0.389$).

Figure 68 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the subgroup including trials carried out in the hospital setting. The highest-ranked interventions are carbetocin, ergometrine plus oxytocin and misoprostol plus oxytocin. Oxytocin is still ranked fourth and its probability of being ranked in the top three interventions was close to 20%.

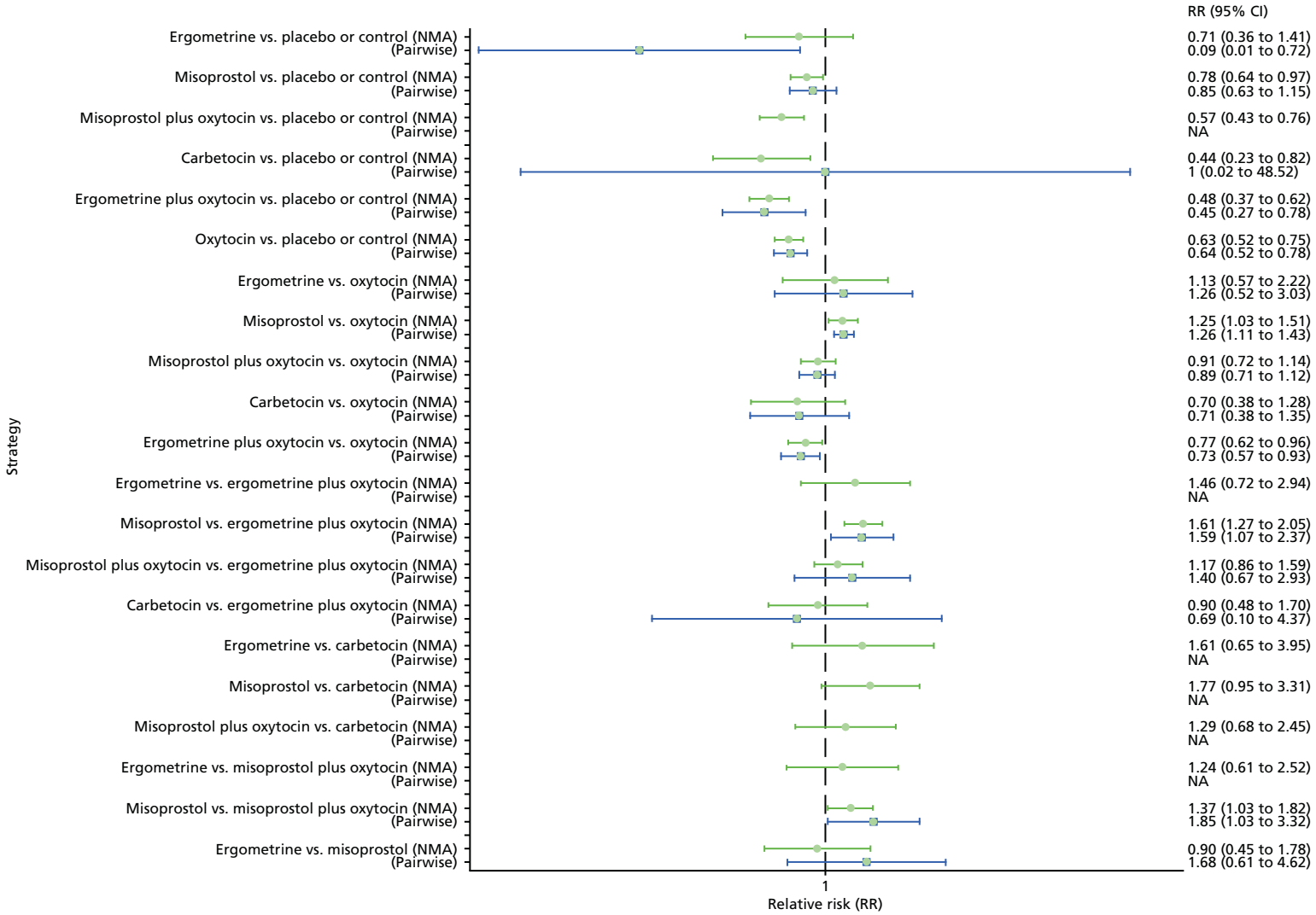

FIGURE 67 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, by health-care setting (hospital setting). NA, not applicable.

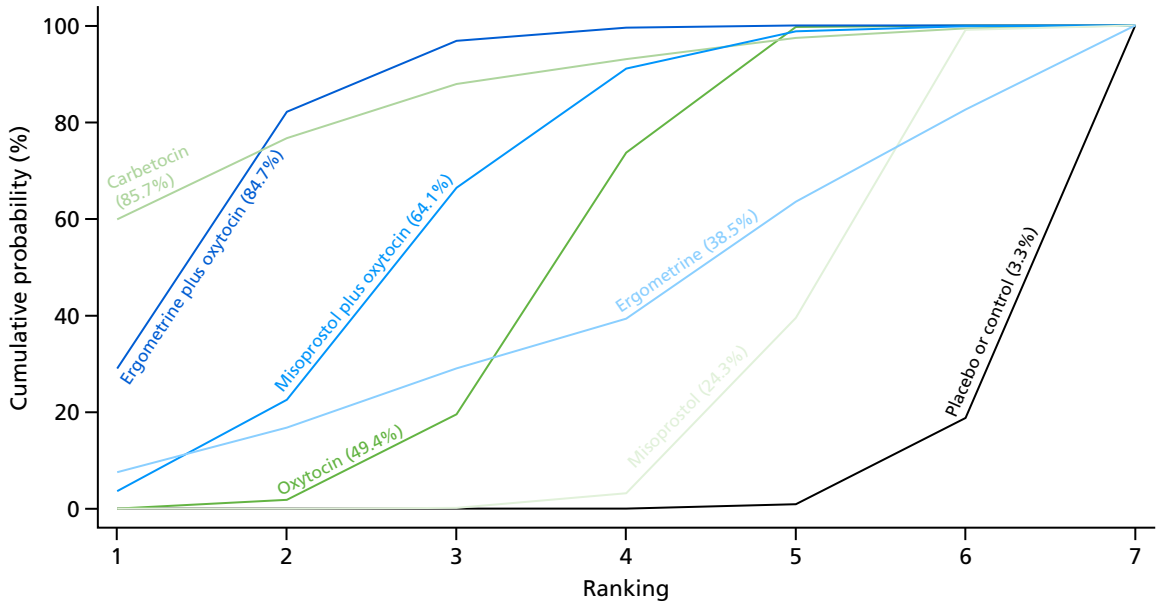

FIGURE 68 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, by health-care setting (hospital setting).

Community setting

Primary postpartum haemorrhage blood loss of ≥ 500 ml

Pooled effect sizes from the NMA of four trials suggested that only oxytocin and misoprostol are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo for the subgroup including trials carried out in the community setting (*Figure 69*). There was evidence of global inconsistency in this analysis ($p = 0.03$), but most of the comparisons are based on a small number of studies.

Figure 70 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the subgroup including trials carried out in the community setting. No clear ranking emerges in this analysis. Carbetocin, misoprostol plus oxytocin, ergometrine and ergometrine plus oxytocin could not be ranked as there were no studies found comparing those drugs with any other interventions in the network.

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

Pooled effect sizes from the NMA of four trials suggested that only misoprostol is more effective for preventing PPH blood loss of ≥ 1000 ml when compared with placebo, even though oxytocin also demonstrated a trend towards reduction of this outcome for the subgroup including trials carried out in the community setting (*Figure 71*). There was evidence of global inconsistency in this analysis ($p = 0.004$), but most of the comparisons are based on a small number of studies.

Figure 72 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the subgroup including trials carried out in the community setting. No clear ranking emerges in this analysis. Carbetocin, misoprostol plus oxytocin, ergometrine and ergometrine plus oxytocin could not be ranked as there were no studies found comparing those drugs with any other interventions in the network.

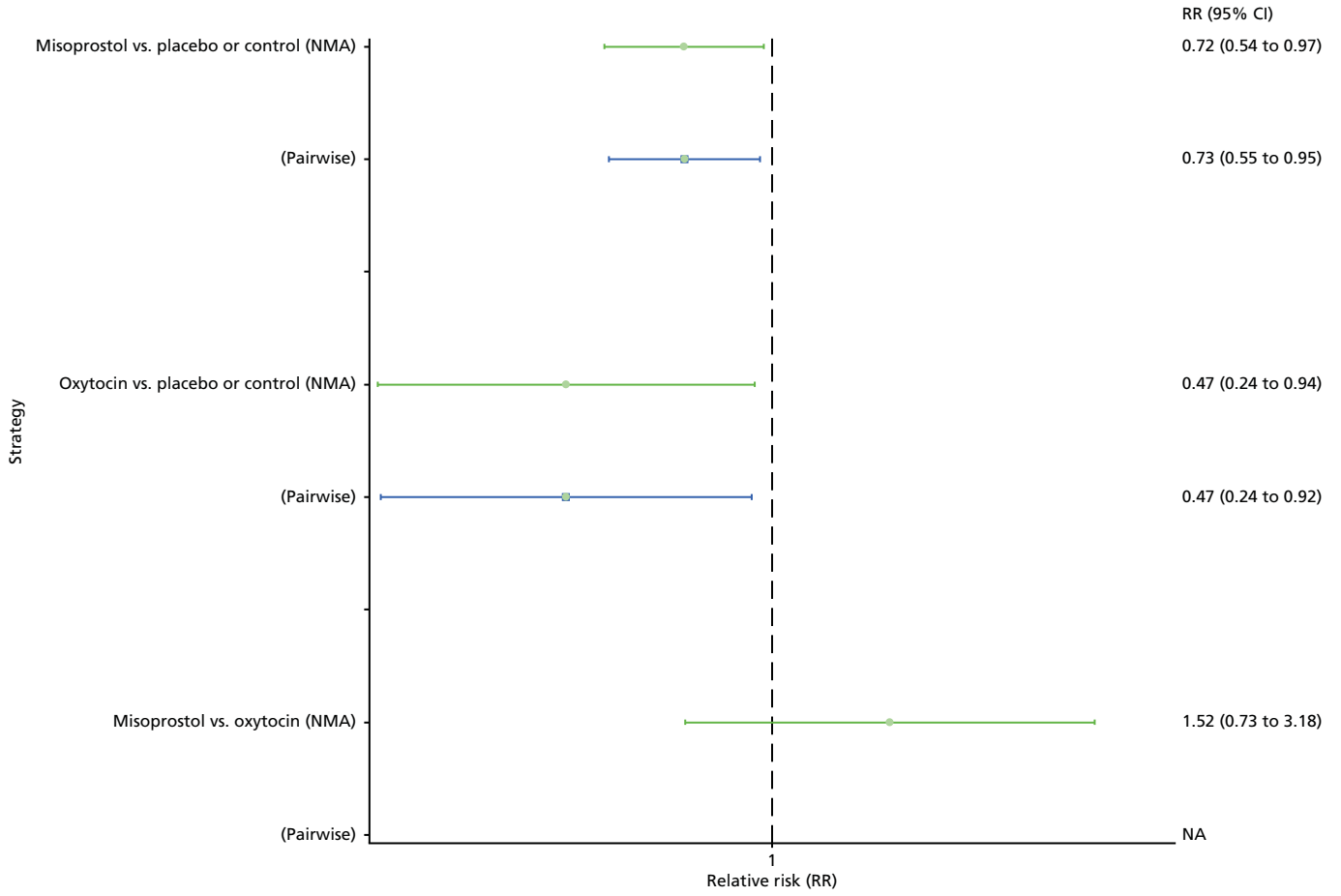

FIGURE 69 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, by health-care setting (community setting).

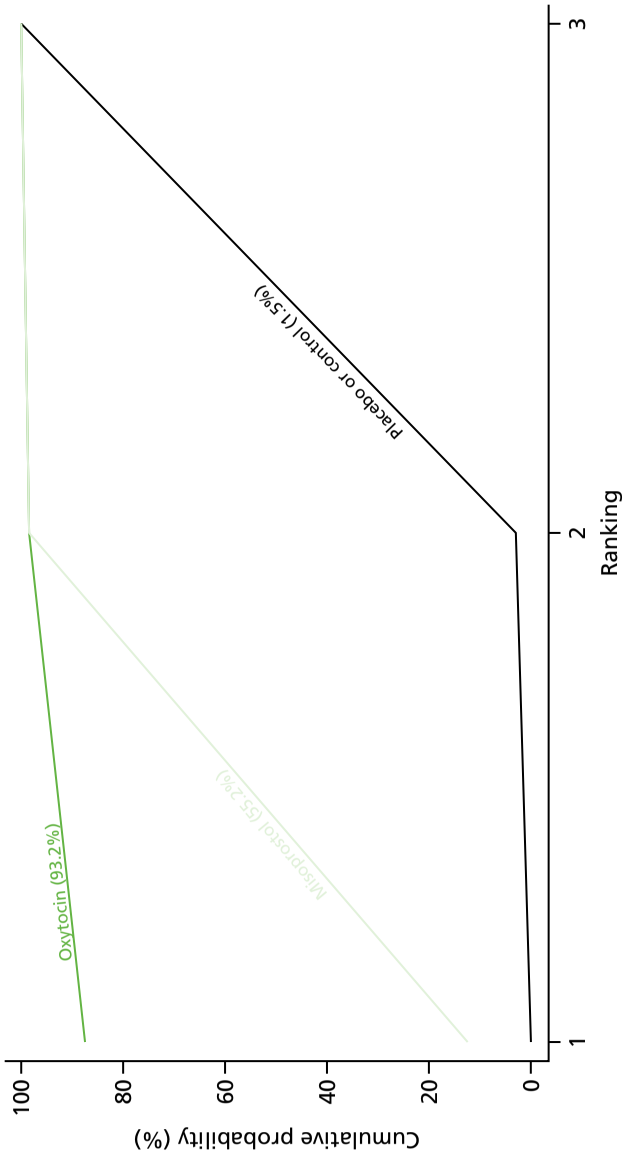

FIGURE 70 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, by health-care setting (community setting).

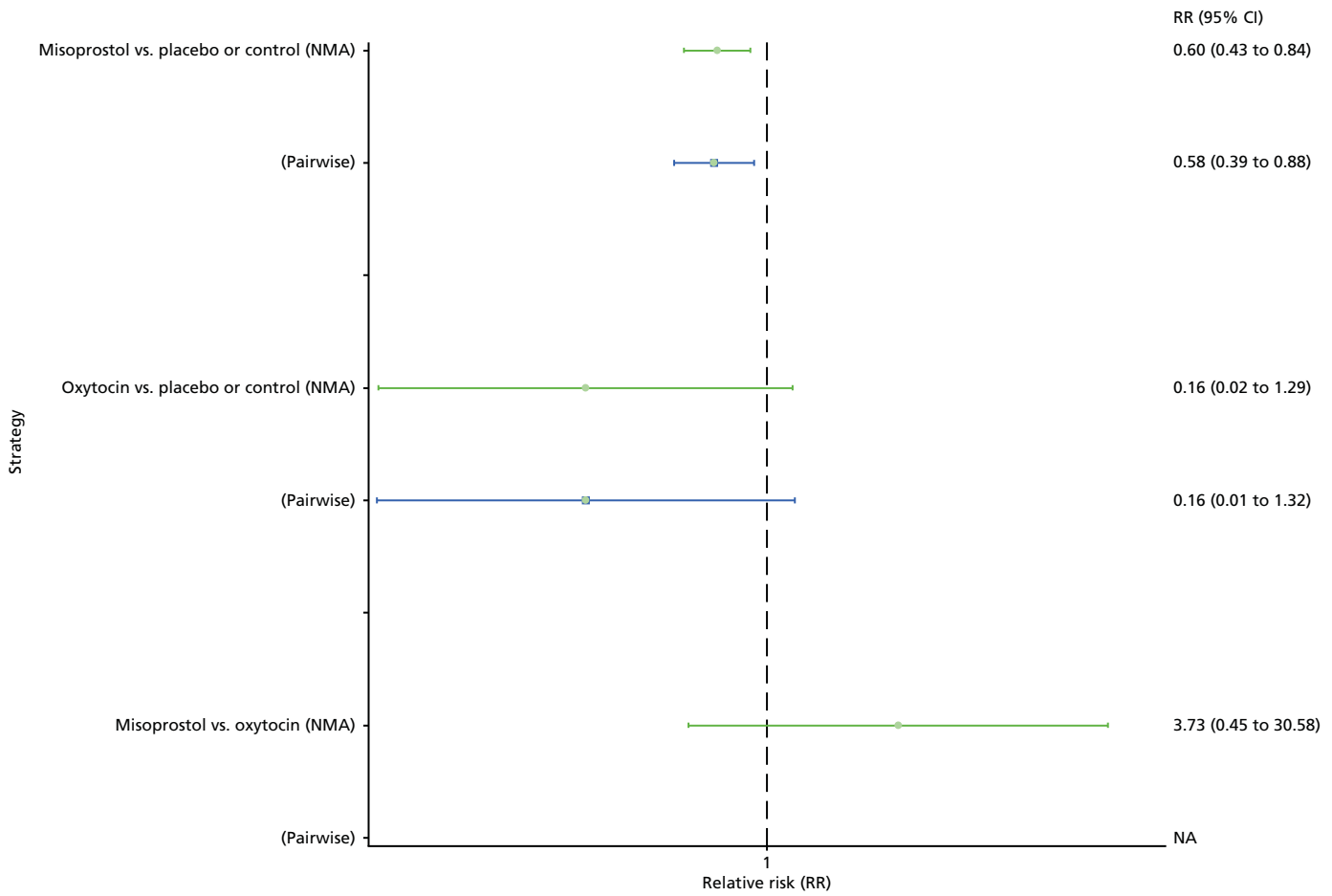

FIGURE 71 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, by health-care setting (community setting). NA, not applicable.

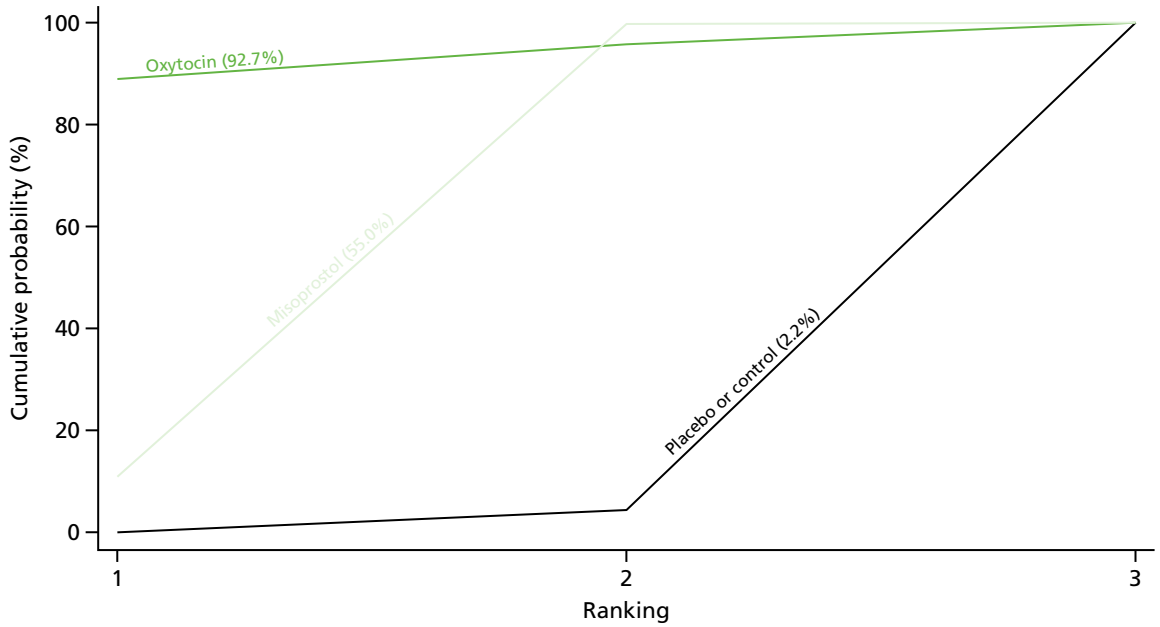

FIGURE 72 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, by health-care setting (community setting).

Intervention dose, regimen or route

Low-dose misoprostol

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml for the subgroup including only misoprostol studies, which used a low dose (i.e. < 500 µg) of misoprostol is presented in *Appendix 8*. Pooled effect sizes from the NMA of 72 trials suggested that all interventions are effective for preventing PPH blood loss of ≥ 500 ml when compared with the placebo (*Figure 73*). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were found to be more effective than the standard intervention, oxytocin (*Figure 73*). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective than misoprostol and ergometrine when used alone. There was evidence of global inconsistency in this analysis ($p = 0.016$). However, it is noted that the CIs for both the NMA and the direct evidence were overlapping across all comparisons, suggesting locally consistent results except for ergometrine versus placebo or the control based on a single study.

Figure 74 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the subgroup including misoprostol trials that used a low dose. The highest-ranked interventions are ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin, with almost 100% probability of these three interventions being ranked first, second or third. Oxytocin is ranked fourth and its probability of being ranked in the top three interventions was close to 0%.

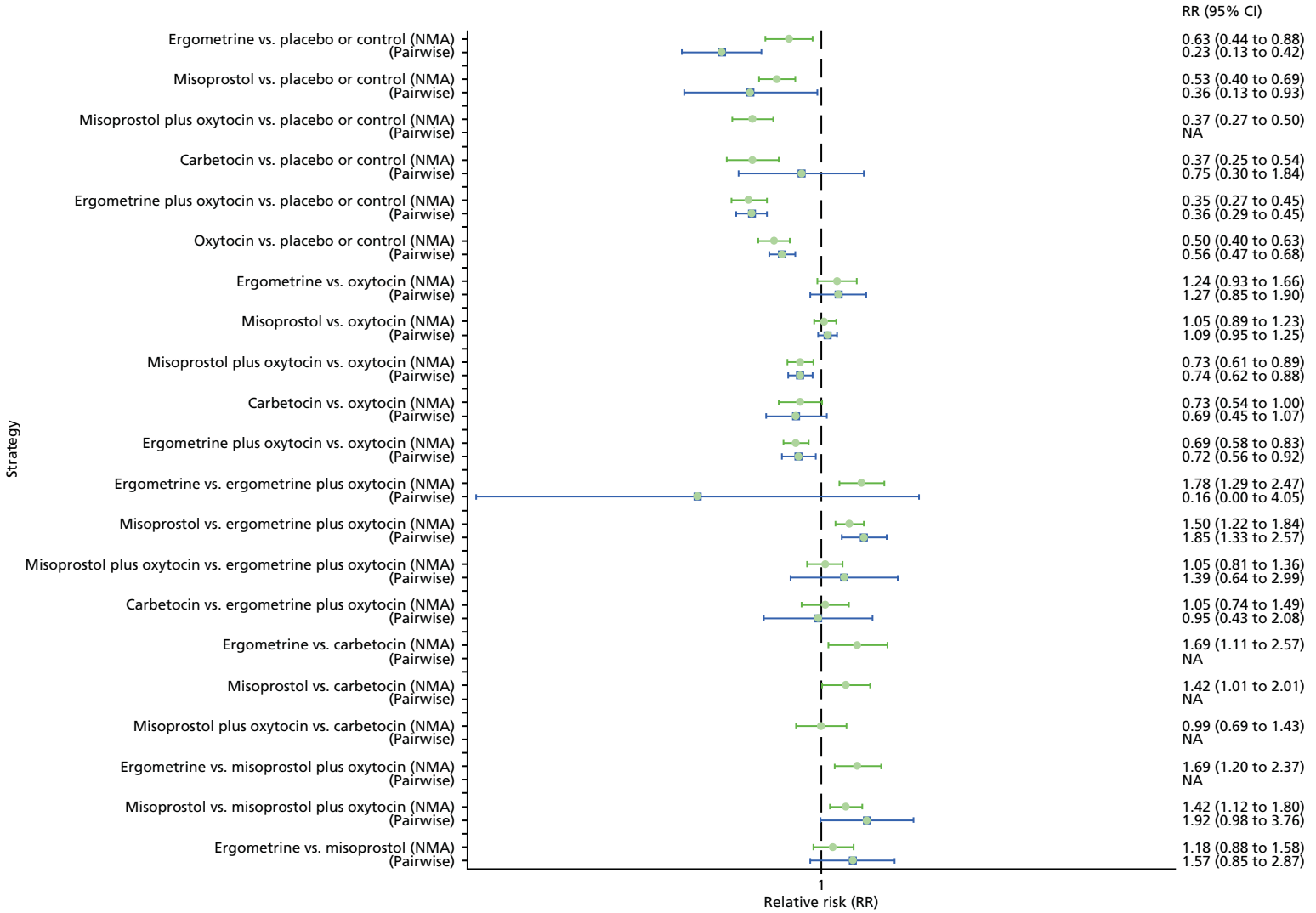

FIGURE 73 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, restricted to misoprostol studies that used a low dose (i.e. ≤ 500 μg). NA, not applicable.

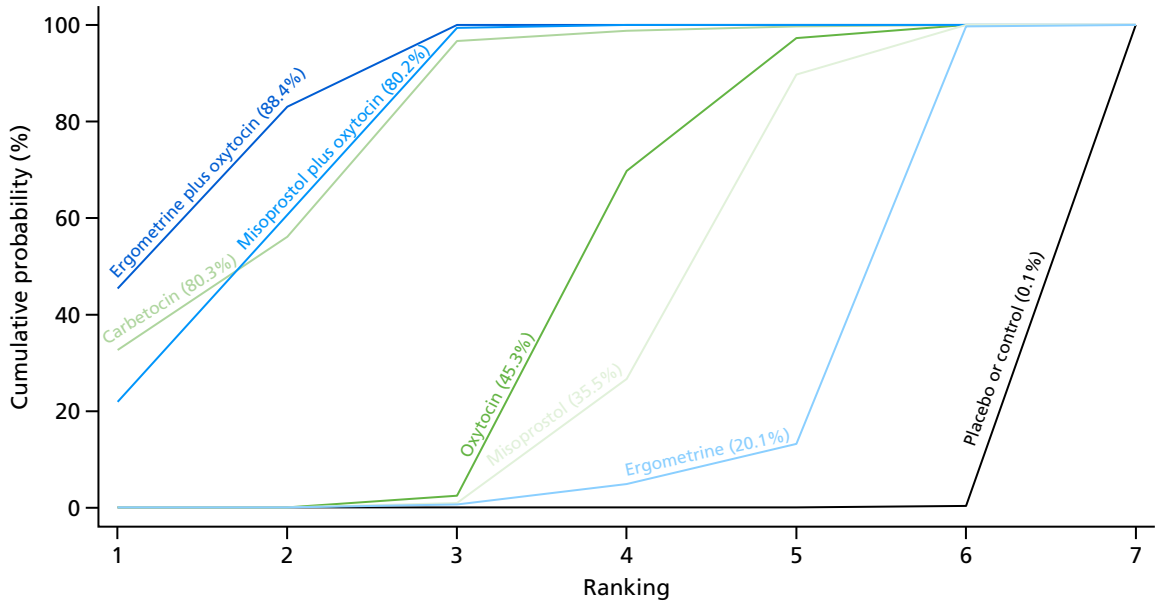

FIGURE 74 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, restricted to misoprostol studies that used a low dose (i.e. ≤ 500 µg).

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

Pooled effect sizes from the NMA of 69 trials suggested that all interventions except ergometrine are effective for preventing PPH blood loss of ≥ 1000 ml when compared with placebo for the subgroup, including misoprostol trials that used a low dose (*Figure 75*). Ergometrine plus oxytocin was the only intervention found to be more effective than the standard intervention, oxytocin, even though carbetocin also demonstrated a trend towards reduction of this outcome (*Figure 75*). There was no evidence of global inconsistency in this analysis ($p = 0.401$).

Figure 76 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the subgroup including misoprostol trials that used a low dose. The highest-ranked interventions are carbetocin, ergometrine plus oxytocin and misoprostol plus oxytocin. Oxytocin is still ranked fourth and its probability of being ranked in the top three interventions was close to 20%.

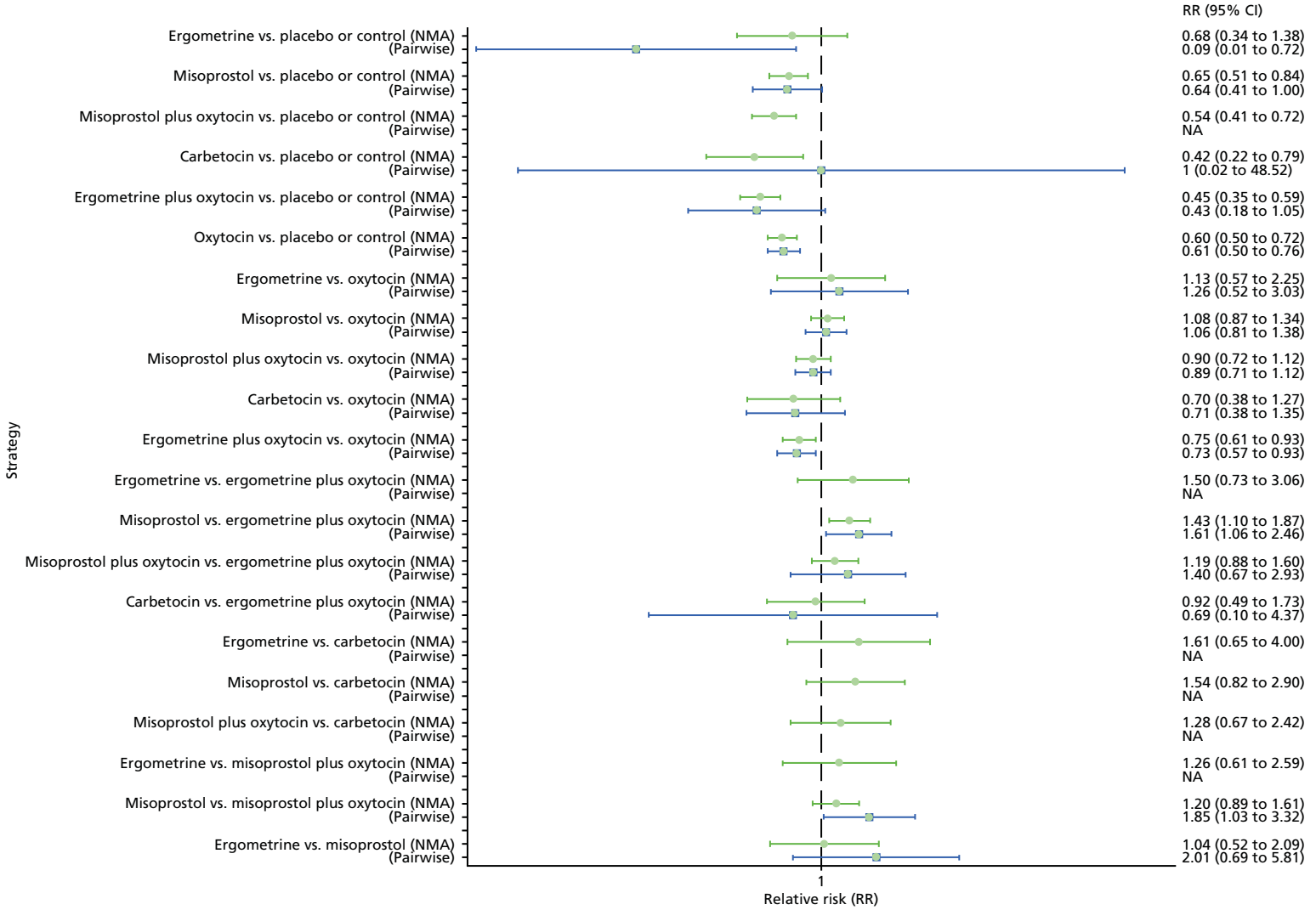

FIGURE 75 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, restricted to misoprostol studies that used a low dose (i.e. ≤ 500 µg). NA, not applicable.

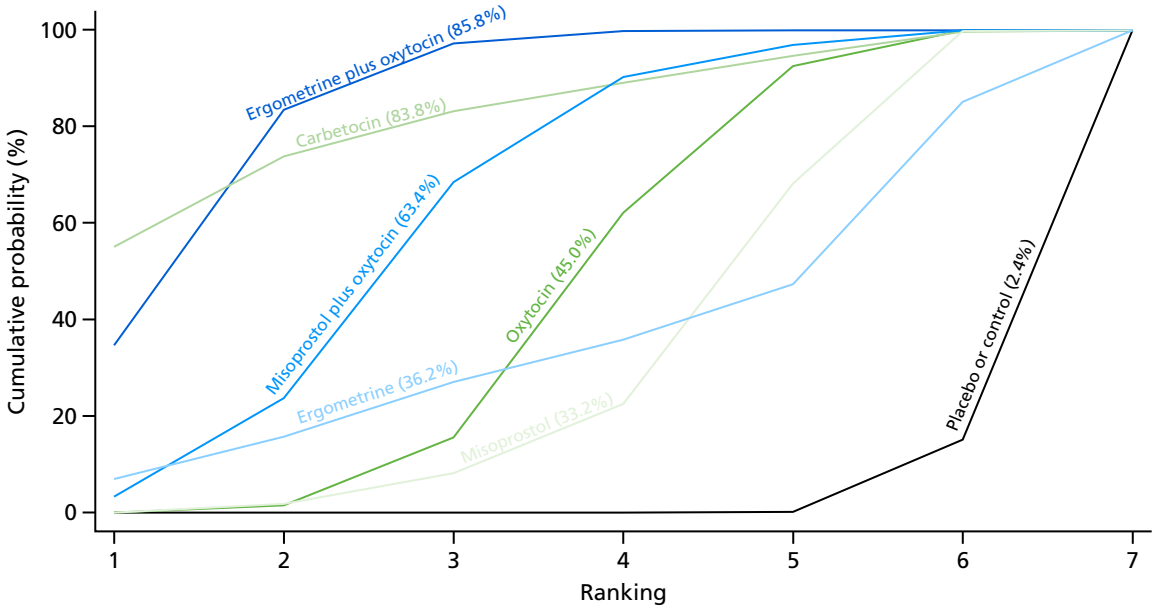

FIGURE 76 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, restricted to misoprostol studies that used a low dose (i.e. ≤ 500 µg).

High-dose misoprostol

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml for the subgroup only misoprostol studies, which used a high dose (i.e. ≥ 600 µg) of misoprostol is presented in *Appendix 8*. Pooled effect sizes from the NMA of 83 trials suggested that all interventions are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo for the subgroup, including only misoprostol trials that used a high dose (*Figure 77*). Ergometrine plus oxytocin and misoprostol plus oxytocin were found to be more effective than the standard intervention, oxytocin, even though carbetocin also showed a trend towards reduction of this outcome (see *Figure 77*). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective than misoprostol when used alone. There was no evidence of global inconsistency in this analysis ($p = 0.322$).

Figure 78 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the subgroup, including misoprostol trials that used a low dose. The highest-ranked interventions are ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin, with > 80% probability of these three interventions being ranked first, second or third. Oxytocin is ranked fifth behind ergometrine and its probability of being ranked in the top three interventions was close to 0%.

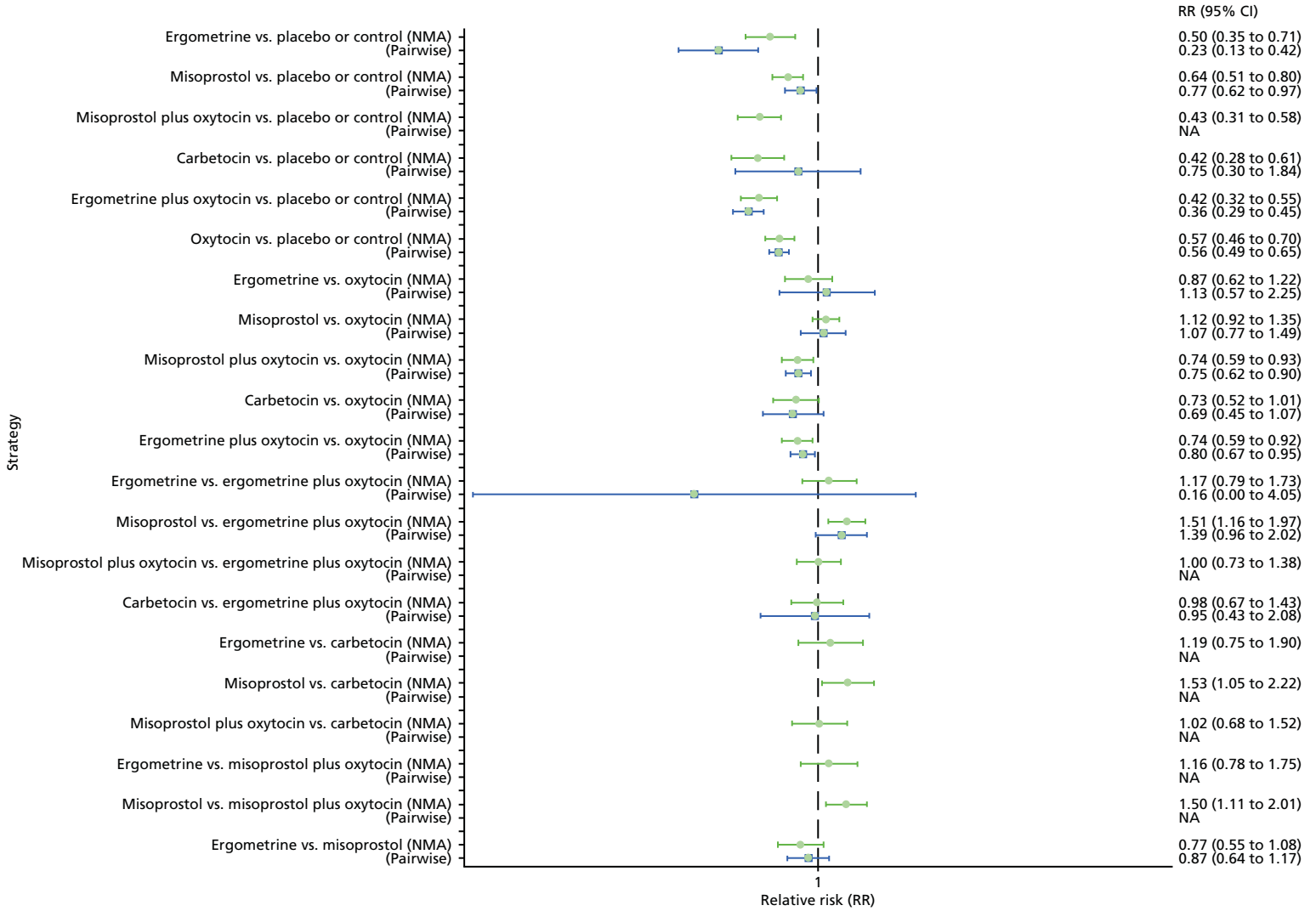

FIGURE 77 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, restricted to misoprostol studies that used a high dose (i.e. ≥ 600 µg). NA, not applicable.

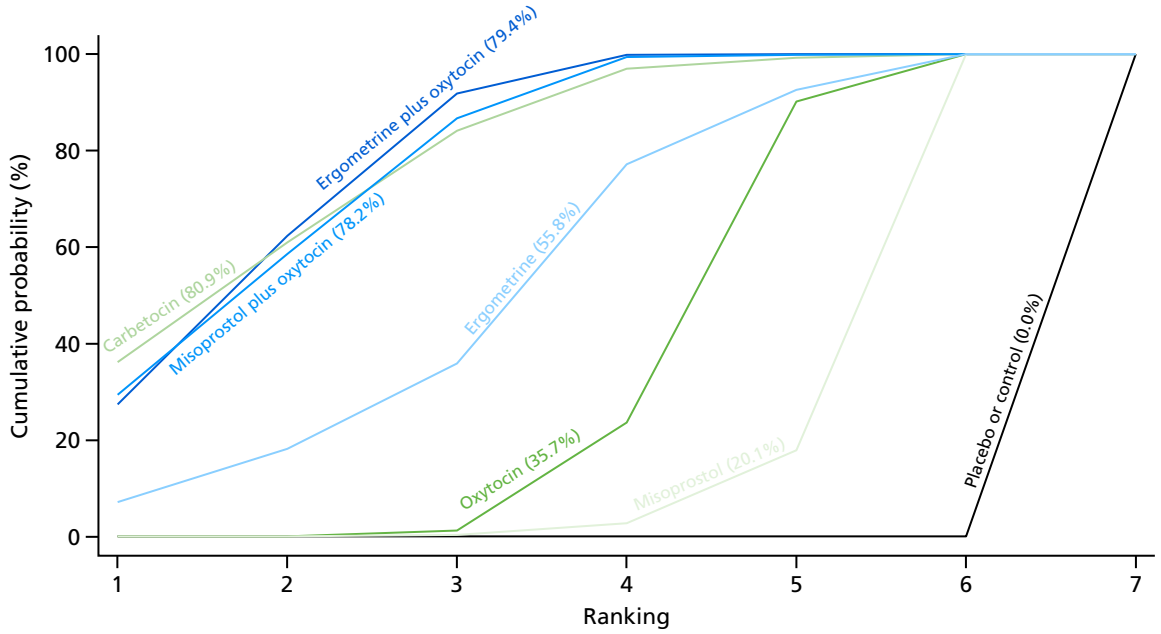

FIGURE 78 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, restricted to misoprostol studies that used a high dose (i.e. ≥ 600 µg).

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

Pooled effect sizes from the NMA of 62 trials suggested that all interventions except ergometrine are effective for preventing PPH blood loss of ≥ 1000 ml when compared with placebo for the subgroup including misoprostol trials that used a low dose (*Figure 79*). Ergometrine plus oxytocin was the only intervention found to be more effective than the standard intervention, oxytocin, even though carbetocin also demonstrated a trend towards reduction of this outcome (see *Figure 79*). Ergometrine plus oxytocin, carbetocin, misoprostol plus oxytocin and oxytocin when used alone were found to be more effective than misoprostol, despite misoprostol being used at a higher dose. There was no evidence of global inconsistency in this analysis ($p = 0.625$).

Figure 80 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the subgroup including misoprostol trials that used a high dose. The highest-ranked interventions are carbetocin, ergometrine plus oxytocin, ergometrine and misoprostol plus oxytocin. Oxytocin is still ranked fifth and its probability of being ranked in the top three interventions was < 20%.

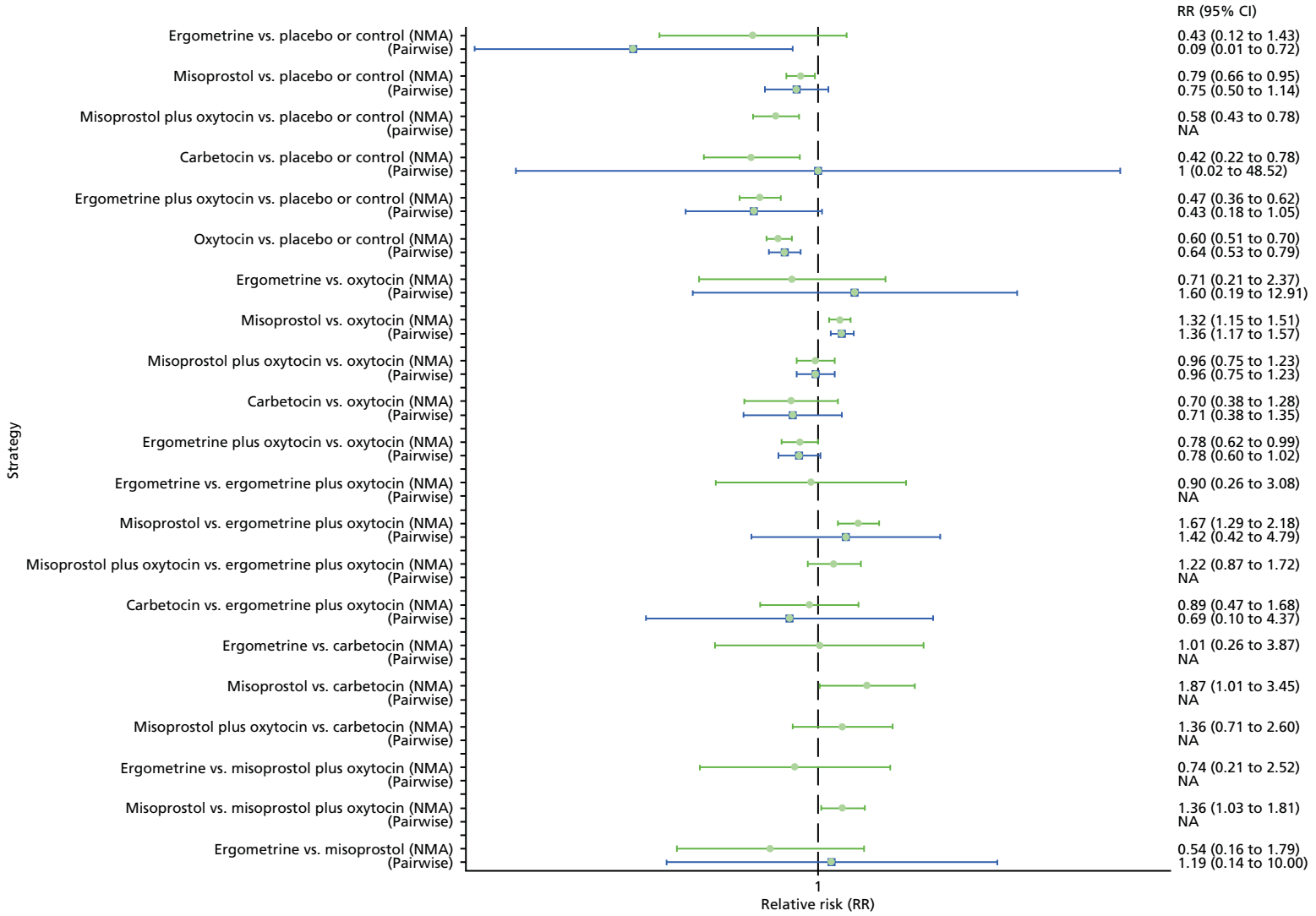

FIGURE 79 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, restricted to misoprostol studies that used a high dose (i.e. ≥ 600 µg). NA, not applicable.

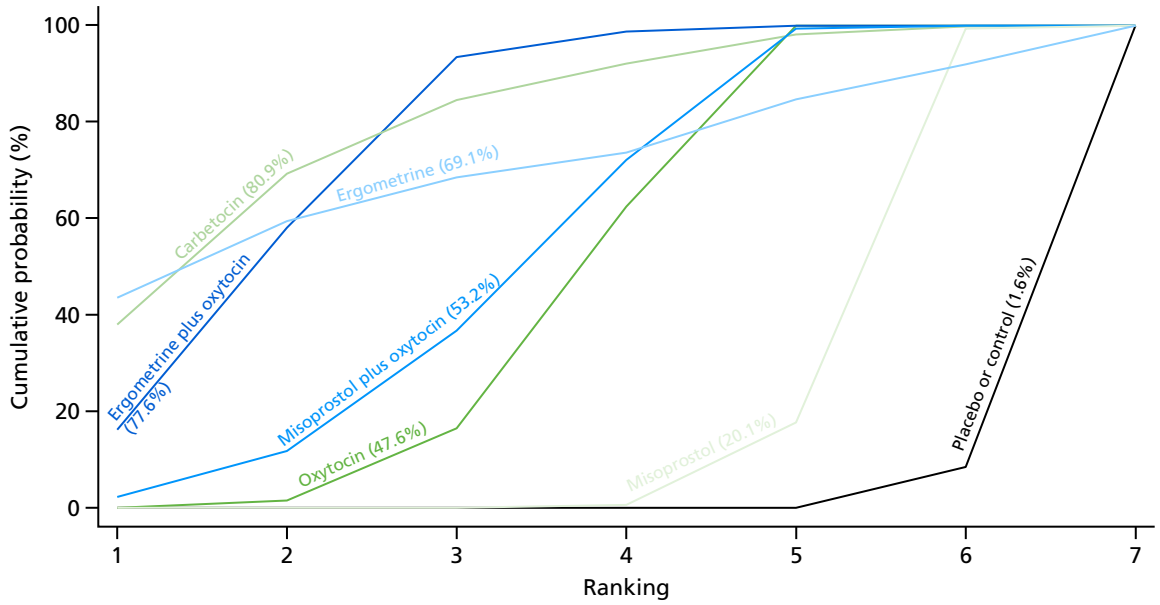

FIGURE 80 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, restricted to misoprostol studies that used a high dose (i.e. ≥ 600 µg).

Oxytocin bolus only

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml for the subgroup is presented in *Appendix 8*. This subgroup includes all trials, but when oxytocin was used as an arm in the trial this analysis is restricted to oxytocin studies that used an intravenous or intramuscular bolus of any dose and excluded studies that used a bolus plus infusion or infusion only of oxytocin. Pooled effect sizes from the NMA of 84 trials suggested that all interventions are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo for the subgroup, including oxytocin trials that used an intramuscular or intravenous bolus of any dose (*Figure 81*). Ergometrine plus oxytocin was the only intervention found to be more effective than the standard intervention, oxytocin, even though carbetocin and misoprostol plus oxytocin also demonstrated a trend towards reduction of this outcome (see *Figure 81*). Ergometrine plus oxytocin was also found to be more effective than misoprostol when used alone. There was no evidence of global inconsistency in this analysis ($p = 0.134$).

Figure 82 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the subgroup including oxytocin trials that used an intramuscular or intravenous bolus of any dose. The highest-ranked interventions are ergometrine plus oxytocin, misoprostol plus oxytocin and carbetocin, with > 80% probability of these three interventions being ranked first, second or third. Oxytocin is ranked fourth and its probability of being ranked in the top three interventions was > 20%.

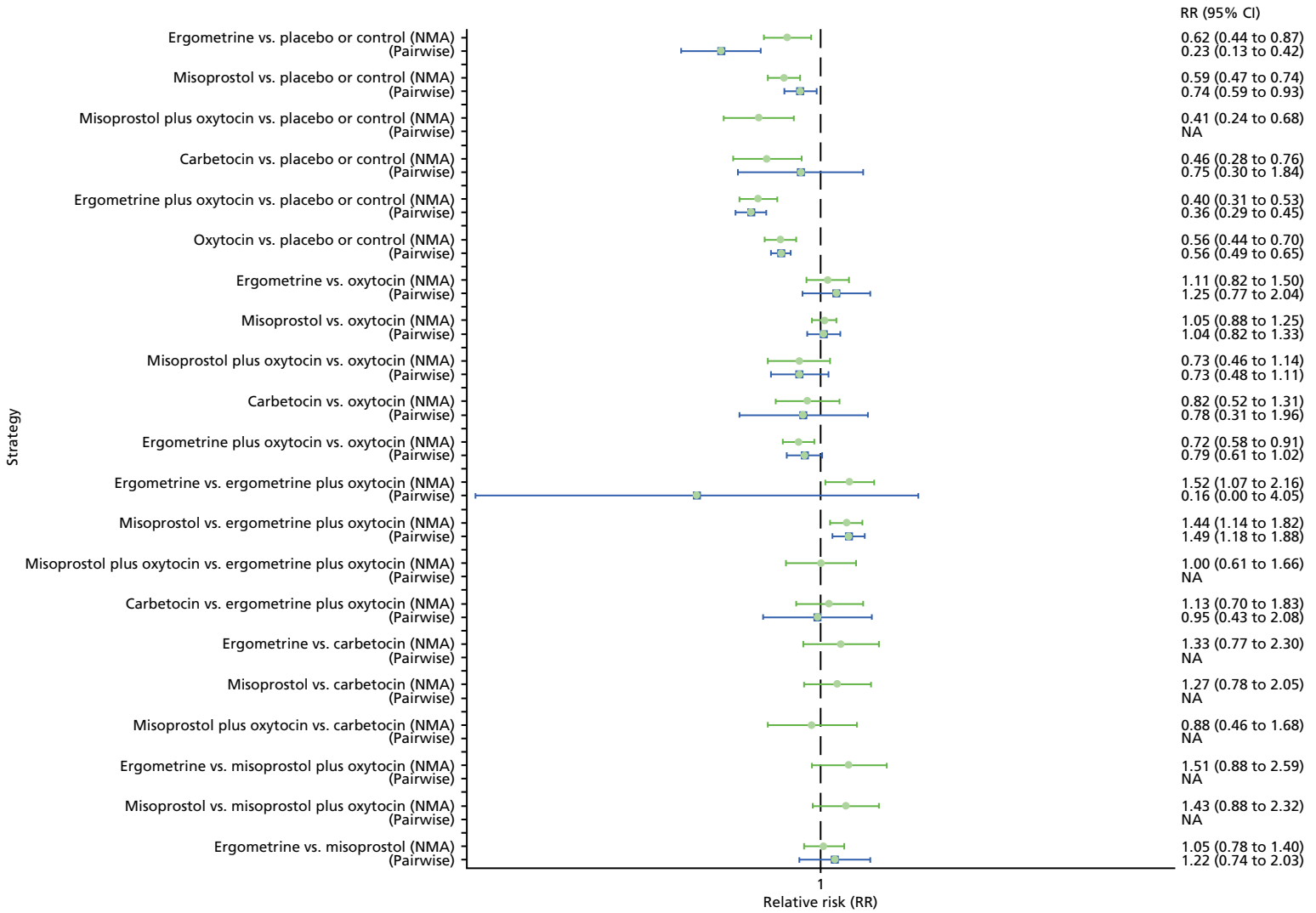

FIGURE 81 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, restricted to oxytocin studies that used an intramuscular or intravenous bolus of any dose. NA, not applicable.

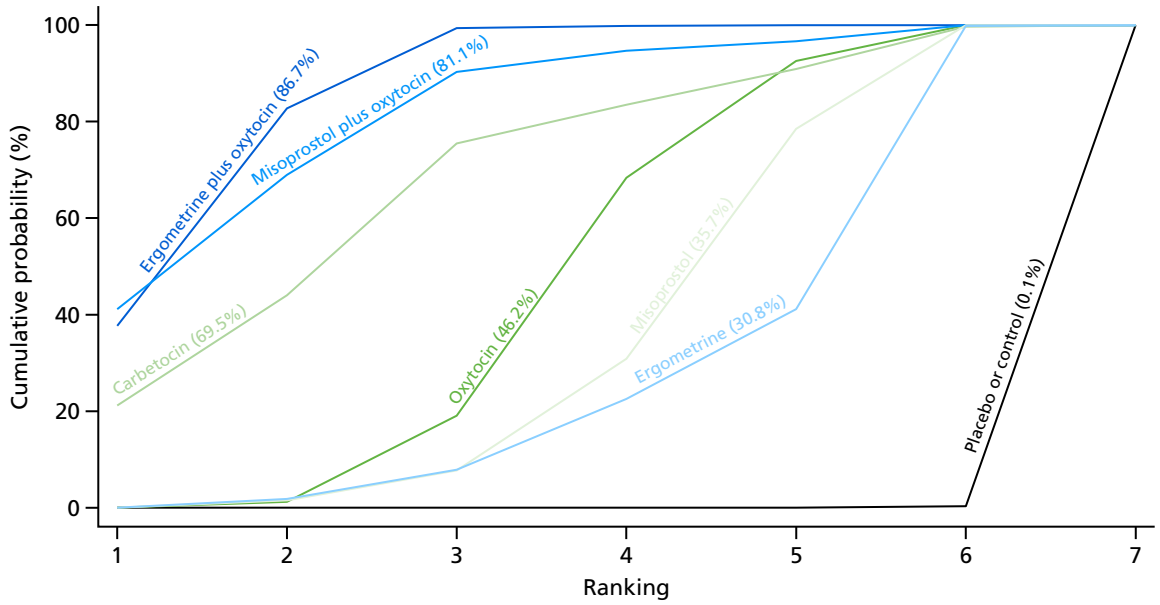

FIGURE 82 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, restricted to oxytocin studies that used an intramuscular or intravenous bolus of any dose.

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

The network diagram for PPH blood loss of ≥ 1000 ml for the subgroup including all trials, but restricting to oxytocin trials that used an intravenous or intramuscular bolus of any dose, is presented in *Appendix 8*. Pooled effect sizes from the NMA of 68 trials suggested that all interventions, except carbetocin and ergometrine, are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo for the subgroup including only oxytocin trials that used an intramuscular or intravenous bolus of any dose (*Figure 83*). None of the interventions was found to be more effective than the standard intervention, oxytocin (see *Figure 83*). Ergometrine plus oxytocin and oxytocin when used alone were found to be more effective than misoprostol. There was no evidence of global inconsistency in this analysis ($p = 0.468$).

Figure 84 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the subgroup restricted to oxytocin studies that used an intramuscular or intravenous bolus of any dose. The highest-ranked intervention is ergometrine plus oxytocin, with a less clear ranking among the other interventions.

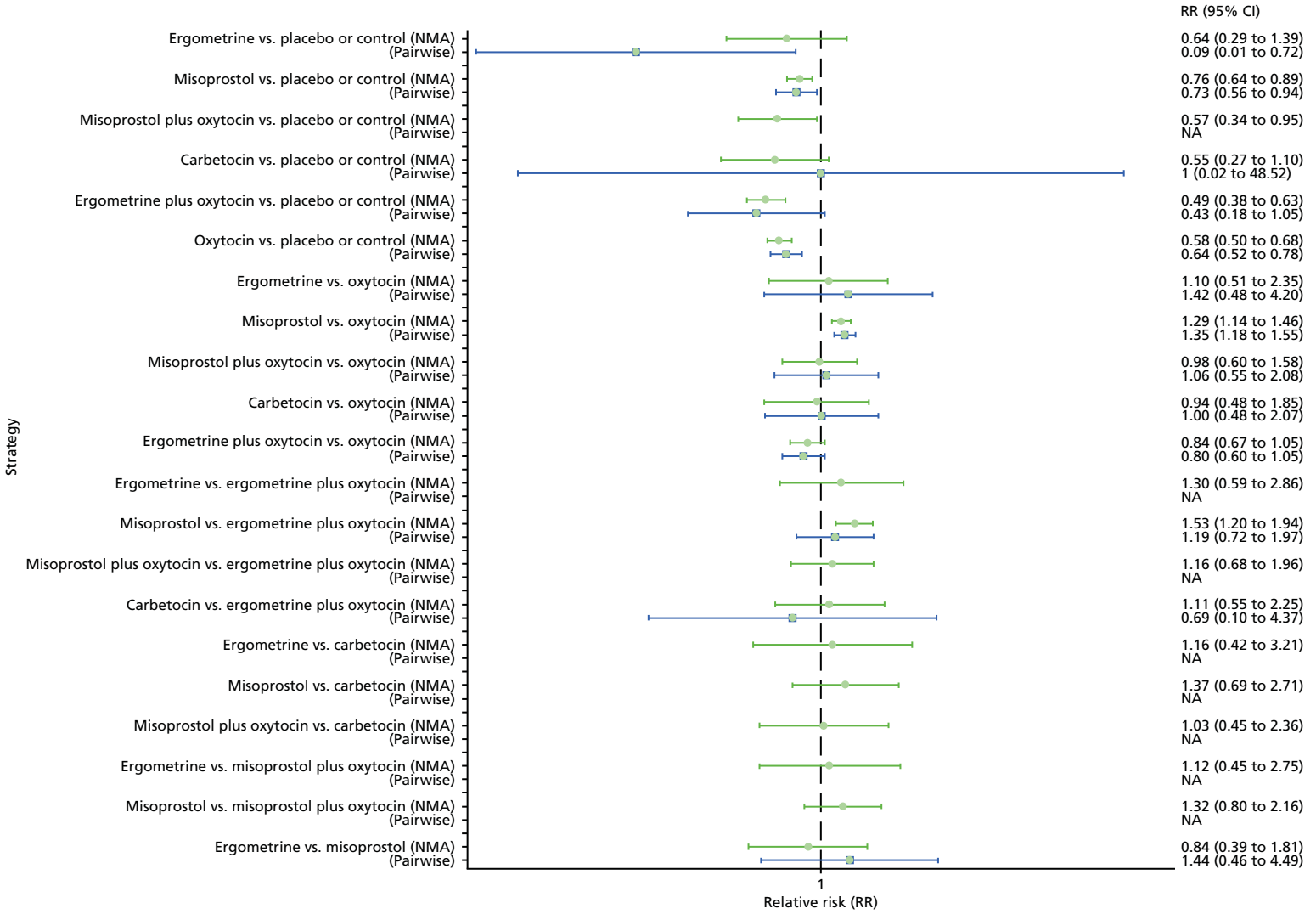

FIGURE 83 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, restricted to oxytocin studies that used an intramuscular or intravenous bolus of any dose. NA, not applicable.

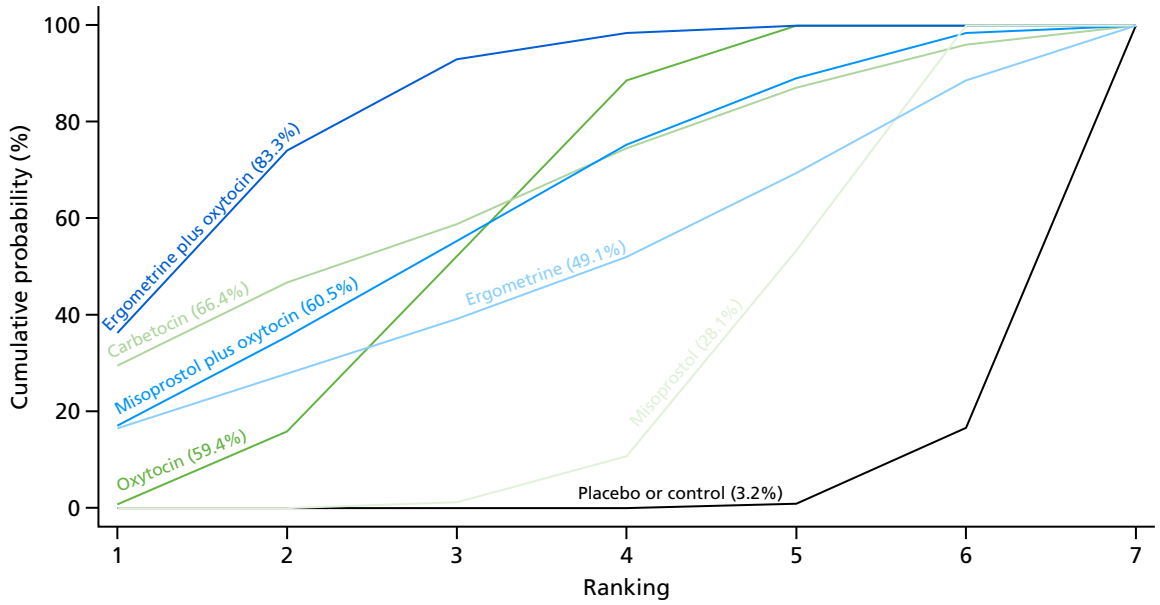

FIGURE 84 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, restricted to oxytocin studies that used an intramuscular or intravenous bolus of any dose.

Oxytocin bolus plus infusion

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml for this subgroup is presented in *Appendix 8*. This subgroup includes all trials, but when oxytocin was used as an arm in the trial this analysis is restricted to oxytocin studies that used an intravenous bolus with an intravenous infusion of any dose and excluded studies that used an intravenous or intramuscular bolus or an intravenous infusion only of oxytocin. Pooled effect sizes from the NMA of 31 trials suggested that all interventions, except oxytocin and misoprostol plus oxytocin, are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo for the subgroup including oxytocin trials that used an intravenous bolus plus an infusion of any dose (*Figure 85*). The active interventions were comparable between them, but most of the comparisons were too underpowered to detect a difference. There was no evidence of global inconsistency in this analysis ($p = 0.081$).

Figure 86 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the subgroup, including trials only of oxytocin that used an intravenous bolus plus an infusion of any dose. No clear ranking emerges in this analysis.

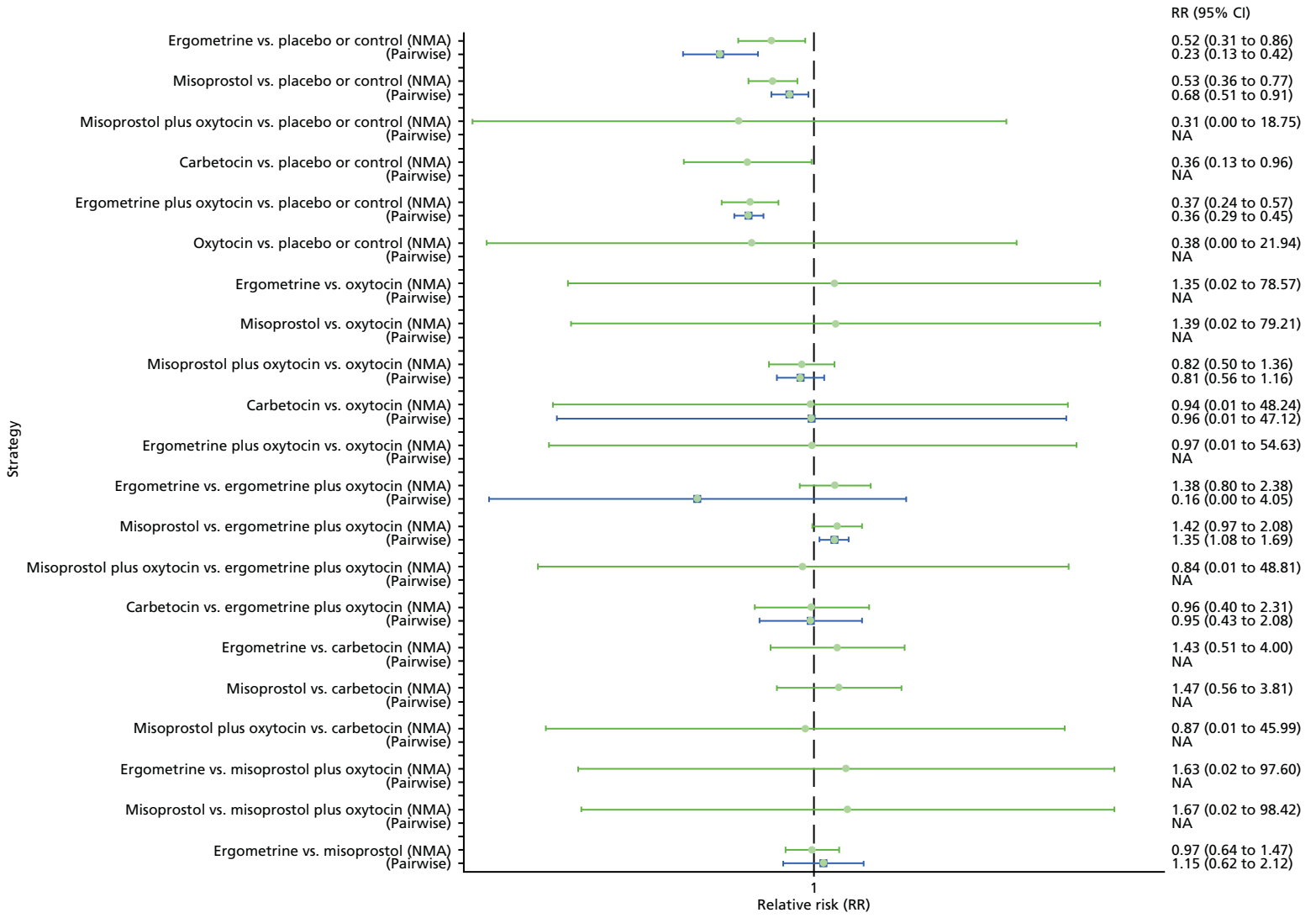

FIGURE 85 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, restricted to oxytocin studies that used an intravenous bolus plus an infusion of any dose. NA, not applicable.

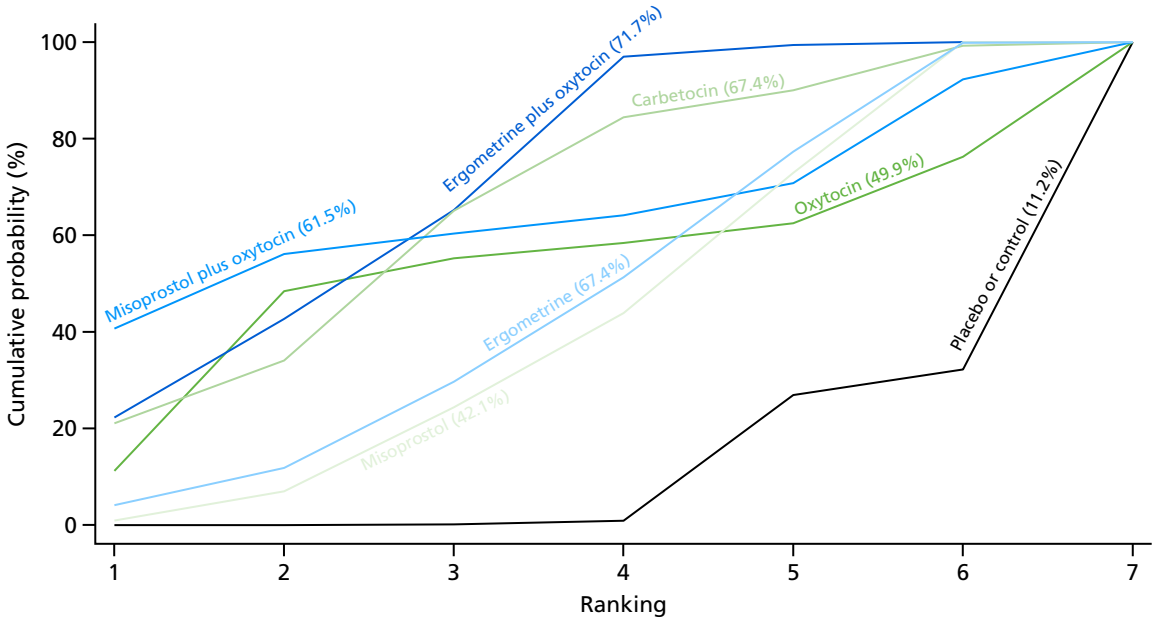

FIGURE 86 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, restricted to oxytocin studies that used an intravenous bolus plus an infusion of any dose.

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

The network diagram for PPH blood loss of ≥ 1000 ml for this subgroup is presented in *Appendix 8*. This subgroup includes all trials, but it is restricted to oxytocin studies that used an intravenous bolus with an intravenous infusion of any dose. Pooled effect sizes from the NMA of 29 trials suggested that all interventions demonstrated a similar trend for reducing occurrence of this outcome, but only ergometrine, misoprostol and ergometrine plus oxytocin reached statistical significance when compared with the placebo for this subgroup (*Figure 87*). The active interventions were comparable between them, but most of the comparisons were too underpowered to detect a difference. There was no evidence of global inconsistency in this analysis ($p = 0.315$).

Figure 88 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the subgroup including oxytocin studies that used an intravenous bolus plus an infusion of any dose. No clear ranking emerges in this analysis.

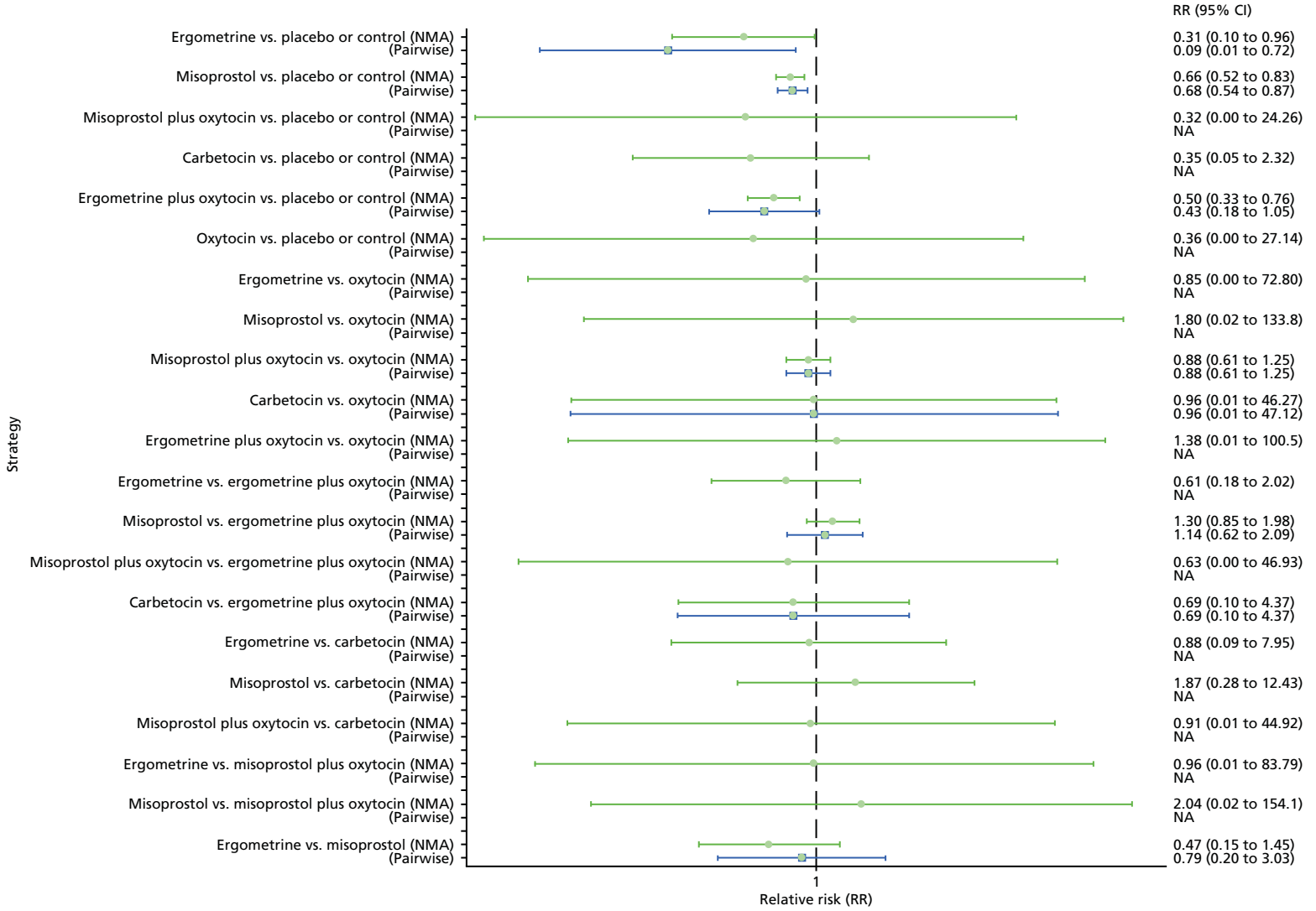

FIGURE 87 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, restricted to oxytocin studies that used an intravenous bolus plus an infusion of any dose. NA, not applicable.

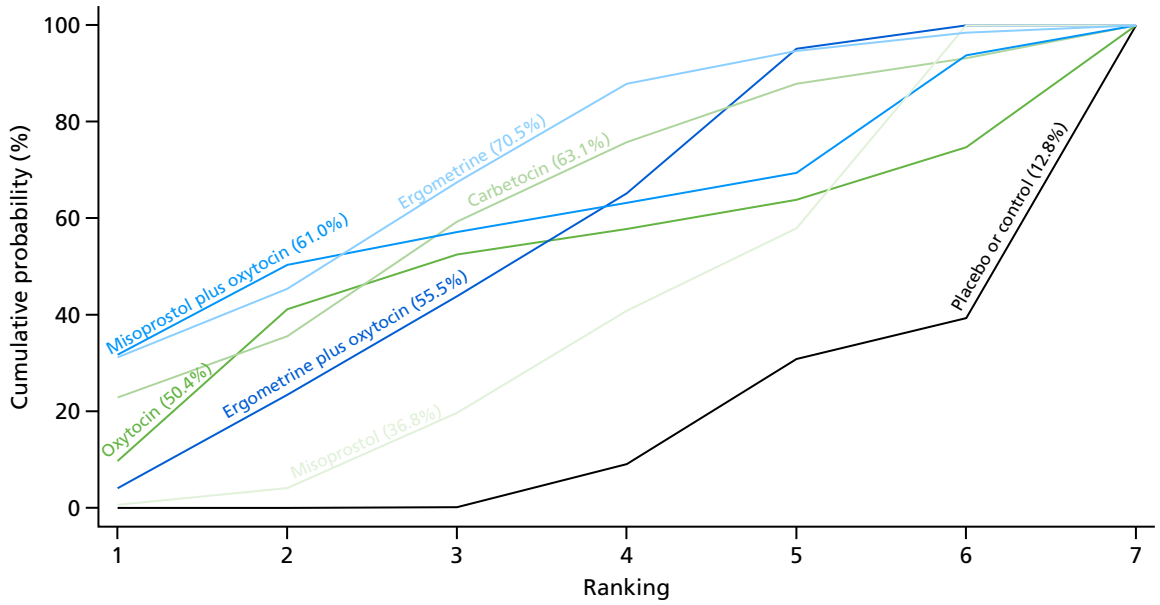

FIGURE 88 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, restricted to oxytocin studies that used an intravenous bolus plus an infusion of any dose.

Oxytocin infusion only

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml for this subgroup is presented in *Appendix 8*. This subgroup includes all trials, but when oxytocin was used as an arm in the trial this analysis is restricted to oxytocin studies that used an intravenous infusion only of any dose, and excluded studies that used an intravenous or intramuscular bolus or an intravenous bolus plus an intravenous infusion of oxytocin. Pooled effect sizes from the NMA of 48 trials suggested that all interventions are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo for the subgroup, including oxytocin trials that used an intravenous infusion only of any dose (*Figure 89*). The active interventions were comparable between them, but most of the comparisons were too underpowered to detect a difference. There was no evidence of global inconsistency in this analysis ($p = 0.135$).

Figure 90 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the subgroup, including oxytocin trials trials that used an intravenous infusion only of any dose. The highest-ranked interventions are carbetocin, ergometrine plus oxytocin and misoprostol plus oxytocin, with almost 100% probability of these three interventions being ranked first, second or third. Oxytocin is ranked fourth and its probability in being ranked in the top three interventions was almost 0%.

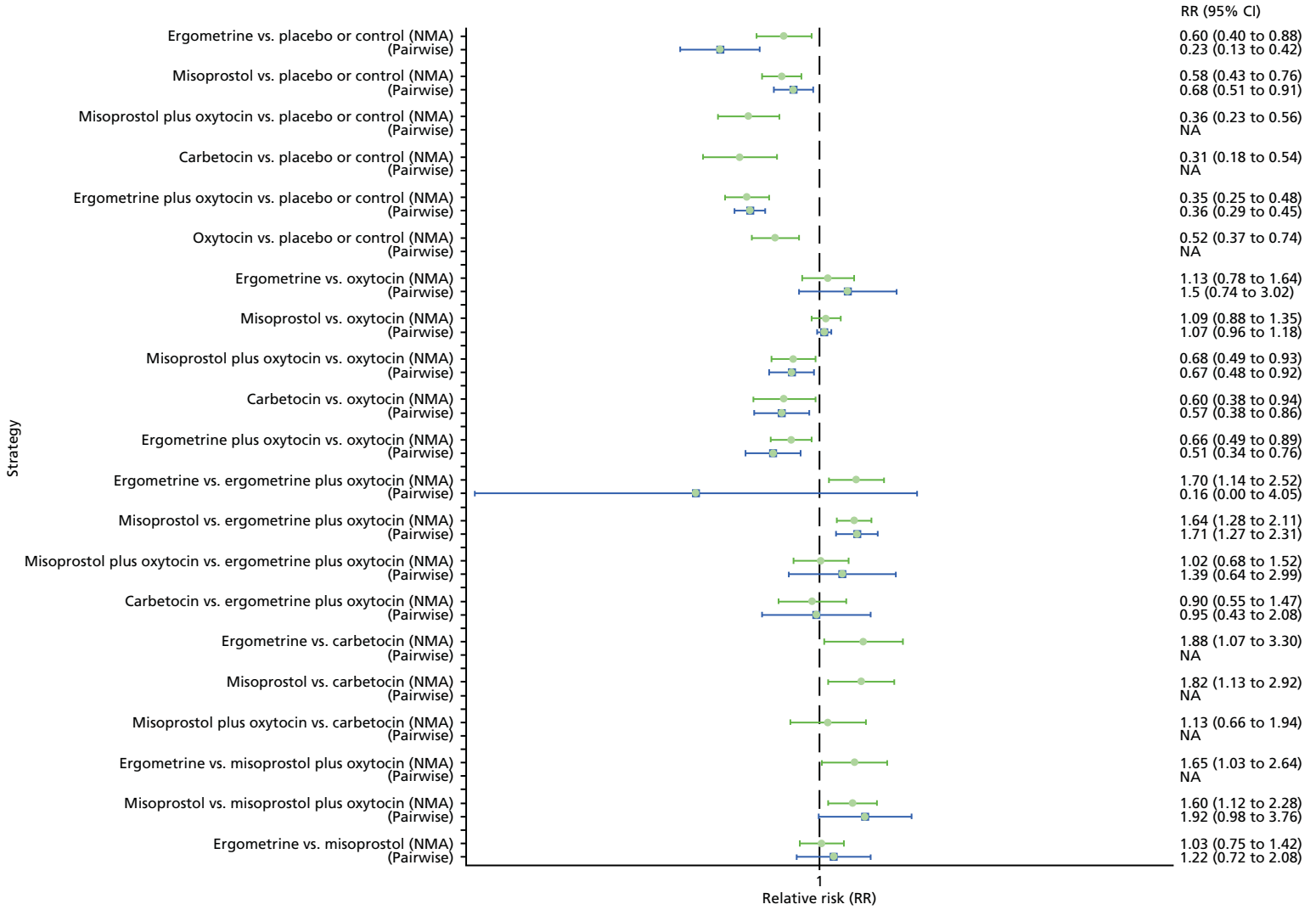

FIGURE 89 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, restricted to oxytocin studies that used an intravenous infusion only of any dose. NA, not applicable.

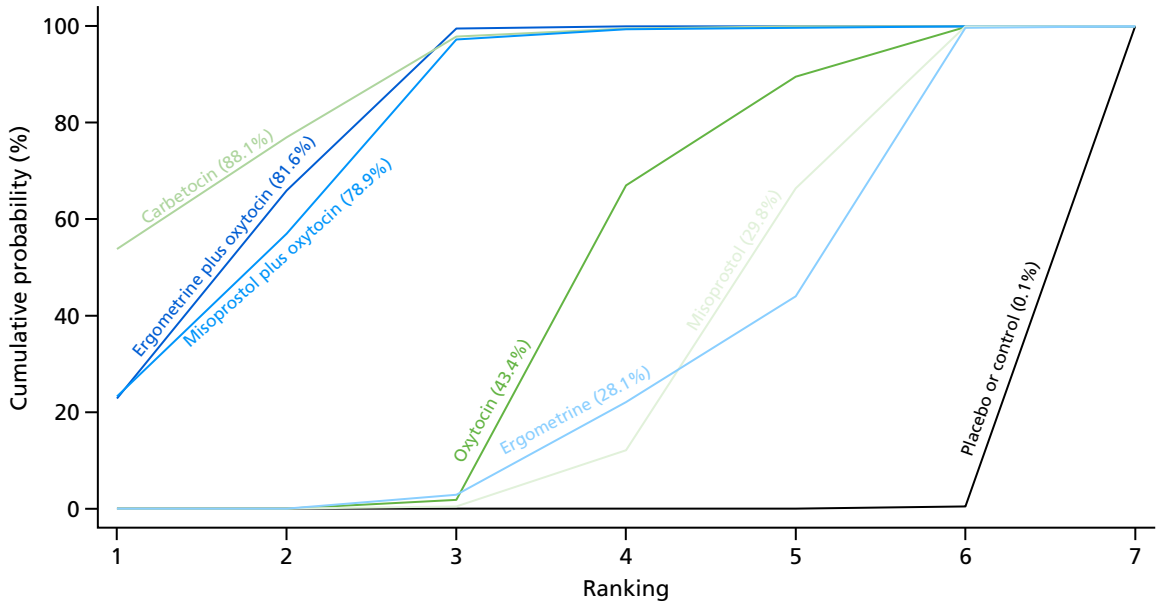

FIGURE 90 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, restricted to oxytocin studies that used an intravenous infusion only of any dose.

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

The network diagram for PPH blood loss of ≥ 1000 ml for the subgroup including all trials, but restricting to oxytocin trials that used an intravenous infusion only of any dose is presented in *Appendix 8*. Pooled effect sizes from the NMA of 41 trials suggested that all interventions except oxytocin and ergometrine are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo for the subgroup, including only oxytocin trials that used an intravenous infusion only of any dose (see *Figure 83*). Ergometrine plus oxytocin and carbetocin were found to be more effective than the standard intervention, oxytocin (*Figure 91*). Ergometrine plus oxytocin and carbetocin were also found to be more effective than misoprostol. There was no evidence of global inconsistency in this analysis ($p = 0.232$).

Figure 92 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the subgroup including oxytocin studies that used an intravenous infusion only of any dose. The highest-ranked intervention is carbetocin. There is less clear ranking for the rest of the interventions, but on this analysis, oxytocin is ranked sixth, lower than ergometrine and misoprostol, with 0% probability of it being ranked in the top three.

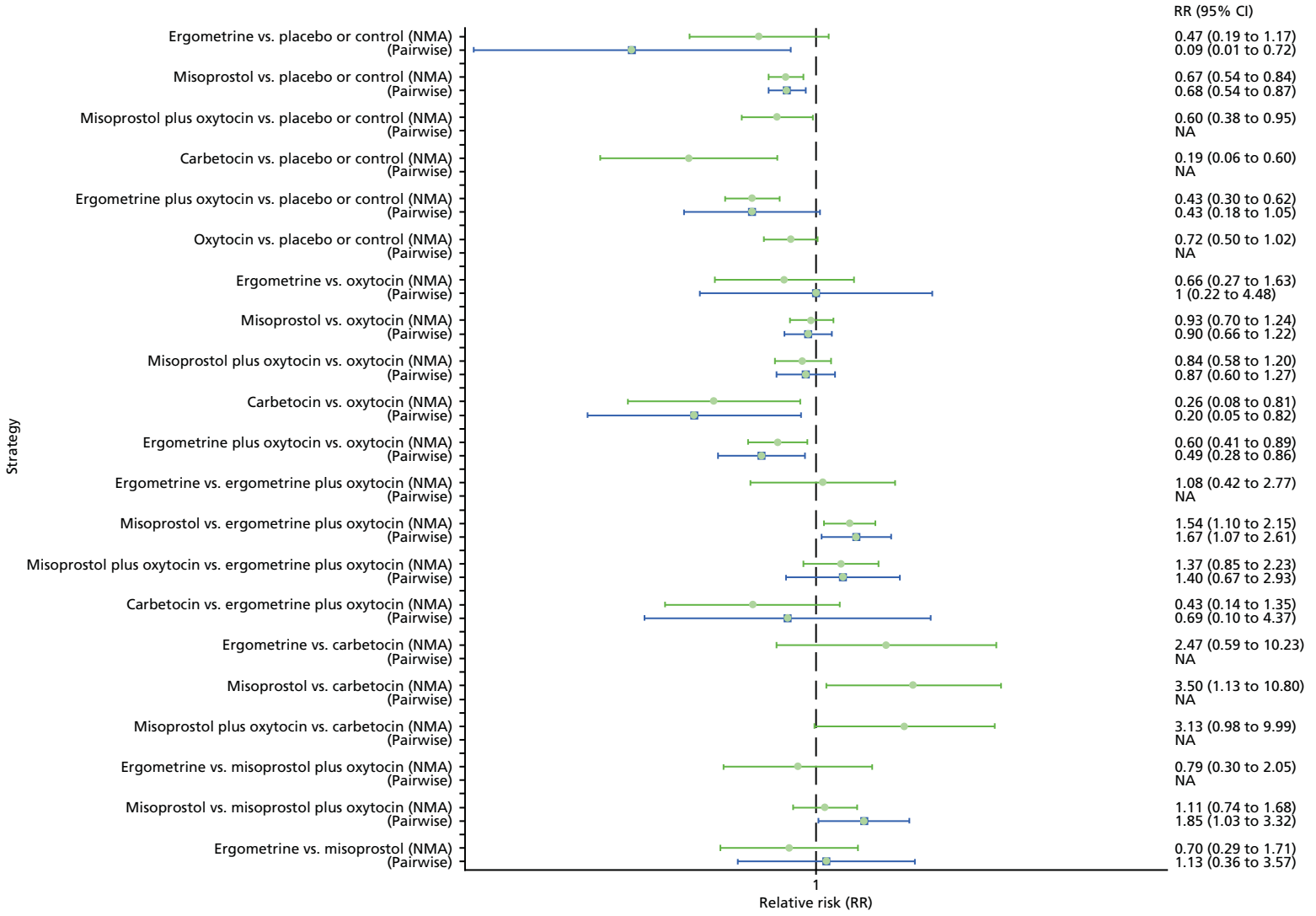

FIGURE 91 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, restricted to oxytocin studies that used an intravenous infusion only of any dose. NA, not applicable.

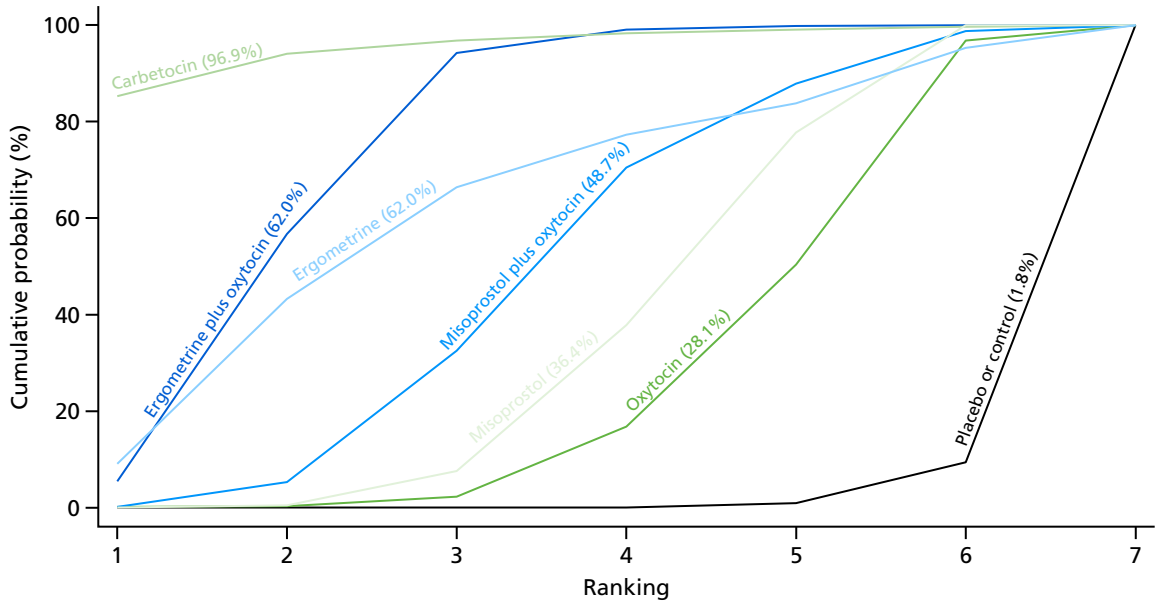

FIGURE 92 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, restricted to oxytocin studies that used an intravenous infusion only of any dose.

Sensitivity analyses

High-quality studies

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml for high-quality trials (double-blinded, adequately concealed, with < 10% loss to follow-up) is presented in *Appendix 8*. Pooled effect sizes from the NMA of 29 high-quality trials suggested that all interventions, except carbetocin, are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo, even though carbetocin demonstrated a similar trend towards reduction of this outcome (*Figure 93*). Ergometrine plus oxytocin, and ergometrine were found to be more effective than the standard intervention, oxytocin (see *Figure 93*). Ergometrine plus oxytocin and ergometrine were also found to be more effective than misoprostol when used alone. There was no evidence of global inconsistency in this analysis ($p = 0.844$).

Figure 94 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for the high-quality trials. The highest-ranked interventions are ergometrine, ergometrine plus oxytocin and misoprostol plus oxytocin. Oxytocin is ranked fourth and its probability of being ranked in the top three interventions was < 10%. Carbetocin dropped its ranking from second in the global analysis for PPH blood loss of ≥ 500 ml to fifth behind oxytocin in this analysis including only high-quality trials. The ranking of ergometrine is an outlier in this analysis and is based on a single study.

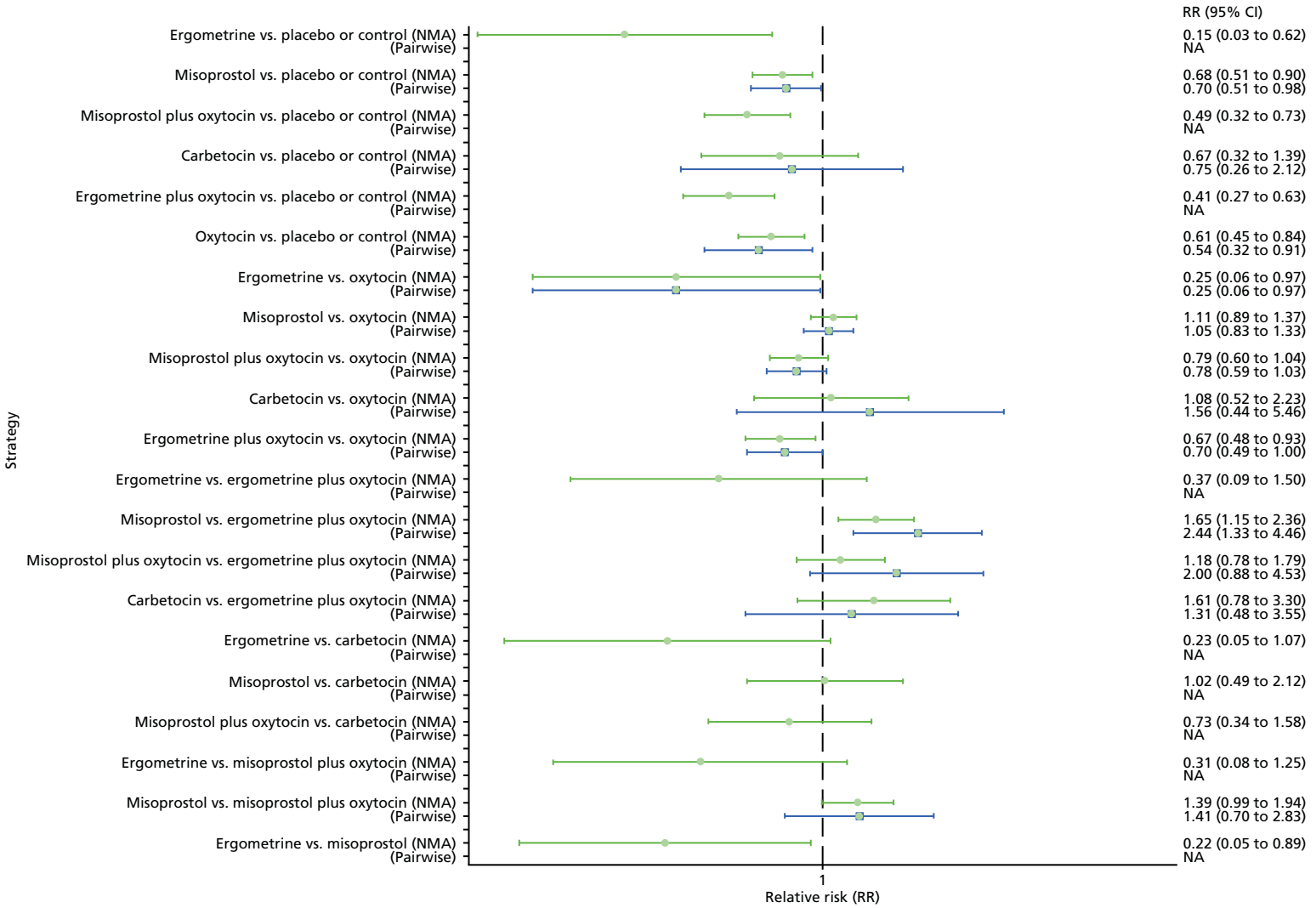

FIGURE 93 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, restricted to only high-quality studies. NA, not applicable.

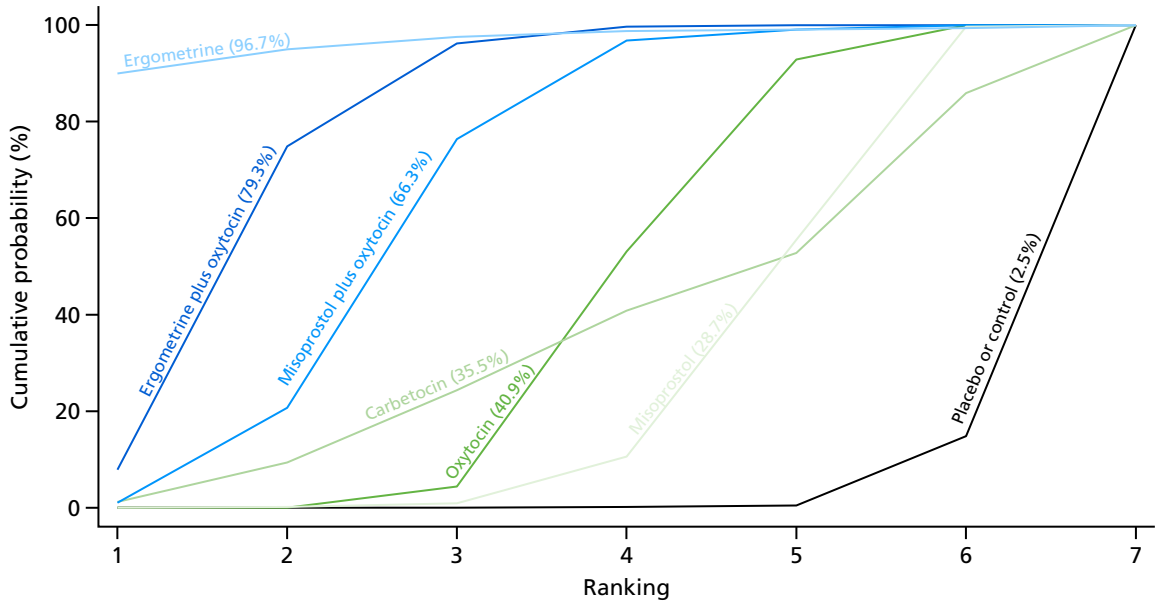

FIGURE 94 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, restricted to only high-quality studies.

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

The network diagram for PPH blood loss of ≥ 1000 ml for high-quality trials is presented in *Appendix 8*. Pooled effect sizes from the NMA of 30 high-quality trials suggested that all interventions, except carbetocin, are effective for preventing PPH blood loss of ≥ 1000 ml when compared with placebo, even though carbetocin demonstrated a similar trend towards reduction of this outcome (*Figure 95*). Oxytocin was found to be better than misoprostol when used alone (see *Figure 95*). Ergometrine plus oxytocin was also found to be more effective than misoprostol when used alone. There was no evidence of global inconsistency in this analysis ($p = 0.802$).

Figure 96 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the high-quality trials. The highest-ranked intervention is ergometrine plus oxytocin. The ranking for carbetocin, oxytocin and misoprostol plus oxytocin is very close, without a clear hierarchy.

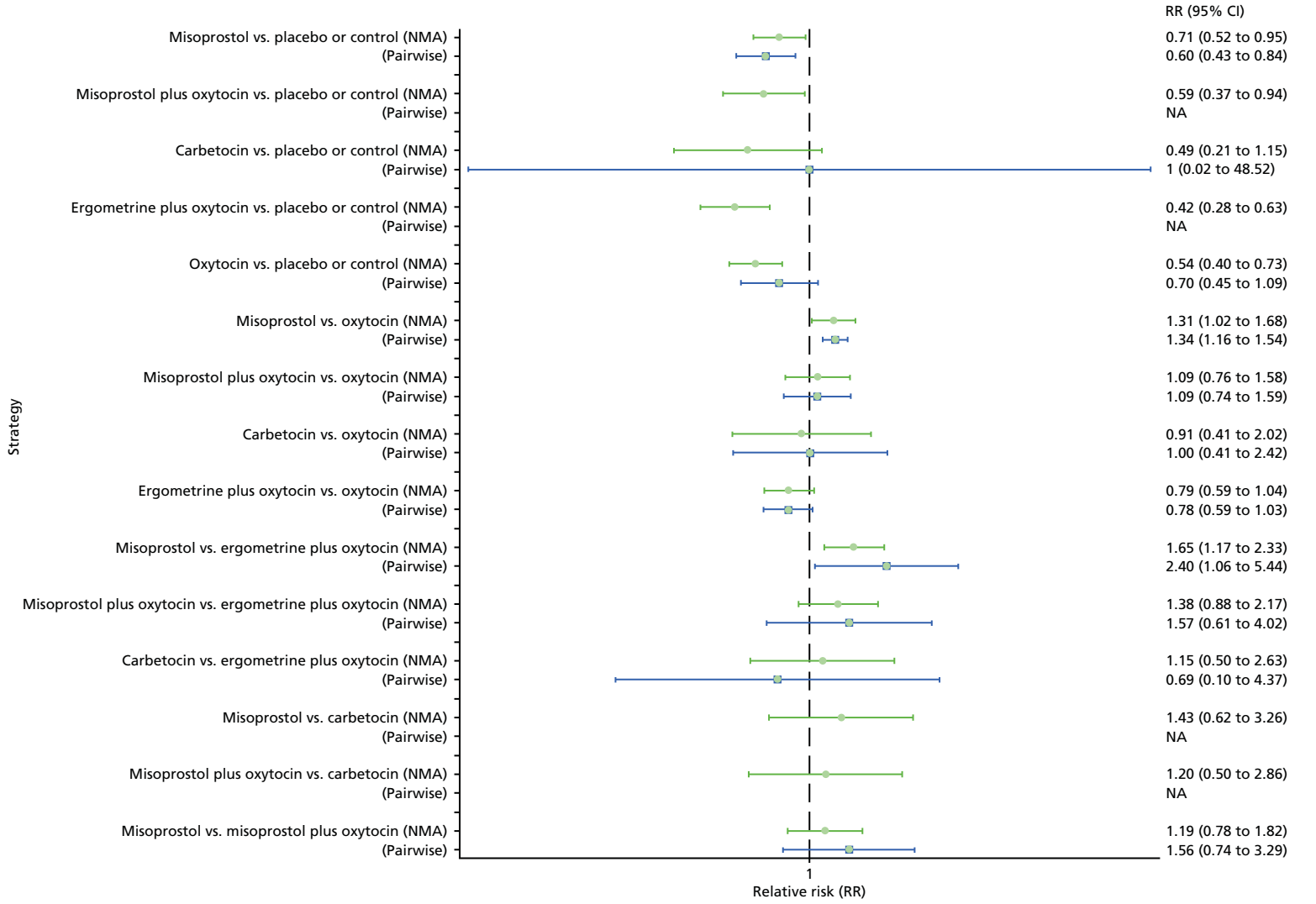

FIGURE 95 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, restricted to only high-quality studies. NA, not applicable.

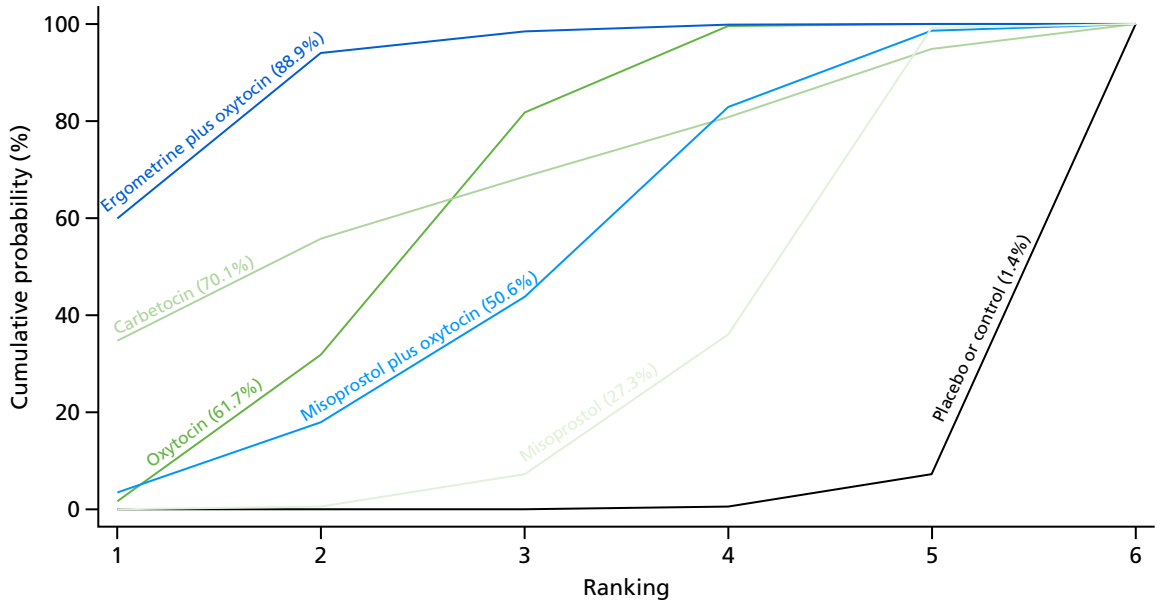

FIGURE 96 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, restricted to only high-quality studies.

Studies with funding source rated as being at low risk of bias (public or no funding)

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml for studies with public or no funding is presented in *Appendix 8*. Pooled effect sizes from the NMA of 32 trials suggested that all interventions, except carbetocin and ergometrine, are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo, even though they all demonstrated a similar trend towards reduction of this outcome (*Figure 97*). There were no significant differences between the active interventions. There was evidence of global inconsistency in this analysis ($p = 0.0003$). However, it is noted that the CIs for both the NMA and direct evidence were overlapping across all comparisons, suggesting locally consistent results except for ergometrine versus misoprostol based on a single study.

Figure 98 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for trials with public or no funding. The highest-ranked intervention is ergometrine plus oxytocin. The ranking for carbetocin, oxytocin and misoprostol plus oxytocin is very close without a clear hierarchy.

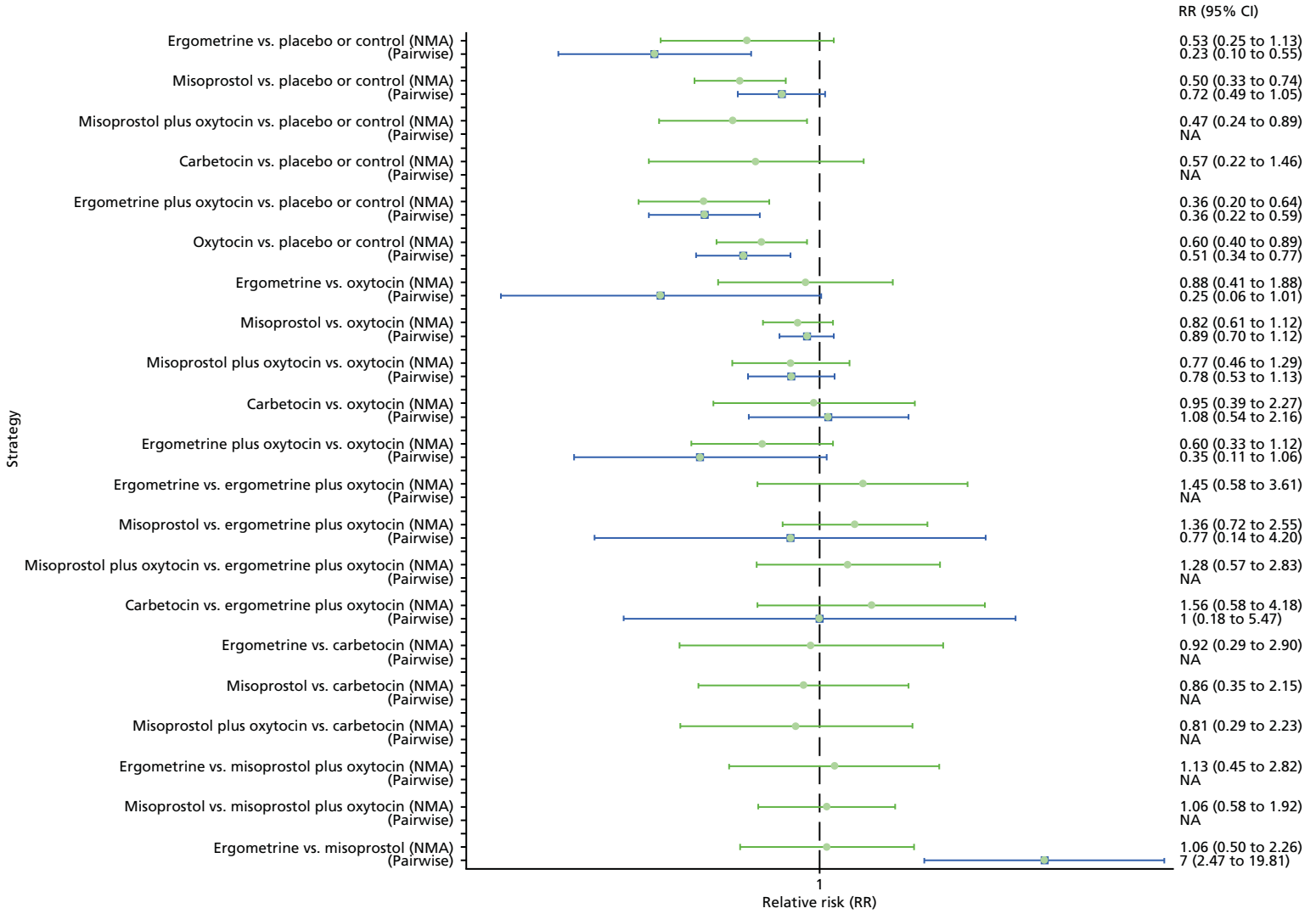

FIGURE 97 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, restricted to studies with funding source rated as being at a low risk of bias (public or no funding). NA, not applicable.

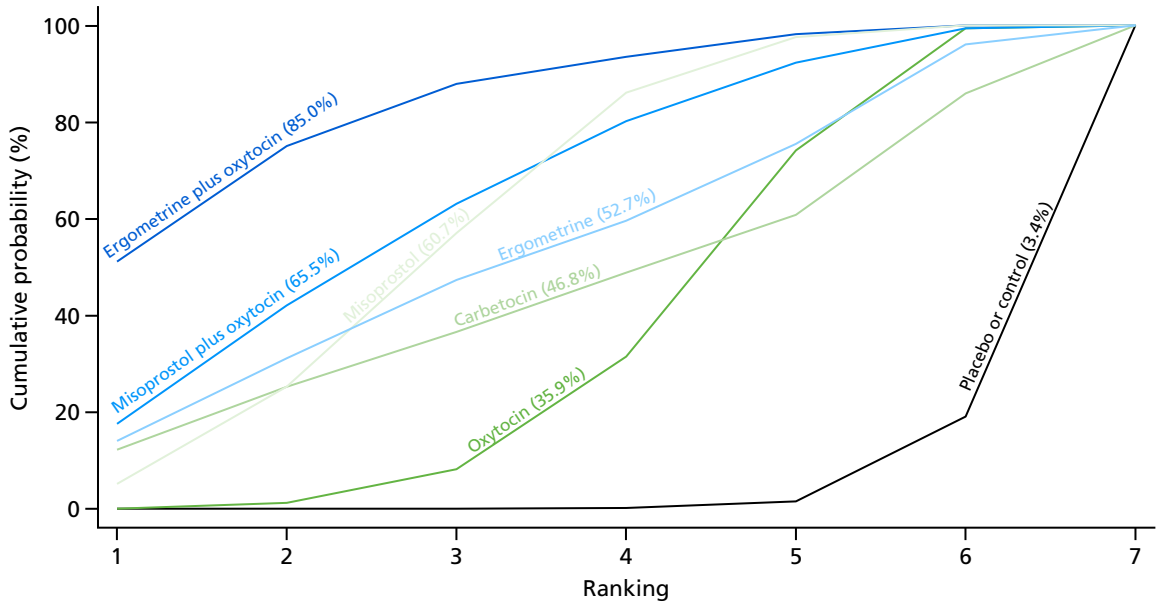

FIGURE 98 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, restricted to studies with funding source rated as being at a low risk of bias (public or no funding).

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

The network diagram for PPH blood loss of ≥ 1000 ml for trials with public or no funding is presented in *Appendix 8*. Pooled effect sizes from the NMA of 35 trials suggested that all interventions, except carbetocin, are effective for preventing PPH blood loss of ≥ 1000 ml when compared with placebo, even though carbetocin demonstrated a similar trend towards reduction of this outcome (*Figure 99*). No intervention was found to be significantly better or worse than oxytocin (see *Figure 99*). Ergometrine was found to be more effective than misoprostol. There was no evidence of global inconsistency in this analysis ($p = 0.739$).

Figure 100 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the trials with public or no funding. The highest-ranked interventions are ergometrine and ergometrine plus oxytocin. The ranking for carbetocin, oxytocin and misoprostol plus oxytocin is very close without a clear hierarchy. The ranking of ergometrine is an outlier in this analysis and is based on a single study.

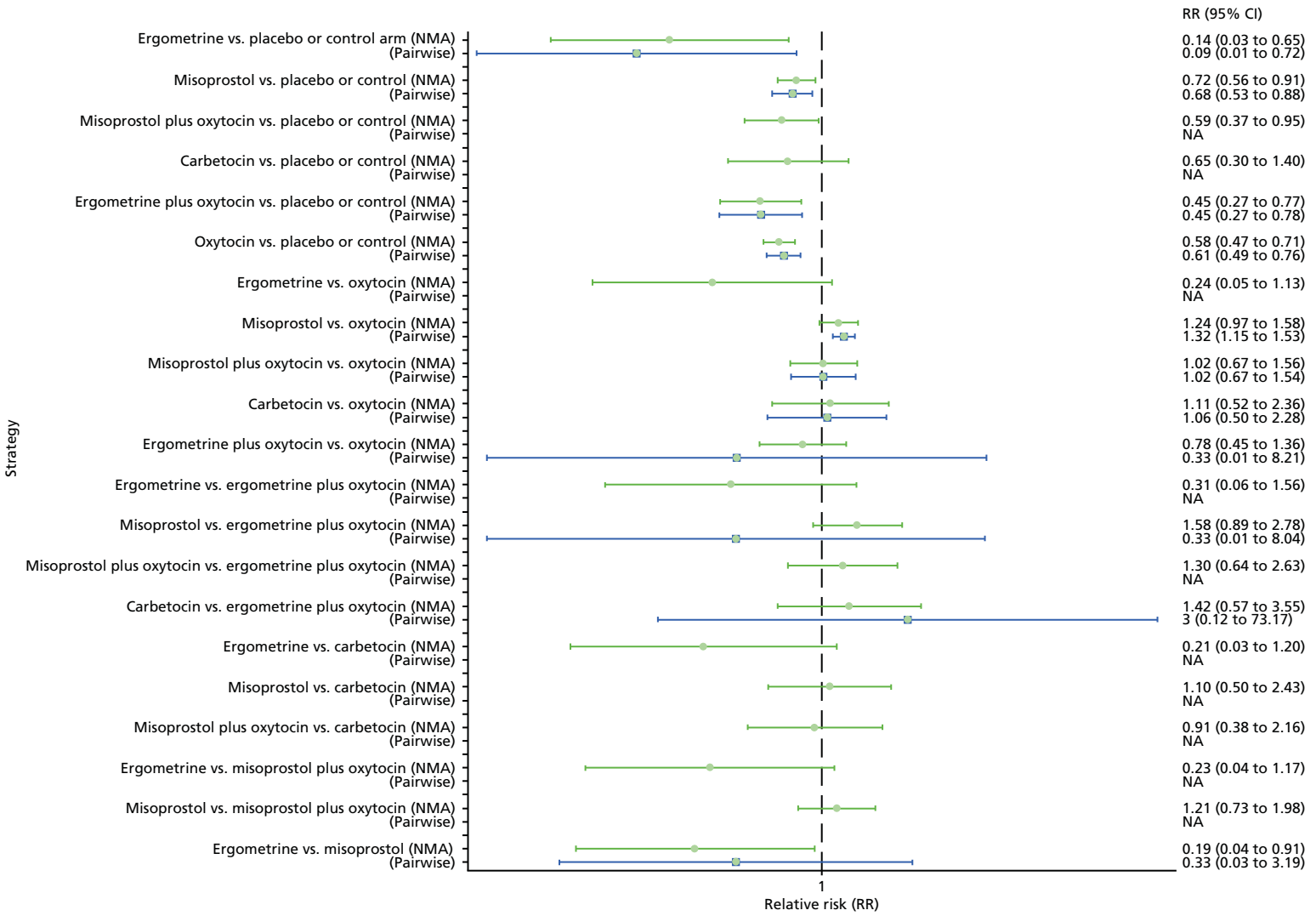

FIGURE 99 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, restricted to studies with funding source rated as being at a low risk of bias (public or no funding). NA, not applicable.

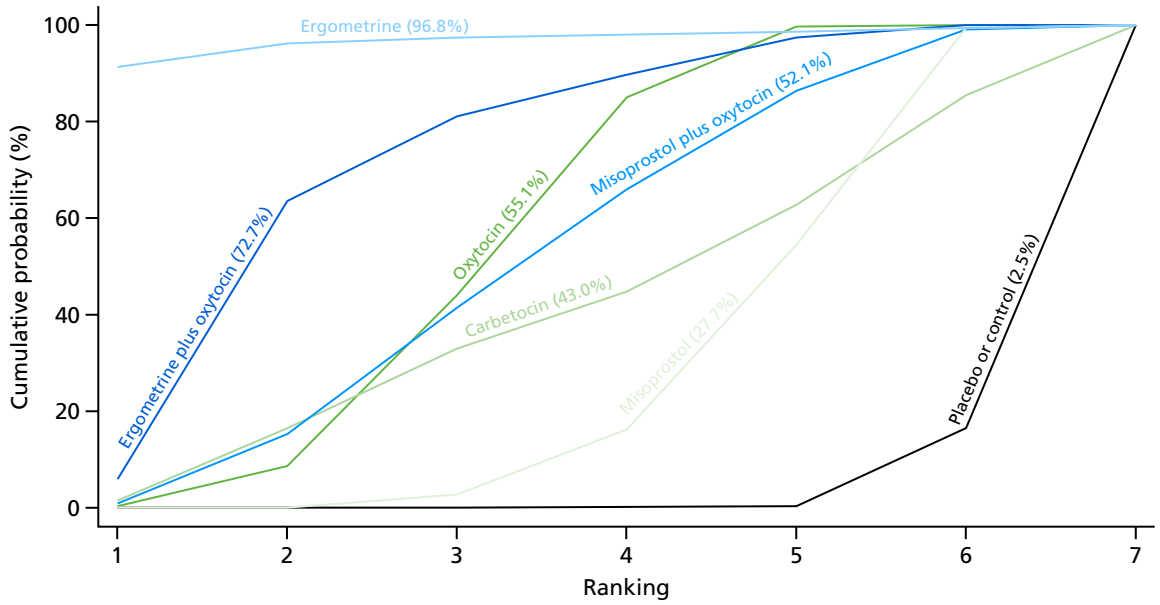

FIGURE 100 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, restricted to studies with funding source rated as being at a low risk of bias (public or no funding).

Studies with an objective method of measuring blood loss

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml for the trials with an objective method for measuring blood loss is presented in *Appendix 8*. Pooled effect sizes from the NMA of 56 trials suggested that all interventions, except ergometrine, are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo (*Figure 101*). Ergometrine plus oxytocin and misoprostol plus oxytocin were found to be more effective than the standard intervention, oxytocin, with carbetocin also demonstrating a similar trend (see *Figure 101*). Ergometrine plus oxytocin and misoprostol plus oxytocin were also found to be more effective than misoprostol and ergometrine when used alone. There was no evidence of global inconsistency in this analysis ($p = 0.455$).

Figure 102 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for trials with an objective method of measuring blood loss. The highest-ranked interventions are ergometrine plus oxytocin and misoprostol plus oxytocin followed closely by carbetocin, with almost 100% probability of these three interventions being ranked first, second or third. Oxytocin is ranked fourth and its probability of being ranked in the top three interventions was < 0%.

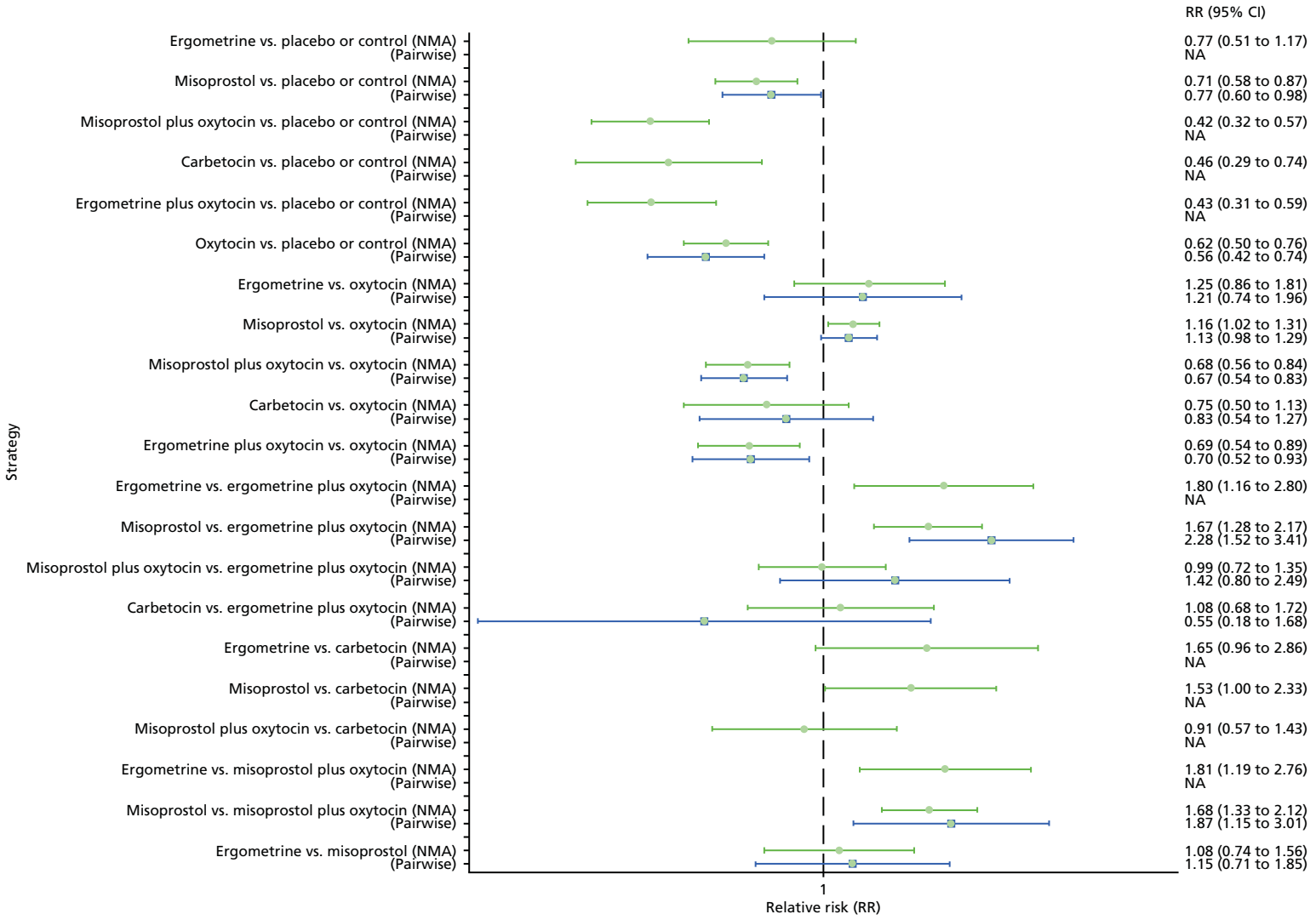

FIGURE 101 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, restricted to studies with an objective method of measuring blood loss. NA, not applicable.

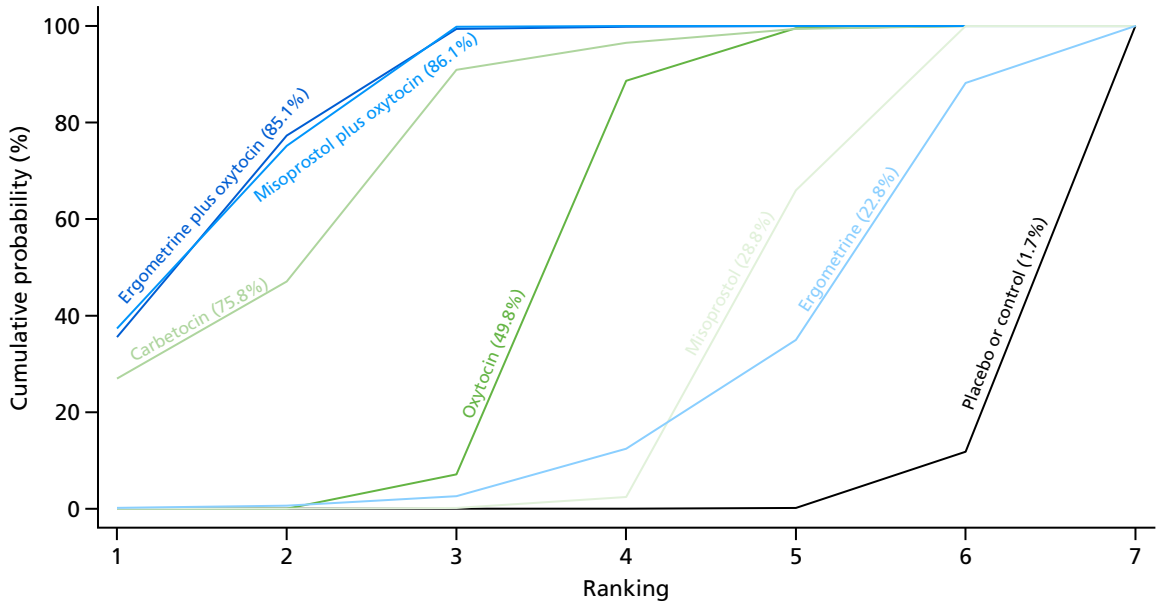

FIGURE 102 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, restricted to studies with an objective method of measuring blood loss.

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

The network diagram for PPH blood loss of ≥ 1000 ml for studies with an objective method of measuring blood loss is presented in *Appendix 8*. Pooled effect sizes from the NMA of 49 high-quality trials suggested that all interventions, except carbetocin and ergometrine, are effective for preventing PPH blood loss of ≥ 1000 ml when compared with the placebo, even though carbetocin demonstrated a similar trend towards reduction of this outcome (*Figure 103*). Ergometrine plus oxytocin was found to be more effective than the standard intervention, oxytocin. Ergometrine plus oxytocin was also found to be more effective than misoprostol and ergometrine when used alone. There was no evidence of global inconsistency in this analysis ($p = 0.606$).

Figure 104 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the studies that used an objective method of measuring blood loss. The highest-ranked intervention is ergometrine plus oxytocin. The ranking for carbetocin, oxytocin and misoprostol plus oxytocin is very close, without a clear hierarchy.

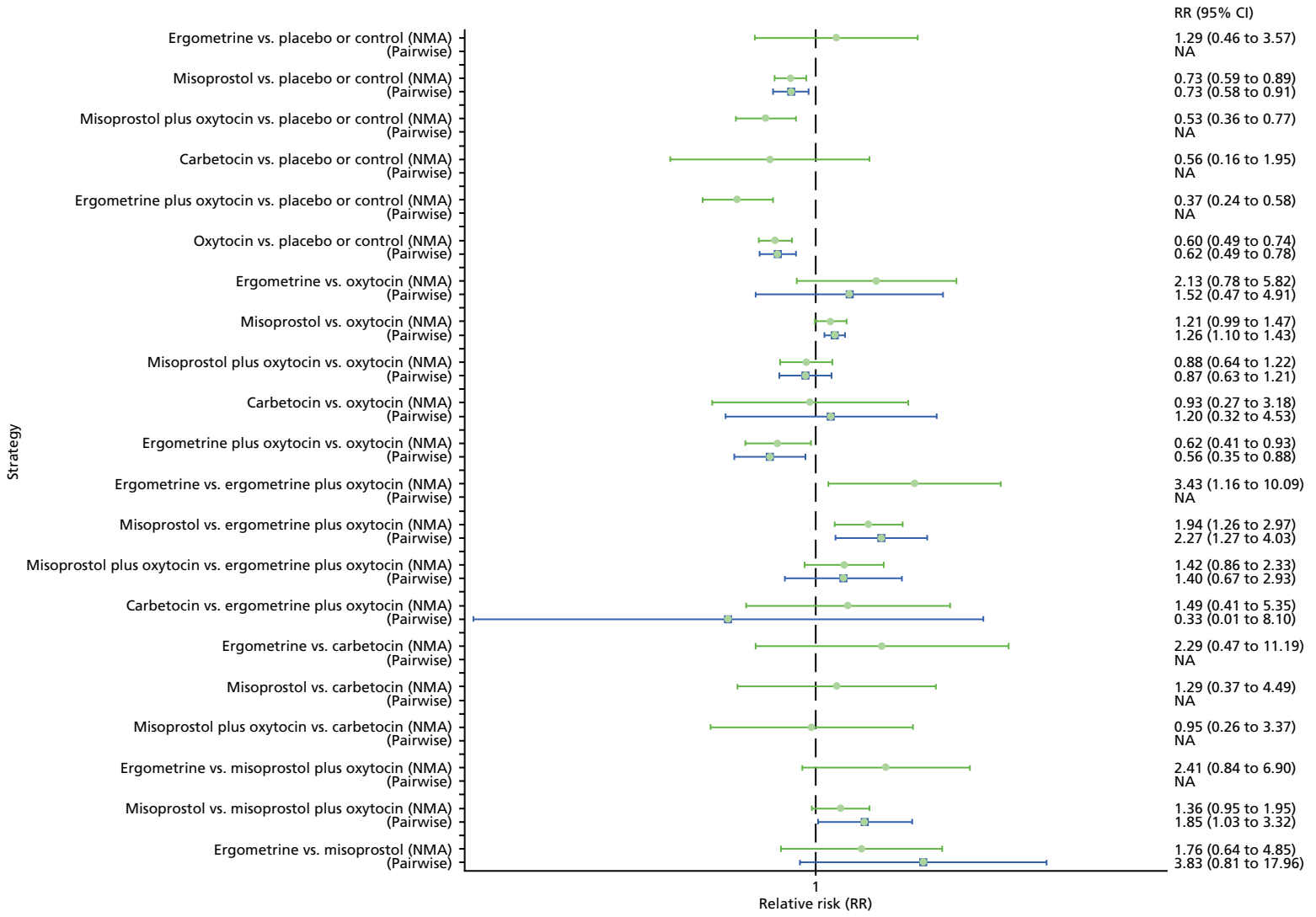

FIGURE 103 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, restricted to studies with an objective method of measuring blood loss. NA, not applicable.

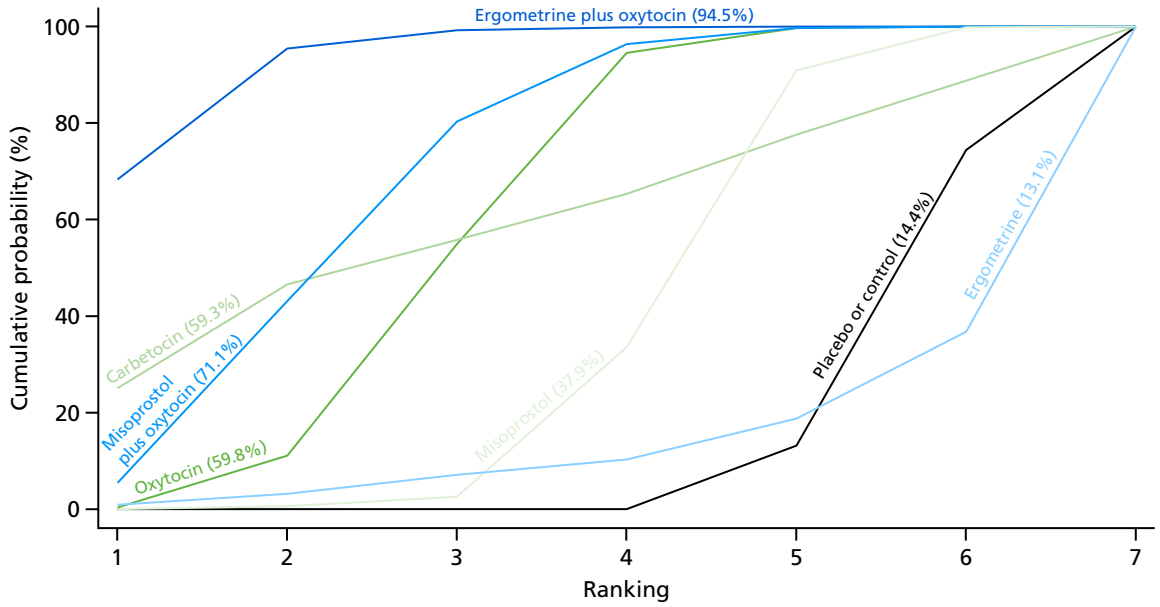

FIGURE 104 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, restricted to studies with an objective method of measuring blood loss.

Large studies only (i.e. > 400 participants)

Primary postpartum haemorrhage blood loss of ≥ 500 ml

The network diagram for PPH blood loss of ≥ 500 ml for the large trials with > 400 participants is presented in *Appendix 8*. Pooled effect sizes from the NMA of 46 trials suggested that all interventions, except ergometrine, are effective for preventing PPH blood loss of ≥ 500 ml when compared with the placebo (*Figure 105*). Ergometrine plus oxytocin and misoprostol plus oxytocin were found to be more effective than with the standard intervention, oxytocin, with carbetocin not being included in this analysis as there were no large studies comparing carbetocin with any of the other interventions (see *Figure 105*). Ergometrine plus oxytocin and misoprostol plus oxytocin were also found to be more effective than misoprostol and ergometrine when used alone. There was evidence of global inconsistency in this analysis ($p = 0.011$). However, it is noted that the CIs for both the NMA and the direct evidence were overlapping across all comparisons, suggesting locally consistent results, except for ergometrine versus placebo or the control based on a single study.

Figure 106 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 500 ml for large trials with > 400 participants. The highest-ranked interventions are ergometrine plus oxytocin and misoprostol plus oxytocin. Oxytocin is ranked third and its probability of being ranked in the top two interventions was close to 0%. Carbetocin could not be ranked as there were no studies found comparing it with any other interventions in the network.

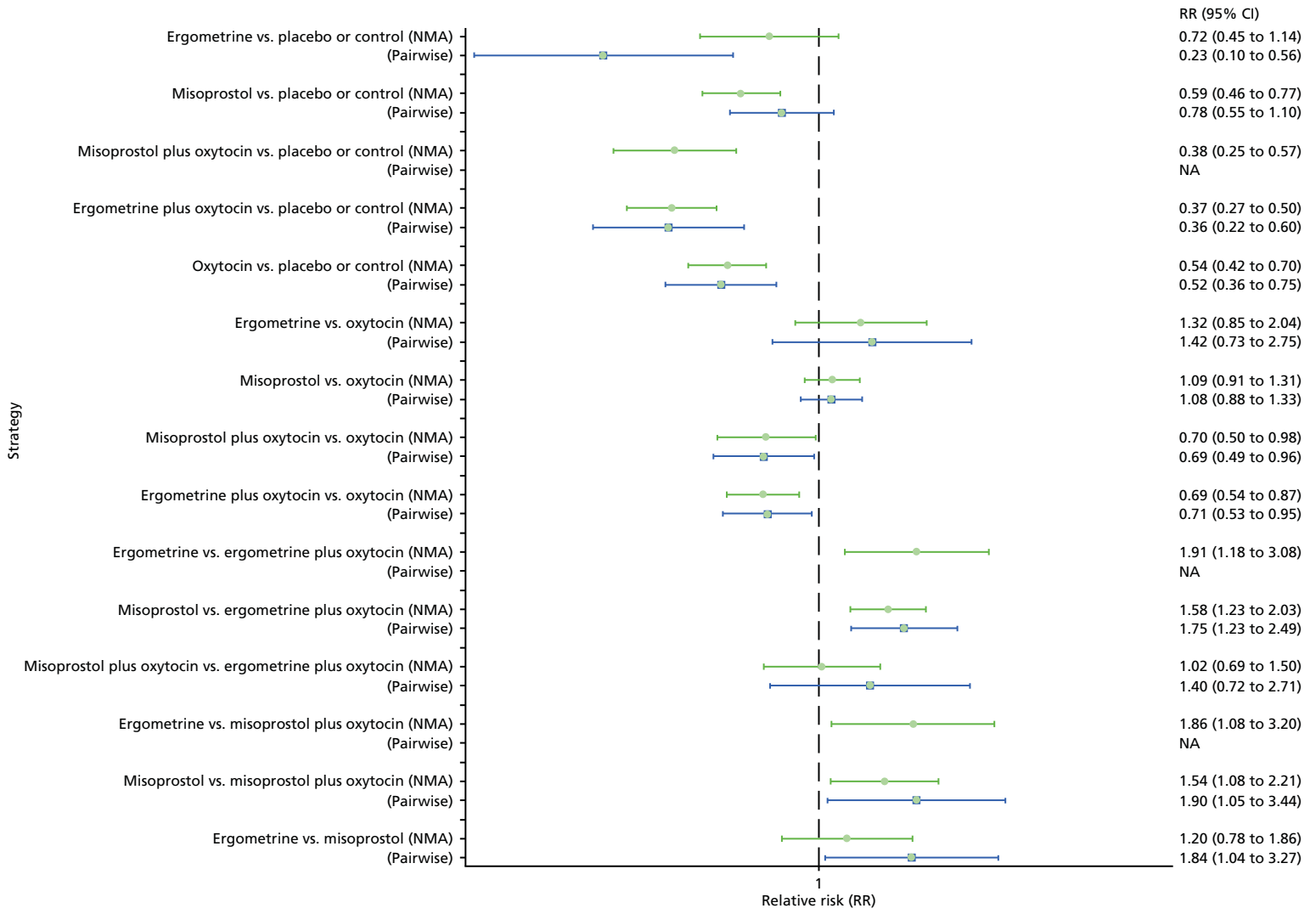

FIGURE 105 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 500 ml, restricted to large studies (i.e. > 400 participants). NA, not applicable.

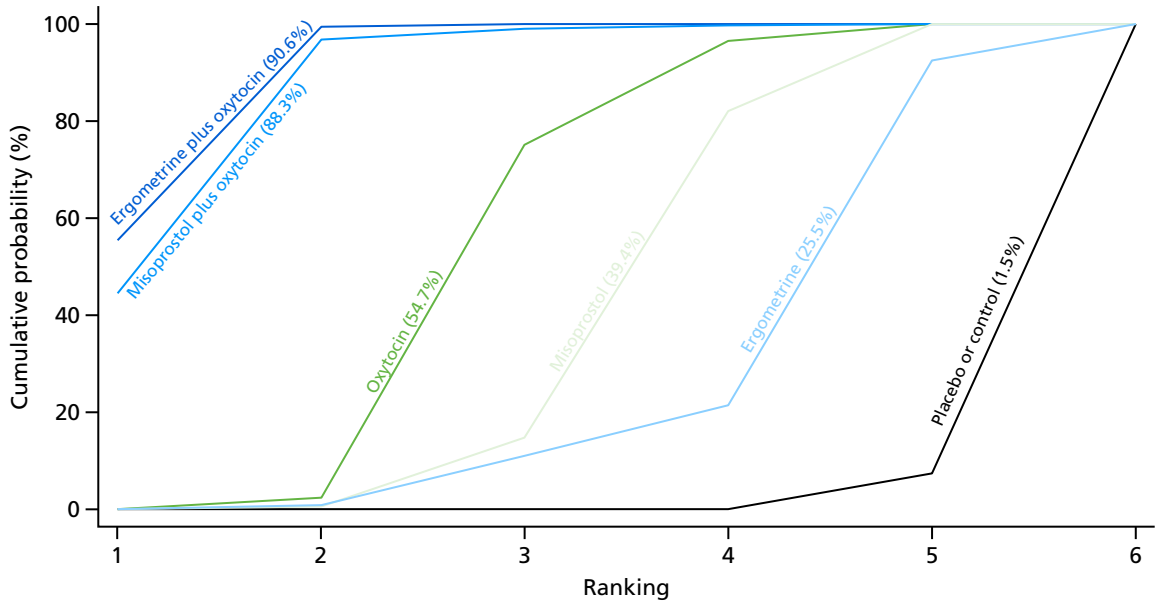

FIGURE 106 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 500 ml, restricted to large studies (i.e. > 400 participants).

Primary postpartum haemorrhage blood loss of ≥ 1000 ml

The network diagram for PPH blood loss of ≥ 1000 ml for the large trials with > 400 participants is presented in *Appendix 8*. Pooled effect sizes from the NMA of 46 trials suggested that all interventions, except ergometrine, are effective for preventing PPH blood loss of ≥ 500 ml when compared with placebo (*Figure 107*). Ergometrine plus oxytocin was found to be more effective than the standard intervention, oxytocin, with carbetocin not being included in this analysis as there were no large studies comparing carbetocin with any of the other interventions (*Figure 107*). Ergometrine plus oxytocin and oxytocin alone were also found to be more effective than misoprostol when used alone. There was no evidence of global inconsistency in this analysis ($p = 0.122$).

Figure 108 shows the cumulative probabilities for each intervention being at each possible rank for PPH blood loss of ≥ 1000 ml for the large trials. The highest-ranked interventions are ergometrine plus oxytocin and misoprostol plus oxytocin. Oxytocin is ranked third and its probability of being ranked in the top two interventions was close to 10%. Carbetocin could not be ranked as there were no studies found comparing it with any other interventions in the network.

Further sensitivity analyses for our primary outcomes were performed by removing trials published earlier than 1990 (three trials), a cluster trial (one trial), removing trials with a high number of missing data (10 trials) and removing trials in which participants were also randomised to co-interventions such as uterine massage and/or early controlled cord traction (three trials). Sensitivity analyses were also performed according to the choice of relative effect measure (RR vs. OR) and the statistical model (fixed-effects vs. random-effects model). It was found that the overall ranking did not vary, and the CIs of the relative effects did not substantially change. Of note is that the global inconsistency was less when the trials randomising to co-interventions were removed ($p = 0.218$).

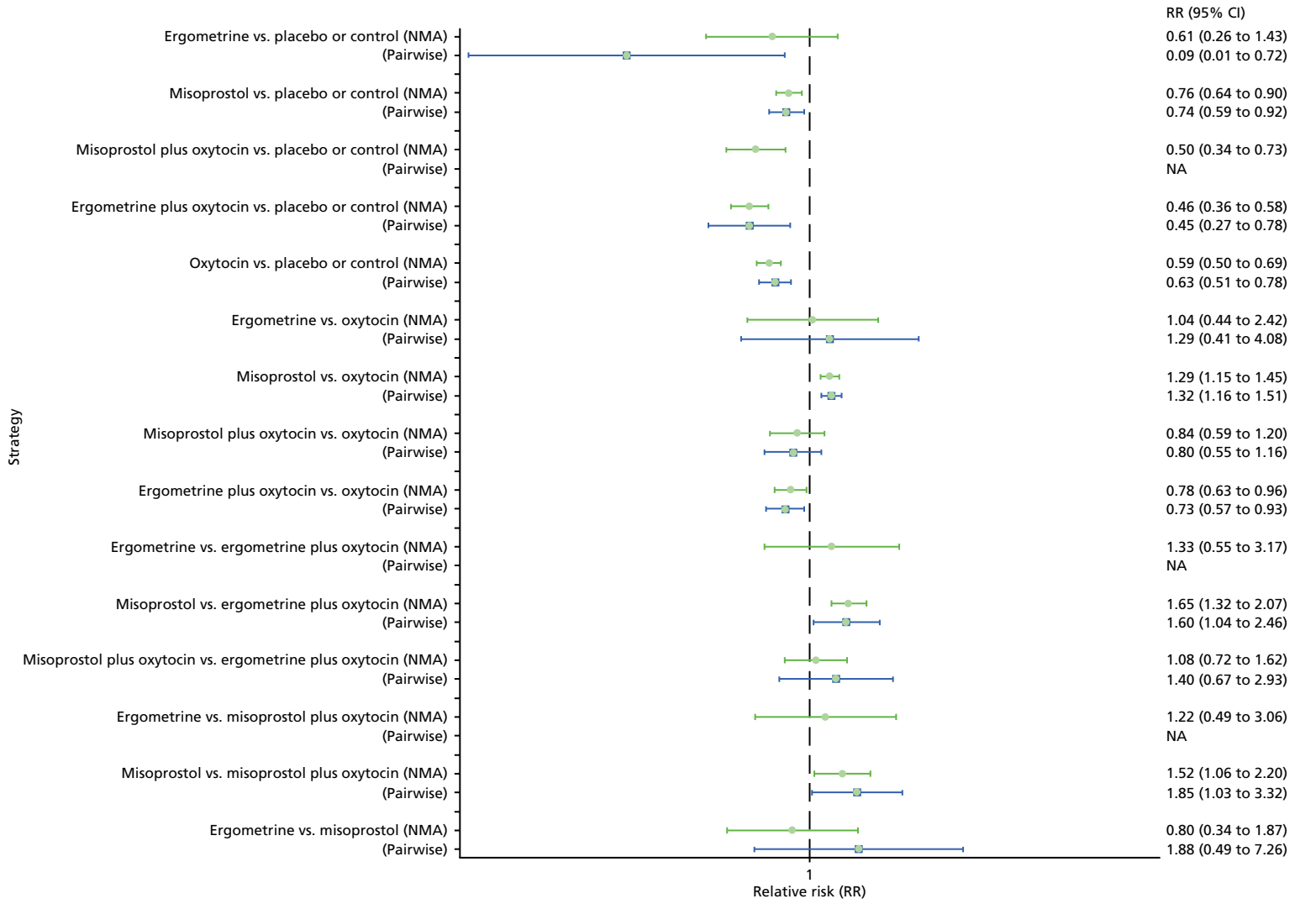

FIGURE 107 Forest plot with relative RRs and 95% CIs from the NMA and pairwise analyses for the prevention of PPH blood loss of ≥ 1000 ml, restricted to large studies (i.e. > 400 participants). NA, not applicable.

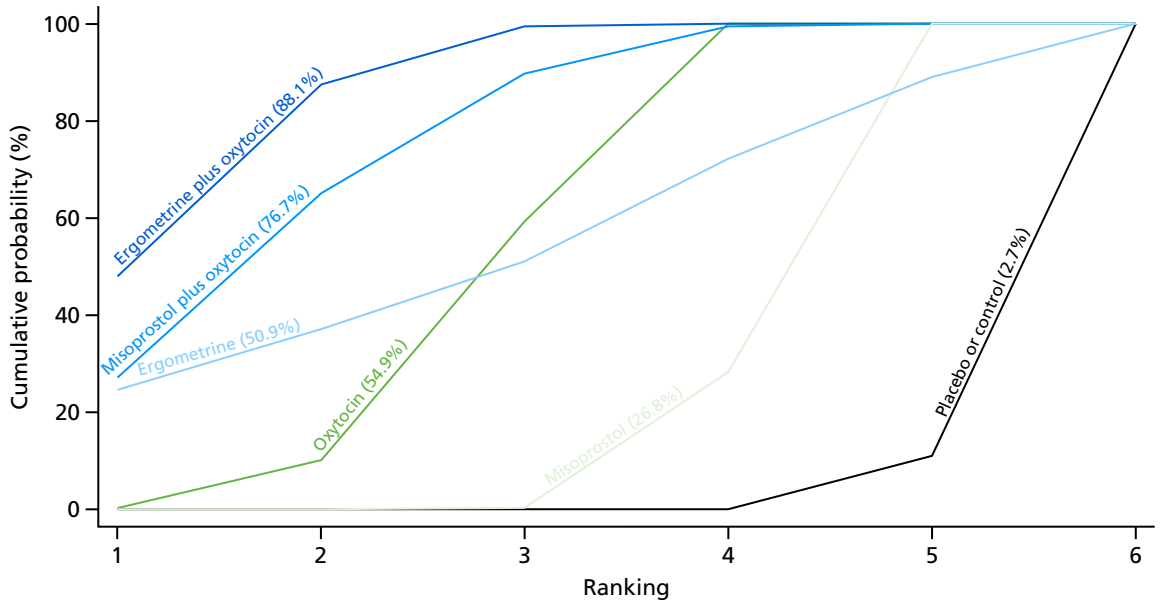

FIGURE 108 Cumulative rankograms comparing each of the uterotonic drugs and combinations thereof for the prevention of PPH blood loss of ≥ 1000 ml, restricted to large studies (i.e. > 400 participants).

Chapter 4 Health economics

Background

Uterotonic drugs administered at the birth of the baby are routinely recommended for the prevention of PPH, but there is lack of clarity over which uterotonic drug is best. Oxytocin is currently recommended in the UK for preventing PPH[23,174] because of its relatively low price and incidence of side effects. Few previous attempts have been made to compare the cost-effectiveness of one uterotonic drug with standard care for the prevention of PPH.[175–179] The literature is lacking any comparison of more than two uterotonic drugs or any ranking of cost-effectiveness for multiple uterotonics.

A model-based economic evaluation was carried out to compare the relative cost-effectiveness of the full range of uterotonic drugs available for the prevention of PPH. The model follows women from the point of administration of the uterotonic drug for the purpose of prevention through a pathway where, in some cases, the same drug or alternatives are given for the treatment of PPH.

In the economic evaluation reported here, the modes of birth (vaginal birth and birth by caesarean section) were separated for the analyses, and vaginal birth in a community health-care setting was also analysed. When possible, the results from the NMA are used in the health economics model. Costs and resource-use data were collected from appropriate sources as described in the *Methods* section.

Methods

The model was constructed to facilitate all the relevant comparisons in order to determine the most cost-effective uterotonic drug for the prevention of PPH. The analyses were carried out from the perspective of the UK NHS, as this cost-effectiveness analysis is targeted at a UK audience. The primary outcome measure was cost per case of haemorrhage avoided (i.e. $\geq$ 500 ml of blood lost). Secondary outcome measures of cost per case of haemorrhage avoided (i.e. $\geq$ 1000 ml of blood lost) and cost per major outcome averted were also analysed. It was not possible to present results in terms of quality-adjusted life-years (QALYs) because of the lack of appropriate utility data in the literature. The results are presented in terms of the incremental cost-effectiveness ratio (ICER), namely the additional cost per case of PPH blood loss of $\geq$ 500 ml avoided, additional cost per case of PPH blood loss of $\geq$ 1000 ml avoided, and additional cost per major outcome averted.

Model structure

A decision tree model was developed in TreeAge Pro 2016 (TreeAge Software, Inc., Williamstown, MA, USA) to represent the alternative strategies. A decision tree was chosen as the most appropriate model for evaluating the cost-effectiveness of uterotonic drugs for the prevention of PPH, because of the relatively short-term impact of the intervention and treatment of PPH.[180] The pathways of the model represent, as far as possible, the clinical steps carried out in a UK hospital in the event of PPH. NICE and the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines for the management and treatment of PPH were followed to establish the model pathways.[23,174] Additional information about the steps taken by clinicians to treat PPH were identified via expert opinion, which consisted of a team of five obstetricians. The obstetricians were part of the research team and helped finalise the model pathways.

The decision tree structure is presented in *Figure 109*. The start of the model is assumed to be when women are approaching what is referred to as the third stage of labour. This is defined as the point when women have given birth to their baby, but the placenta is yet to be delivered.

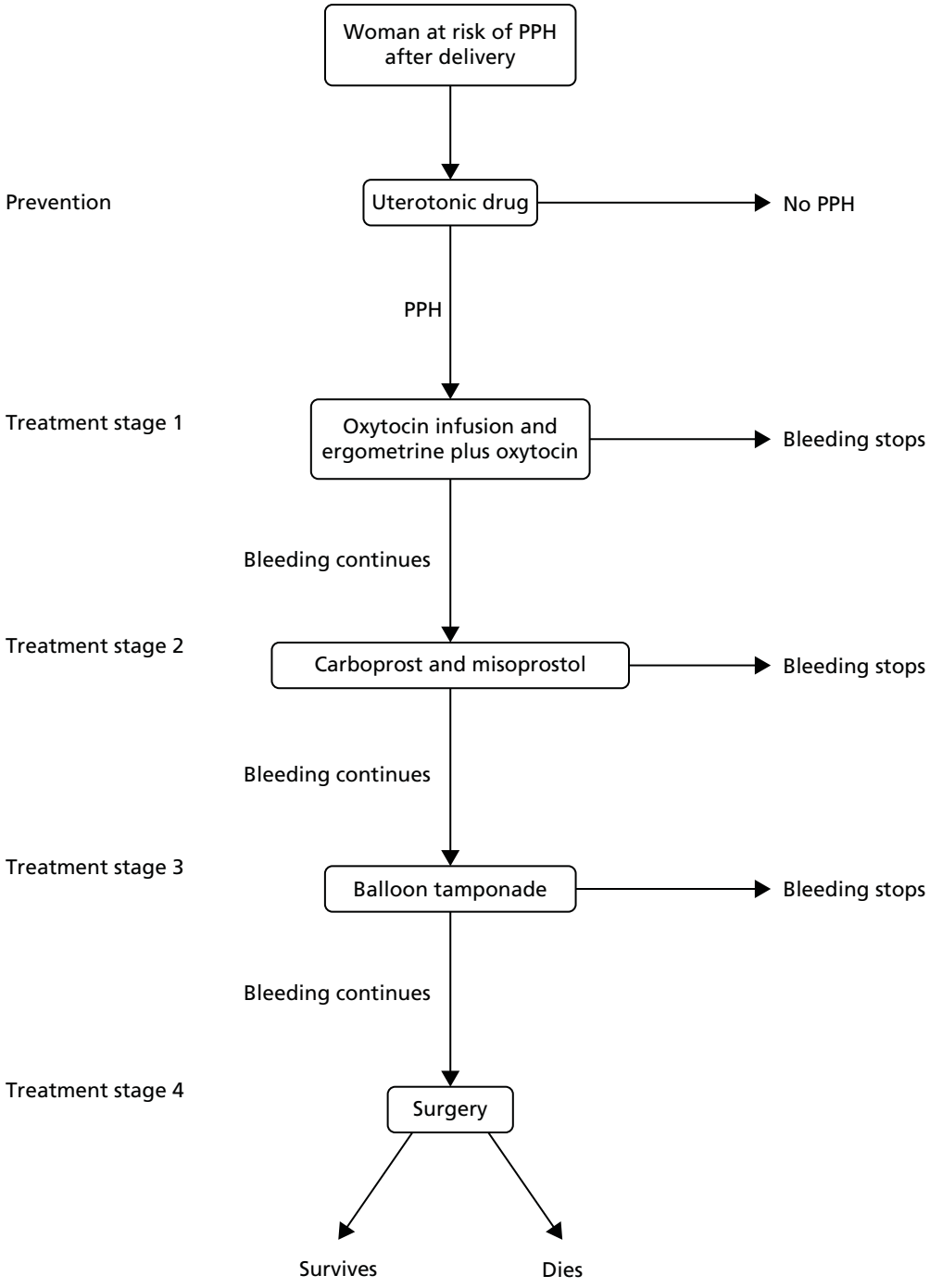

FIGURE 109 Summarised version of the clinical pathways in the model.

At the prevention stage (stage 0) of the model, women are given one of six active-prevention strategies:

- carbetocin
- ergometrine
- ergometrine plus oxytocin
- misoprostol plus oxytocin
- misoprostol
- oxytocin.

After a uterotonic drug has been administered as prevention for PPH, a woman may require treatment for PPH. The pathways are defined as the uterotonic drug that is given for prevention, acknowledging that after a uterotonic drug is given for prevention, treatment for PPH may be required. It is assumed that women receiving each strategy in the model have a possibility of either continuing to bleed (with a PPH blood loss of $\geq$ 500 ml) or experiencing no PPH. The pathways combine the probability of a woman following a particular path and the associated cost.

If, after the prevention stage, a woman continues to bleed, she is assumed to follow a consecutive series of four treatments in an attempt to stop the bleeding:

1. prevention stage
2. treatment stage 1 – if bleeding continues, the woman will be treated with a combination of two drugs: an oxytocin infusion and ergometrine plus oxytocin
3. treatment stage 2 – if bleeding continues, the woman will be treated with two alternative drugs: carboprost and misoprostol
4. treatment stage 3 – if bleeding continues, the woman will receive a non-invasive balloon (balloon tamponade)
5. treatment stage 4 – if bleeding continues, a surgical procedure, such as a hysterectomy, will be carried out on the woman.

In the model, the woman is then assumed to either survive or die.

Vaginal birth versus caesarean section

Expert opinion expressed that the third stage of labour can differ greatly depending on mode of birth. Therefore, vaginal birth and birth by caesarean section were analysed separately using different decision tree models. Both models follow the same structure. Women at high risk and low risk of PPH do not require a separate model analysis, as they would follow the same pathways depending on mode of birth.

In the base case, all births are assumed to take place in an obstetric unit, where appropriate treatment for PPH is readily available should the woman require it. This is true of 87% of births in the UK.[181] Vaginal birth in a community health-care setting, such as at home or in a midwife-led unit, is analysed in the scenario analysis.

Adverse events

It was assumed that after receiving a drug for either prevention or treatment of PPH, a woman has a chance of suffering an adverse event. Adverse events suffered in the model included:

- nausea
- vomiting
- hypertension
- headache
- tachycardia
- hypotension
- fever
- shivering
- abdominal pain.

Adverse events were not given separate branches in the model. The probability of a woman suffering adverse events and the associated costs were included as a weighted average after the woman has been given a drug or combination of drugs to prevent or treat PPH. The model runs for a short time period and is for the immediate postpartum period only.

Data

Effectiveness data

The effectiveness data required for the model were, as far as possible, based on the results of the trials sourced from the NMA. When necessary, data were supplemented by the literature. Owing to limited information on carboprost treatment, the effectiveness of balloon tamponades and surgical procedures reported by the NMA were based on literature estimates.

The absolute probabilities used in the model were defined as relative probabilities, relative to oxytocin. Oxytocin was deemed most suitable as the main comparator in the base case because it is the uterotonic agent currently recommended as prevention for PPH in the UK. The NMA revealed a large number of studies comparing oxytocin with an alternative strategy, so data around the oxytocin strategy were considered to be the most robust.

The main effectiveness data from the NMA were defined by blood loss of ≥ 500 ml and of ≥ 1000 ml. It was assumed that the preventing PPH blood loss of ≥ 500 ml was parallel to reaching the prevention stage of the model (stage 0) and not requiring any treatment. Preventing PPH blood loss of ≥ 1000 ml was assumed to mean that the woman had received treatment stage 1, but no further treatment was required.

No data were available in the NMA for PPH blood loss of ≥ 500 ml and of ≥ 1000 ml for the interventions ergometrine and ergometrine plus oxytocin, for caesarean section. In this case, the relative probabilities used for ergometrine and ergometrine plus oxytocin in vaginal birth were also used for caesarean section.

For the effectiveness of treatment stage 2 (carboprost and misoprostol), the effectiveness of carboprost was used, which was sourced from Butwick *et al.*,[182] who compared the risk of haemorrhage-related morbidity, for birth by caesarean section only, in those women exposed to methylergonovine versus carboprost. Given that this estimate is limited to only one study and, additionally, that it is only for birth by caesarean section, this probability was explored in the sensitivity analysis.

The effectiveness of a balloon tamponade was based on a literature estimate. Doumouchtsis *et al.*,[183] in a systematic review looking at studies that discuss the management of PPH, found nine studies evaluating the success rate of a balloon tamponade.

The effectiveness of a 'surgical procedure' was also based on a literature estimate for hysterectomy. Knight[184] performed a study across all UK hospitals with consultant-led maternity units looking at women undergoing peripartum hysterectomy. Different surgical procedures can be carried out to treat PPH [e.g. laparotomy, B-Lynch suturing technique (brace suture)], but as a hysterectomy is the procedure usually used as a life-saving measure for PPH, the source was considered appropriate.[184,185]

The probability of haemorrhage (i.e. of ≥ 500 ml and ≥ 1000 ml) and the effectiveness of treatment strategies are presented in *Table 2* (vaginal birth) and *Table 3* (caesarean section). The tables provide absolute probabilities with standard errors and 95% CIs. Where no standard errors for probabilities were provided in the literature estimates, they were calculated as one-tenth of one minus its value.[186]

The probability of experiencing an adverse event as a result of a uterotonic drug or combination of drugs is presented in *Appendix 9*. The absolute probabilities used for adverse events were defined via relative probabilities, relative to oxytocin. Owing to the lack of complete data in the NMA, the likelihood of experiencing some adverse events was not recorded for all prevention strategies. Several assumptions were made to complete the data set. Based on the evidence from the NMA, it is reasonable to assume that the adverse event profile of carbetocin and oxytocin is similar. Similarly, the adverse event profile of ergometrine plus oxytocin could be assumed to be identical to ergometrine, and the adverse event profile of misoprostol plus oxytocin to be identical to misoprostol. If data were missing for carbetocin but available for oxytocin, then the probability for the adverse event was based on oxytocin. This reasoning was applied to other

TABLE 2 Effectiveness data: vaginal birth (normal or assisted)

Item	Strategy	Probability of success[a]	Standard error[b]	95% CI (%)	Sources
Prevention	Oxytocin	0.908	0.009	0.891 to 0.925	NMA
Prevention	Carbetocin	0.944	0.288	0.883 to 0.974	NMA
Prevention	Ergometrine plus oxytocin	0.936	0.101	0.908 to 0.958	NMA
Prevention	Ergometrine	0.891	0.140	0.830 to 0.933	NMA
Prevention	Misoprostol plus oxytocin	0.931	0.144	0.892 to 0.958	NMA
Prevention	Misoprostol	0.899	0.078	0.861 to 0.929	NMA
Treatment stage 1	Oxytocin	0.977	0.003	0.971 to 0.997	NMA
Treatment stage 1	Carbetocin	0.988	0.756	0.932 to 0.244	NMA
Treatment stage 1	Ergometrine plus oxytocin	0.982	0.105	0.972 to 0.895	NMA
Treatment stage 1	Ergometrine	0.973	0.342	0.935 to 0.658	NMA
Treatment stage 1	Misoprostol plus oxytocin	0.981	0.176	0.966 to 0.824	NMA
Treatment stage 1	Misoprostol	0.970	0.060	0.958 to 0.940	NMA
Treatment stage 2	Carboprost	0.840	0.016	0.755 to 0.887	Butwick *et al.*[62]
Treatment stage 3	Balloon tamponade	0.840	0.016	0.775 to 0.888	Doumouchtsis *et al.*[183]
Treatment stage 4	Surgery	0.994	0.0006	0.85 to 1.00	Knight[184]

a Probabilities of success are absolute probabilities converted from relative probabilities from the NMA, relative to the oxytocin arm.
b Standard errors shown are the standard errors for their respective relative probabilities.

TABLE 3 Effectiveness data: caesarean section (planned or emergency)

Item	Strategy	Probability of success[a]	Standard error[b]	95% CI (%)	Sources
Prevention	Oxytocin	0.401	0.074	0.256 to 0.547	NMA
Prevention	Carbetocin	0.534	0.197	0.147 to 0.761	NMA
Prevention	Ergometrine plus oxytocin	0.586	0.101	0.372 to 0.743	NMA
Prevention	Ergometrine	0.291	0.140	–0.160 to 0.593	NMA
Prevention	Misoprostol plus oxytocin	0.567	0.139	0.293 to 0.751	NMA
Prevention	Misoprostol	0.382	0.122	0.024 to 0.632	NMA
Treatment stage 1	Oxytocin	0.895	0.019	0.858 to 0.932	NMA
Treatment stage 1	Carbetocin	0.923	0.334	0.799 to 0.974	NMA
Treatment stage 1	Ergometrine plus oxytocin	0.082	0.105	0.864 to 0.956	NMA
Treatment stage 1	Ergometrine	0.121	0.342	0.681 to 0.960	NMA
Treatment stage 1	Misoprostol plus oxytocin	0.897	0.149	0.814 to 0.950	NMA
Treatment stage 1	Misoprostol	0.920	0.234	0.830 to 0.967	NMA
Treatment stage 2	Carboprost	0.840	0.084	0.755 to 0.887	Butwick *et al.*[62]
Treatment stage 3	Balloon tamponade	0.840	0.084	0.775 to 0.888	Doumouchtsis *et al.*[183]
Treatment stage 4	Surgery	0.994	0.099	0.85 to 1.00	Knight[184]

a Probabilities of success are absolute probabilities converted from relative probabilities from the NMA, relative to the oxytocin arm.
b Standard errors shown are the standard errors for their respective relative probabilities.

similar uterotonic drugs. If data were missing for both uterotonic drugs with the same adverse events profile (e.g. data were missing for both carbetocin and oxytocin), then an average of the probabilities available for that side effect was used. Ergometrine is commonly known to be associated with a high level of all side effects, with the exceptions of fever and shivering, so uterotonic drugs containing ergometrine were removed from the averaging process, apart from when considering fever and shivering. Misoprostol is commonly known to be associated with fever and shivering, so uterotonic drugs containing misoprostol were removed from the averaging process for these adverse events.

Resource use and costs

Owing to the large variety of countries included in the NMA, there was no clear justification for any particular choice of country on which to base costs for the whole analysis apart from the UK, where the current study is hosted and funded by the UK research money. All costs sourced are reported in 2016 UK prices, having been appropriately inflated if necessary. Key costs are presented in *Table 4*.

NHS reference costs include information on birth costs. The average birth cost was calculated separately for a vaginal birth in an inpatient setting, a vaginal birth in a community health-care setting and for a caesarean section. A full breakdown of how birth costs were calculated is supplied in *Appendices 11–13*.

Standard-practice dosage and route of administration were identified for each uterotonic drug, via the study team. The costs attached to each uterotonic drug were sourced from the *British National Formulary*[189] and *NHS Electronic Drug Tariff*.[190]

In line with UK practice, it was assumed that women reaching treatment stage 3 (i.e. balloon tamponade) of the model would require admission to theatre. The cost for the balloon tamponade procedure was assumed to be equivalent to the NHS reference costs for a minor upper genital tract procedure at £1280.42.[187]

Being consistent with the effectiveness data for surgery, costs applied to a surgical procedure were based on the cost of a hysterectomy. The cost of this is assumed to be equivalent to the NHS reference cost for a major open upper genital tract procedure with a comorbidities and complications score of 0–5, in an inpatient setting that is £3780.40.[187,192] It was acknowledged that a surgical procedure carried out to treat PPH is performed when the woman is in a life-threatening condition, so there will probably be more serious complications, hence the allowance for a higher comorbidities and complications score (0–5). It was also acknowledged that the cost for a peripartum hysterectomy may be in excess of the assumed standard hysterectomy costs for reasons such as more senior surgeons being required to carry out the procedure. This was tested in the sensitivity analysis to allow for these potential extra costs.

It was assumed that a woman requiring treatment at stage 4 (surgery, having already had a failed attempt at balloon tamponade) will remain in theatre throughout stages 3 and 4. In order to avoid duplication of some costs by summing these procedures, it was assumed that women who ultimately required the more serious intervention of hysterectomy additionally incurred half of the cost for a balloon tamponade. This assumption was explored in the sensitivity analysis.

The assumed lengths of hospital stay were based on blood loss and are based on real data collected for 2000 patients from the Birmingham Women's Hospital over a 3-month period (March–May 2016) (see *Appendix 14*). The data were retrieved through K2 Medical Systems™: Athena™ Maternity Information System (Plymouth, UK). The length of hospital stay data for women reaching treatment stage 4 were unable to be sourced from the Birmingham Women's Hospital because of a lack of patient numbers. Data on length of hospital stay for this stage of the model were based on literature estimates. Women surviving surgery were assumed to stay in hospital for 6 days following both a vaginal birth or a caesarean section.[193]

TABLE 4 Table of costs

Item	Drug/treatment	Unit cost (£)	Other information	Sources
Birth costs	Birth costs associated with vaginal birth	1826.04	Per birth. See *Appendix 10* for a breakdown of the calculation	*NHS Reference Costs 2014–15*[187]
Birth costs	Birth costs associated with birth by caesarean section	3801.70	Per birth. See *Appendix 10* for a breakdown of the calculation	*NHS Reference Costs 2014–15*[187]
Birth costs	Birth costs in a community health-care setting	1282.93	Per birth. See *Appendix 11* for a breakdown of the calculation	*NHS Reference Costs 2013–14*[188]
Uterotonic drug	Oxytocin	0.91	Per 10 IU, intramuscularly	*British National Formulary*[189]
Uterotonic drug	Misoprostol	0.17	Per 200-mcg tablet	*NHS Electronic Drug Tariff*[190]
Uterotonic drug	Ergometrine	1.50	Per 500 mcg, intramuscularly	*British National Formulary*[189]
Uterotonic drug	Ergometrine plus oxytocin	1.57	Per 500 mcg (ergometrine) plus 5 IU, intramuscularly (oxytocin)	*British National Formulary*[189]
Uterotonic drug	Misoprostol plus oxytocin	1.08	Per person (cost of misoprostol plus cost of oxytocin)	*British National Formulary*[189]
Uterotonic drug	Carbetocin	17.64	Per 100 mcg, intramuscular	*British National Formulary*[189]
Treatment for PPH	Oxytocin infusion	0.91	Per 10 IU, infusion	*British National Formulary*[189]
Treatment for PPH	Carboprost	18.2	Per 250 mcg, intramuscular	*British National Formulary*[189]
Treatment for PPH	Balloon tamponade	1280.42	Per procedure	*NHS Reference Costs 2014–15*[187]

continued

TABLE 4 Table of costs (*continued*)

Item	Drug/treatment	Unit cost (£)	Other information	Sources
Treatment for PPH	Postpartum surgery	3780.40	Per procedure	*NHS Reference Costs 2014–15*[187]
Treatment for PPH	Blood transfusion	171.84–163.63	Per unit. £171.84 (first unit), £163.63 (subsequent units)	*Putting NICE Guidance into Practice: Costing Statement Blood Transfusion. Implementing the NICE Guideline on Blood Transfusion*[191]
Hospital stay	Excess bed-days (vaginal birth)	440.49	Per excess day in hospital. The figure is a weighted average of all excess bed-day costs for a vaginal birth (normal or assisted) within an inpatient setting (see *Appendix 12*)	*NHS Reference Costs 2014–15*[187]
Hospital stay	Excess bed-days (caesarean section)	444.39	Per excess day in hospital. The figure is a weighted average of all excess bed-day costs for birth by caesarean section within an inpatient setting (see *Appendix 13*)	*NHS Reference Costs 2014–15*[187]
Transport	Ambulance call out and transfer to hospital	239.99	Per person. Cost includes the cost to see, treat and transfer patient to hospital	*NHS Reference Costs 2014–15*[187]

The associated costs attached to an extra day in hospital were calculated using a weighted average of all excess bed-day costs, identified in the *NHS Reference Costs 2014–15*.[187] The weighted average daily cost of hospitalisation associated with birth is £440.49 (vaginal) and £444.39 (caesarean section). A full breakdown of how excess bed-day costs were calculated is presented in *Appendices 15* and *16*.

Treatment for adverse events in their worst case, and their associated costs are presented in *Appendix 17*. Adverse events were assumed to be treated with drugs, intravenous fluids and monitoring in hospital overnight. Worst-case treatment of adverse events was sourced via expert opinion, which consisted of a team of five obstetricians. The obstetricians were part of the research team. It was acknowledged that the severity of adverse events can differ greatly from person to person. In mild cases, adverse events would not be treated with any drug or intervention, and so the costs attached would be zero. The costs assigned to adverse events were explored in the sensitivity analysis. Other resource use includes costs associated with blood transfusion. Costs associated with blood transfusion were sourced from NICE. Two units of blood were assumed to be given to women reaching treatment stage 3 and an additional two units of blood were assumed to be given to women reaching treatment stage 4 of the model.

Subgroup analysis compares an inpatient setting and community health-care setting for birth. Transportation costs were sourced for those needing to be transferred to hospital. It was assumed that women requiring treatment (PPH blood loss of $\geq$ 500 ml) would be required to be transferred to hospital.

Assumptions

Several assumptions were required in order to develop a workable model. These are summarised and described below and divided into three categories: birth, model pathways and model inputs.

Birth

Women are assumed to enter the model when approaching the third stage of labour.

In the principal analyses, all births are assumed to take place in an obstetric unit, where appropriate treatment for PPH is readily available should the woman require it. This is true of 87% of births in the UK.[181]

Women giving birth in a community health-care setting, such as at home or in a midwife-led unit, are assumed to only give birth via vaginal birth and not caesarean section. All deliveries by caesarean section are assumed to take place in hospital.

Birth costs are calculated for all levels of comorbidities and complications. It is assumed, therefore, that the costs for any other complications other than PPH are included in the birth costs.

Model pathways

It is assumed that no routine drug for PPH has been administered to women prior to them entering the model.

All prevention strategies follow the same stages of treatment, apart from where misoprostol has been given for prevention of PPH. In this case the same drug may not be repeated for treatment and the patient will forgo this stage of treatment, that is, misoprostol is not to be replaced by another drug or form of treatment.

After ‘no PPH’, ‘bleeding stops’ and ‘survive’ pathways, women are assumed to return to full health.

It is assumed that women who reached PPH blood loss of $\geq$ 500 ml would have completed the first stage of treatment, women reaching PPH blood loss of $\geq$ 1000 ml have completed the second stage of treatment, and women reaching PPH blood loss of $\geq$ 1500 ml have completed the third stage of treatment.

It is assumed that a probability of death can only occur after treatment stage 4.

Model inputs

The relative probability used for the probability of PPH blood loss of ≥ 500 ml from using ergometrine in vaginal birth was assumed to be equal to the relative probability used for the probability of PPH blood loss of ≥ 500 ml when using ergometrine in birth by caesarean section. Similarly, the relative probability used for the probability of PPH blood loss of ≥ 1000 ml when using ergometrine in vaginal birth was assumed to be equal to the relative probability used for the probability of PPH blood loss of ≥ 1000 ml when using ergometrine in birth by caesarean section.

The relative probability used for the probability of PPH blood loss of ≥ 500 ml from using ergometrine plus oxytocin in vaginal birth was assumed to be equal to the relative probability used for the probability of PPH blood loss of ≥ 500 ml when using ergometrine plus oxytocin in birth by caesarean section. Similarly, the relative probability used for the probability of PPH blood loss of ≥ 1000 ml when using ergometrine plus oxytocin in vaginal birth was assumed to be equal to the relative probability used for the probability of PPH blood loss of ≥ 1000 ml when using ergometrine plus oxytocin in birth by caesarean section.

Effectiveness of carboprost, balloon tamponade and surgery were assumed to be standard across modes of birth.

Costs for uterotonic drugs were assumed to be standard across the model. That is, drug costs are assumed to carry the same cost, regardless of whether they are given for prevention or treatment.

Costs for administration of treatment, that is, staff time, were assumed to be included in birth costs and excess bed-day costs. Therefore, no extra staff costs were attached to treatment costs of PPH.

Nausea, vomiting, hypertension, headache, tachycardia, hypotension, fever, shivering and abdominal pain were assumed to be the only adverse events that can occur as a side effect of taking a uterotonic drug.

The effectiveness of treatments used for adverse events was assumed to be 100% successful.

The cost of treatment for adverse events, as a weighted average, was attached to every outcome of the model, except death.

An outcome of death assumed no excess bed-day costs.

Analysis

Various alternative analyses were carried out. Because of the multiple missing data for adverse events, analyses were carried out including and excluding adverse events. Additionally, because of the lack of data for ergometrine and ergometrine plus oxytocin PPH blood loss of ≥ 500 ml and PPH blood loss of ≥ 1000 ml for caesarean section, analysis was carried out including and excluding these uterotonic drugs. Each analysis was carried out for three outcome measures:

1. cost per case of PPH blood loss of ≥ 500 ml avoided
2. cost per case of PPH blood loss of ≥ 1000 ml avoided
3. cost per major outcome averted, in which a major outcome refers to treatment stage 4 of the model (surgery).

Principal analyses

- Analysis 1. A deterministic analysis analysing the relative cost-effectiveness of a range of uterotonic drugs for the prevention of PPH for vaginal birth. The results are presented in terms of the ICER, namely the additional cost per case of PPH blood loss of ≥ 500ml avoided. In this analysis, no adverse events are included in the model.
- Analysis 2. A deterministic analysis similar to analysis 1, but adverse events are included in this analysis.
- Analysis 3. A deterministic analysis similar to analysis 1, but birth is by caesarean section. Ergometrine plus oxytocin and ergometrine are excluded from this analysis because of a lack of any data on these interventions related to caesarean sections.
- Analysis 4. A deterministic analysis for caesarean section (similar to analysis 3), but adverse events are included in this analysis. Ergometrine and ergometrine plus oxytocin are excluded from this analysis.
- Analysis 5. A deterministic analysis for caesarean section including ergometrine plus oxytocin and ergometrine in the analysis. Adverse events are excluded from this analysis. There were no data available in the NMA for the probability of PPH blood loss of ≥ 500 ml and PPH blood loss of ≥ 1000 ml when using ergometrine or ergometrine plus oxytocin as prevention for PPH in the case of birth by caesarean section. Probabilities for PPH blood loss of ≥ 500 ml and ≥ 1000 ml when using ergometrine or ergometrine plus oxytocin for prevention were included in this analysis by making the following assumptions:

    - The relative probability used for the probability of PPH blood loss of ≥ 500 ml from using ergometrine in vaginal birth was assumed to be equal to the relative probability used for the probability of PPH blood loss of ≥ 500 ml when using ergometrine in birth by caesarean section. Similarly, the relative probability used for the probability of PPH blood loss of ≥ 1000 ml when using ergometrine in vaginal birth was assumed to be equal to the relative probability used for the probability of PPH blood loss of ≥ 1000 ml when using ergometrine in birth by caesarean section.
    - The relative probability used for the probability of PPH blood loss of ≥ 500 ml from using ergometrine plus oxytocin in vaginal birth was assumed to be equal to the relative probability used for the probability of PPH blood loss of ≥ 500 ml when using ergometrine plus oxytocin in birth by caesarean section. Similarly, the relative probability used for the probability of PPH blood loss of ≥ 1000 ml when using ergometrine plus oxytocin in vaginal birth was assumed to be equal to the relative probability used for the probability of PPH blood loss of ≥ 1000 ml when using ergometrine plus oxytocin in birth by caesarean section.

- Analysis 6. A deterministic analysis similar to analysis 5, but adverse events are included in this analysis.

Scenario analysis

In addition to the six principal analyses, scenario analyses were carried out to explore the results of the cost-effectiveness of the uterotonic drugs in a different setting, namely a community health-care setting. All scenario analyses were for vaginal birth only.

- Scenario analysis. A deterministic analysis, similar to analysis 2, but for birth in a community health-care setting. Birth costs for a community health-care setting are included, as well as transport costs to transfer the woman to hospital in the event of PPH blood loss of ≥ 500 ml. The probability of PPH blood loss of ≥ 1000 ml was also doubled to account for the potential delay in the woman receiving these drugs, because she is being transferred to hospital.

Sensitivity analyses

Deterministic and probabilistic sensitivity analyses (PSAs) were carried out to explore the uncertainty of the model input data. In deterministic analysis, there is no randomness and individual parameters are explored using their specified point value. In PSA, distributions are assigned to uncertain model parameters, and by drawing randomly from these distributions, a large number (i.e. 10,000) of mean cost and effectiveness

estimates are generated. These estimates are used jointly, to form an empirical distribution of the differences in cost and effectiveness of the interventions.

Probabilistic sensitivity analyses

Sensitivity analysis 1
A PSA of analyses 2 and 6.

One-way sensitivity analyses
Deterministic one-way sensitivity analyses were carried out to further explore the robustness of costs of surgery (treatment stage 4) and the effectiveness of carboprost (treatment stage 3).

Sensitivity analysis 2
Similar to analyses 2 and 6, but increasing the cost of treatment stage 4 to allow the full cost of the balloon tamponade on top of surgery.

Sensitivity analysis 3
Similar to analyses 2 and 6, but decreasing the cost of treatment stage 4 to discount the cost of the balloon tamponade completely.

Sensitivity analysis 4
Similar to analyses 2 and 6, but increasing the cost of a hysterectomy by 50% to allow for an increase in costs caused by complications or extra/more senior staff being required to be present for the procedure.

Sensitivity analysis 5
Similar to analyses 2 and 6, but changing the effectiveness of carboprost (treatment stage 3). The range of probabilities explored was from 0 to 1 in 10 intervals.

Results

In the majority of cases effectiveness results are given to three decimal places. When rounding resulted in identical effectiveness ratios, effectiveness ratios are given to six decimal places. The results of the analyses are presented in *Table 5*.

Analysis 1: vaginal birth with no adverse events
Table 5 shows that ergometrine plus oxytocin is the least costly prevention strategy, with an average cost of £2537.67 per woman. The strategy in which carbetocin is given as the uterotonic drug for prevention, is the most effective strategy, and ergometrine plus oxytocin is the second most effective strategy. All other prevention strategies are dominated by ergometrine plus oxytocin, as they are both more costly and less effective than ergometrine plus oxytocin. However, carbetocin is more effective than ergometrine plus oxytocin. Therefore, compared with ergometrine plus oxytocin, carbetocin is both more costly but more effective. The estimated ICER for prevention with carbetocin compared with ergometrine plus oxytocin is £1888.75 per case of PPH blood loss of $\geq$ 500 ml avoided. This means that every additional case of PPH blood loss of $\geq$ 500 ml avoided by using carbetocin over oxytocin costs an extra £1888.75 (see *Table 5*).

Similarly, an outcome measure of PPH blood loss of $\geq$ 1000 ml avoided results in an ICER of £30,012.87 per case of PPH blood loss of $\geq$ 1000 ml avoided for prevention with carbetocin compared with ergometrine plus oxytocin (see *Table 5*).

An outcome measure of major outcome averted results in an ICER for prevention with carbetocin compared with ergometrine plus oxytocin is £1,172,377.79 per major outcome averted (see *Table 5*).

TABLE 5 Summary of results

Analysis	Cost (£) per average woman	PPH				Major outcome averted	
		≥ 500ml avoided		≥ 1000ml avoided			
		Effectiveness	ICER[a] (£)	Effectiveness	ICER[a] (£)	Effectiveness	ICER[a] (£)
1: vaginal birth with no adverse events							
Ergometrine plus oxytocin	2537.67	0.936	–	0.998843	–	0.999970	–
Carbetocin	2551.43	0.944	1888.75	0.999301	30,012.87	0.999982	1,172,377.79
Misoprostol plus oxytocin	2538.78	0.931	Dominated	0.998843	Dominated	0.999966	Dominated
Oxytocin	2545.02	0.908	Dominated	0.998668	Dominated	0.999946	Dominated
Misoprostol	2547.85	0.899	Dominated	0.997859	Dominated	0.999924	Dominated
Ergometrine	2551.32	0.891	Dominated	0.996982	Dominated	0.999926	Dominated
2: vaginal birth with adverse events							
Oxytocin	2617.78	0.908	–	0.997859	–	0.999945	–
Carbetocin	2650.79	0.944	927.65	0.999301	22,899.57	0.999982	894,514.46
Ergometrine plus oxytocin	2662.87	0.936	Dominated	0.998843	Dominated	0.999970	Dominated
Ergometrine	2752.04	0.891	Dominated	0.997082	Dominated	0.999925	Dominated
Misoprostol plus oxytocin	2762.39	0.931	Dominated	0.998668	Dominated	0.999966	Dominated
Misoprostol	2771.66	0.899	Dominated	0.996982	Dominated	0.999923	Dominated
3: caesarean section excluding ergometrine and ergometrine plus oxytocin, and with no adverse events							
Misoprostol plus oxytocin	5170.13	0.567	–	0.955	–	0.998858	–
Carbetocin	5189.25	0.534	Dominated	0.964	2251.77	0.999076	87,959.83
Misoprostol	5213.50	0.382	Dominated	0.951	Dominated	0.998737	Dominated
Oxytocin	5217.92	0.401	Dominated	0.937	Dominated	0.998387	Dominated
4: caesarean section excluding ergometrine and ergometrine plus oxytocin, and with adverse events							
Carbetocin	5469.57	0.534	–	0.964	–	0.999076	–
Misoprostol plus oxytocin	5552.12	0.567	2480.19	0.955	Dominated	0.998858	Dominated
Oxytocin	5474.38	0.401	Dominated	0.937	Dominated	0.998387	Dominated
Misoprostol	5519.16	0.382	Dominated	0.951	Dominated	0.998737	Dominated
5: caesarean section including ergometrine and ergometrine plus oxytocin, and with no adverse events							
Ergometrine plus oxytocin	5160.36	0.586	–	0.966	–	0.999128	–
Misoprostol plus oxytocin	5170.13	0.567	Dominated	0.955	Dominated	0.998858	Dominated
Carbetocin	5189.25	0.534	Dominated	0.964	Dominated	0.999076	Dominated
Misoprostol	5213.50	0.382	Dominated	0.951	Dominated	0.998737	Dominated
Oxytocin	5217.92	0.401	Dominated	0.937	Dominated	0.998387	Dominated
Ergometrine	5256.46	0.291	Dominated	0.914	Dominated	0.997802	Dominated

continued

TABLE 5 Summary of results (*continued*)

Analysis	Cost (£) per average woman	PPH					
		≥ 500ml avoided		≥ 1000ml avoided		Major outcome averted	
		Effectiveness	ICER[a] (£)	Effectiveness	ICER[a] (£)	Effectiveness	ICER[a] (£)
6: caesarean section including ergometrine and ergometrine plus oxytocin, and with adverse events							
Ergometrine plus oxytocin	5452.77	0.586	–	0.966	–	0.999128	–
Carbetocin	5469.57	0.534	Dominated	0.964	Dominated	0.999076	Dominated
Oxytocin	5474.38	0.401	Dominated	0.937	Dominated	0.998387	Dominated
Misoprostol	5519.16	0.382	Dominated	0.951	Dominated	0.998737	Dominated
Ergometrine	5548.87	0.291	Dominated	0.914	Dominated	0.997802	Dominated
Misoprostol plus oxytocin	5552.12	0.567	Dominated	0.955	Dominated	0.998858	Dominated

a The ICER was expressed as the additional cost per additional case of PPH (blood loss of ≥ 500ml) avoided.
Notes
All calculations are rounded. Simple arithmetic based on the numbers presented will not give the same answer.

Analysis 2: vaginal birth with adverse events

Table 5 shows that oxytocin is the least costly prevention strategy, with an average cost of £2617.78 per woman. Carbetocin is the most effective strategy, and oxytocin is the fourth most effective strategy. All other prevention strategies are dominated by carbetocin, as they are both more costly and less effective than carbetocin. However, oxytocin is less costly than carbetocin. Therefore, compared with oxytocin, carbetocin is both more costly but more effective. The estimated ICER for prevention with carbetocin compared with oxytocin is £927.65 per case of PPH blood loss of ≥ 500 ml avoided. This means that every additional case of PPH blood loss of ≥ 500 ml avoided by using carbetocin over oxytocin costs an extra £927.65.

Analysis 3: birth by caesarean section excluding ergometrine and ergometrine plus oxytocin, and with no adverse events

Table 5 shows that the strategy of misoprostol plus oxytocin dominates all other strategies. The strategy of misoprostol plus oxytocin is both less costly and more effective than all other strategies.

For an outcome measure of PPH blood loss of ≥ 1000 ml avoided, oxytocin is the least costly prevention strategy, with an average cost of £5170.13 per woman. Carbetocin is shown to be the most effective strategy and misoprostol plus oxytocin is shown to be the second most effective strategy. All other strategies are dominated by misoprostol plus oxytocin, as they are both more costly and less effective than misoprostol plus oxytocin. Therefore, compared with misoprostol plus oxytocin, carbetocin is both more costly and more effective. The estimated ICER for prevention with carbetocin compared with misoprostol plus oxytocin is £2251.77 per case of PPH blood loss of ≥ 1000 ml avoided. This means that every additional case of PPH blood loss of ≥ 1000 ml avoided by using carbetocin over oxytocin costs an extra £2251.77.

Similarly, an outcome measure of major outcome averted results in an ICER for prevention with carbetocin compared with misoprostol plus oxytocin is £87,959.83 per major outcome averted.

Analysis 4: birth by caesarean section excluding ergometrine and ergometrine plus oxytocin, and with adverse events

Table 5 shows that carbetocin is the least costly prevention strategy, with an average cost of £5469.57 per woman. Misoprostol plus oxytocin is the most effective strategy, and carbetocin is the second-most effective strategy. All other prevention strategies are dominated by carbetocin, as they are both more costly and less effective than carbetocin. However, misoprostol plus oxytocin is more effective than carbetocin. Therefore, compared with carbetocin, misoprostol plus oxytocin is both more costly and more effective. The estimated ICER for prevention with misoprostol plus oxytocin compared with carbetocin is £2480.19 per case of PPH blood loss of ≥ 500 ml avoided. This means that every additional case of PPH blood loss of ≥ 500 ml avoided by using misoprostol plus oxytocin over carbetocin costs an extra £2480.19.

The results in *Table 5* show that the strategy of carbetocin dominates all other strategies. The strategy of carbetocin is both less costly and more effective than all other strategies.

Analysis 5: birth by caesarean section including ergometrine and ergometrine plus oxytocin, and with no adverse events

The results in *Table 5* show that the strategy of ergometrine plus oxytocin dominates all other strategies. The strategy of ergometrine plus oxytocin is both less costly and more effective than all other strategies.

Analysis 6: birth by caesarean section including ergometrine and ergometrine plus oxytocin, and with adverse events

Table 5 shows that the strategy of ergometrine plus oxytocin dominates all other strategies. The strategy of ergometrine plus oxytocin is both less costly and more effective than all other strategies.

Scenario analyses: vaginal birth in a community health-care setting

The results in the table show that the addition of transport costs and doubling the probability of PPH blood loss of ≥ 1000 ml (treatment stage 1) to account for a delay in effectiveness do not change the decisions from analysis 2. Full results are presented in *Appendix 18*.

Sensitivity analysis 1: probabilistic sensitivity analysis

(a) Vaginal birth

The results of the PSA for analysis 2 show moderate uncertainty in the results.

The cost-effectiveness acceptability curve (CEAC) is presented in *Figure 110*. The CEAC shows the probability that each intervention is cost-effective, compared with the alternative, for a range of values of the maximum acceptable ceiling ratio.[194]

Figure 110 shows the CEAC for the leading strategies, carbetocin and oxytocin. For a maximum willingness-to-pay (WTP) threshold of £863 per PPH blood loss of ≥ 500 ml avoided, oxytocin is considered the optimal strategy. Given a maximum WTP threshold of £864 per PPH blood loss of ≥ 500 ml avoided, there is an equal probability that carbetocin and oxytocin are cost-effective compared with the other strategy. At a WTP threshold of £865 per PPH blood loss of ≥ 500 ml avoided, carbetocin is the optimal strategy. As the WTP per PPH blood loss of ≥ 500 ml avoided tends to infinity, the probability that carbetocin is cost-effective compared with oxytocin tends to 95%. The difference in probabilities over WTP thresholds reflects uncertainty in the model.

(b) Caesarean section

Figure 111 shows the CEAC for the dominant strategy, ergometrine plus oxytocin, and UK current practice, oxytocin. The CEAC shows that at any WTP threshold greater than zero, ergometrine plus oxytocin is shown to be the optimal strategy compared with oxytocin. As the WTP per PPH blood loss of ≥ 500ml avoided tends to infinity, the probability that ergometrine plus oxytocin is cost-effective compared with oxytocin tends to 99%.

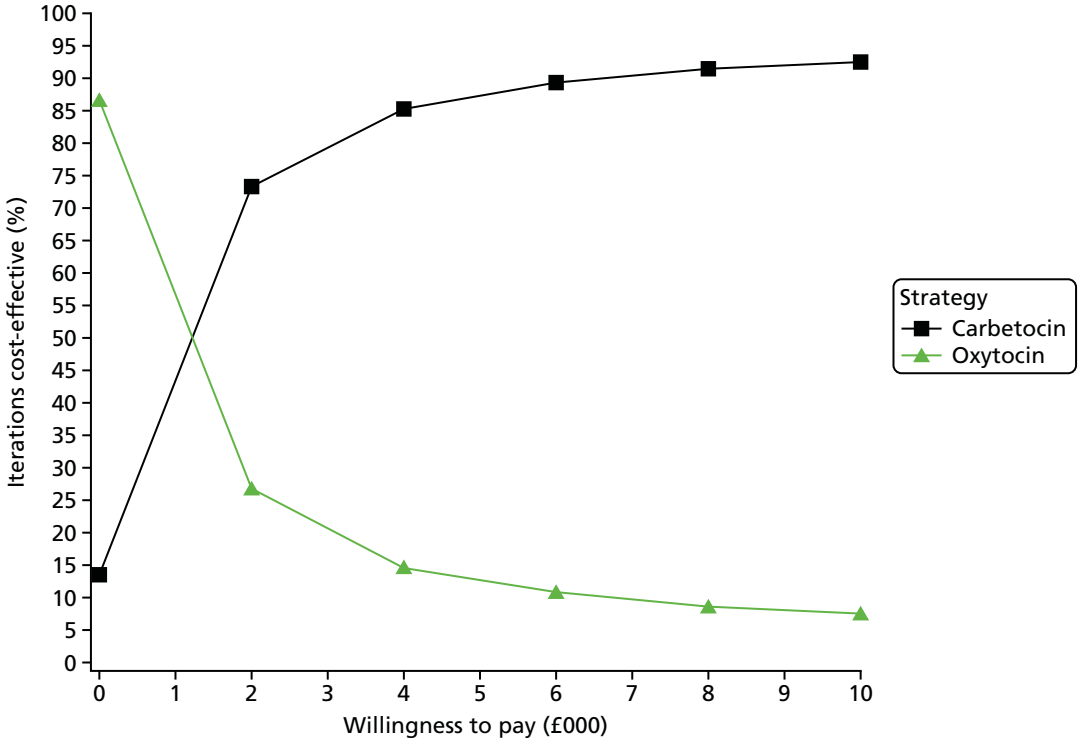

FIGURE 110 Cost-effectiveness acceptability curve between prevention strategies oxytocin and carbetocin, for vaginal birth, using distributions around the accuracy data.

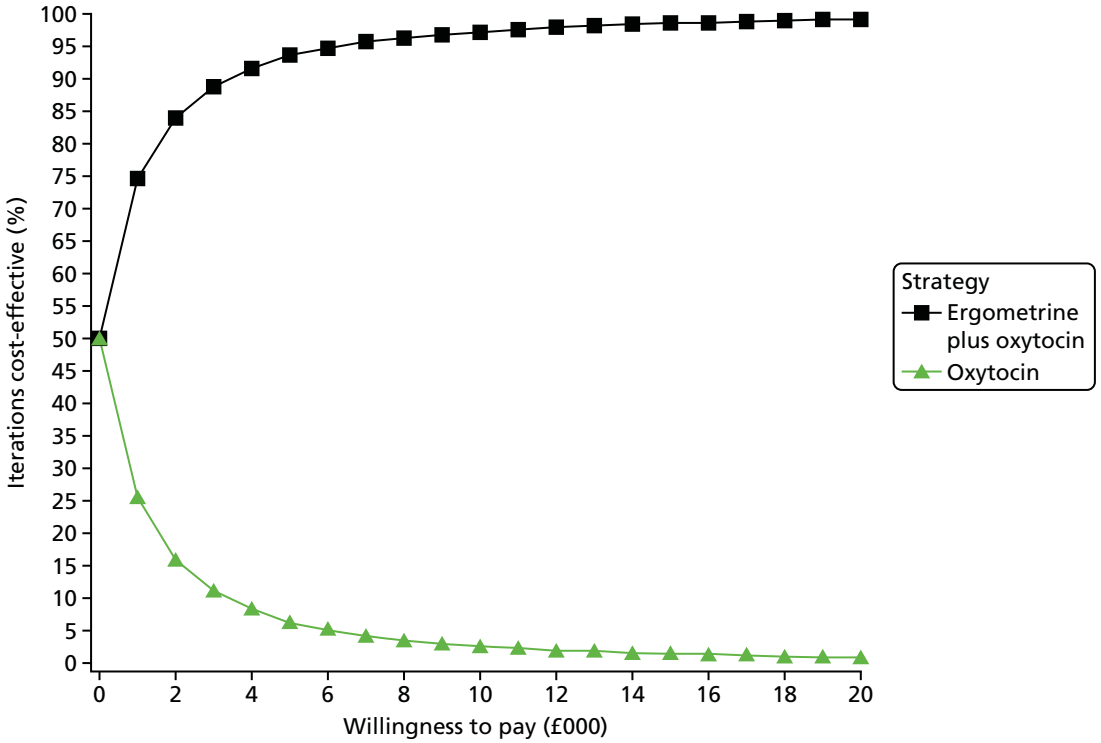

FIGURE 111 Cost-effectiveness acceptability curve between prevention strategies ergometrine plus oxytocin, and oxytocin, for caesarean section birth, using distributions around the accuracy data.

Figure 112 shows the CEAC for the dominant strategy ergometrine plus oxytocin, and second-place prevention strategy, carbetocin. The CEAC shows that at any WTP threshold below £1105 per PPH blood loss of ≥ 500 ml avoided, carbetocin is the optimal strategy compared with oxytocin. Given a maximum WTP threshold of £1106 per PPH blood loss of ≥ 500 ml avoided, there is an equal probability that ergometrine and carbetocin are cost-effective compared with the other strategy. At a WTP threshold of £1107 per PPH blood loss of ≥ 500 ml avoided, ergometrine plus oxytocin is the optimal strategy. As the WTP per PPH blood loss of ≥ 500 ml avoided tends to infinity, the probability that ergometrine plus oxytocin is the optimal strategy compared with carbetocin tends to 70%.

Sensitivity analyses 2–4: changing the cost of treatment stage 4 (surgery)

Allowing for an increase or decrease in treatment stage 4 made no substantial difference to the results. Full results are presented in *Appendix 18*.

Sensitivity analysis 5: changing the effectiveness of treatment stage 3 (carboprost)

Allowing for a change in the effectiveness of treatment stage 3 made no substantial difference to the results. Full results are presented in *Appendix 18*.

Discussion

Principal findings and interpretation of the results

(a) Vaginal birth

Analysis 1: vaginal birth with no adverse events

The results of the full range of model-based analyses on the range of different outcomes show that for vaginal birth, all but one of the prevention strategies are dominated by ergometrine plus oxytocin, as they are all more costly and less effective than ergometrine plus oxytocin. The only exception is prevention with

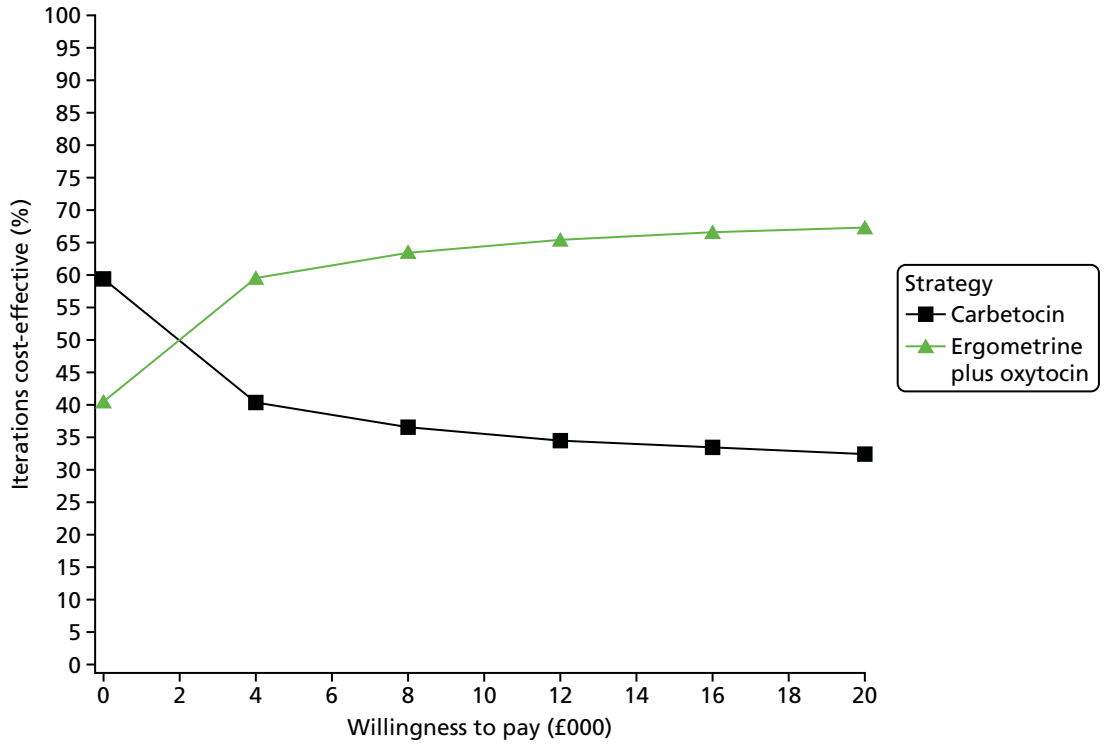

FIGURE 112 Cost-effectiveness acceptability curve between prevention strategies carbetocin and ergometrine plus oxytocin, for caesarean section birth, using distributions around the accuracy data.

carbetocin. Carbetocin is the most effective strategy, but it is also the most costly. Carbetocin is both more costly and more effective than prevention with ergometrine plus oxytocin in the prevention of PPH for the three main outcomes of PPH blood loss of ≥ 500 ml, PPH blood loss of ≥ 1000 ml and avoiding a major outcome (surgery).

Analysis 2: vaginal birth with adverse events

When including adverse events into the model for vaginal birth, the results show that all but one of the prevention strategies are dominated by carbetocin, as the prevention strategies are all more costly and less effective than carbetocin. The only exception is prevention with the UK's current practice drug, oxytocin. Oxytocin is the least costly strategy, but it is ranked fourth in terms of effectiveness. Carbetocin is both more costly and more effective than prevention with oxytocin in the prevention of PPH for the three main outcomes of PPH blood loss of ≥ 500 ml, PPH blood loss of ≥ 1000 ml and avoiding a major outcome (surgery). These results are also valid in women giving birth in a community health-care setting.

Information or data on the impact of the outcome on quality of life were not available in this analysis. Therefore, presenting results in terms of outcomes in natural units, such as extent of haemorrhage avoided, is necessary but such results are difficult to interpret for the purpose of determining the most cost-effective uterotonic drug. To inform considerations about the relative cost-effectiveness of the different interventions, the resulting ICERs can be considered in the light of the accepted thresholds used by NICE even though such thresholds are presented in QALYs.[195] For example, to convert the ICER for analysis 2(a) of £927.65 into cost per QALY, the ICER is divided by the upper limit of NICE's cost-effectiveness threshold (£30,000 per QALY). This gives a quality-of-life value of 0.031 (= £927.65/£30,000). If 1 QALY is equal to 1 year in full health, then 0.031 is roughly equal to 11 days in full health [= 0.031/(1/365)]. The result can therefore be interpreted as follows: for carbetocin to be considered cost-effective compared with oxytocin for preventing PPH blood loss of ≥ 500 ml, having an outcome of PPH blood loss of ≥ 500 ml must be equivalent to losing 11 days of full health.

Given that a typical blood donation is typically 470 ml[196] with no loss to health, it can be argued the state of losing 500 ml is probably not equivalent to losing 11 days at full health. Although being in labour is very different from a person donating blood, this reasoning suggests that carbetocin is not likely to be considered a cost-effective strategy compared with oxytocin.

By similar reasoning:

1. For carbetocin to be considered cost-effective compared with oxytocin for preventing PPH blood loss of ≥ 1000 ml, having an outcome of PPH blood loss of ≥ 1000 ml must be equivalent to losing over 9 months of full health (referring to analysis 2b).
2. For carbetocin to be considered cost-effective compared with oxytocin for preventing a major outcome (i.e. surgery) having an outcome of major surgery must be equivalent to losing almost 30 years of full health (referring to analysis 2c).

Thus, the prevention strategy of carbetocin is not likely to be considered cost-effective for preventing PPH blood loss of ≥ 1000 ml and surgery.

The ICERs were lower in the scenario analysis for a community health-care setting. This may be more transferable to developing countries.

The results of the sensitivity analysis show moderate uncertainty in the input parameters. The one-way sensitivity analysis demonstrates robustness in the surgery costs, but the PSA shows that a small change in input parameters can change the decision ICER. The CEAC (see *Figure 110*) shows a WTP threshold of £865 per PPH blood loss of ≥ 500 ml avoided changes the decision as to whether carbetocin or oxytocin is the preferred prevention strategy. Being in natural units makes this result difficult to interpret. At a WTP threshold of £927.65 (the ICER value, analysis 2a), the probability that carbetocin is the optimal strategy

compared with oxytocin is 53%. This probability is not much higher than that probability that oxytocin is the optimal strategy at the same WTP threshold (47%), which further reflects uncertainty in interpreting the results.

(b) Caesarean section

For women delivering by caesarean section, the results are mixed.

Analysis 3: birth by caesarean section excluding ergometrine and ergometrine plus oxytocin, and with no adverse events

For analysis 3, misoprostol plus oxytocin is the dominant strategy for an outcome of PPH blood loss of ≥ 500 ml. For an outcome measure of PPH blood loss of ≥ 1000 ml avoided carbetocin is shown to be the most effective strategy and misoprostol plus oxytocin is shown to be the second most effective strategy. The estimated ICER for prevention with carbetocin compared with misoprostol plus oxytocin is £2251.77 per case of PPH blood loss of ≥ 1000 ml avoided. Similarly, an outcome measure of major outcome averted results in an ICER for prevention with carbetocin compared with misoprostol plus oxytocin is £87,959.83 per major outcome averted.

Analysis 4: birth by caesarean section excluding ergometrine and ergometrine plus oxytocin, and with adverse events

When adverse events are included in analysis 4, carbetocin is the least costly prevention strategy. For an outcome of PPH blood loss of ≥ 500 ml, carbetocin dominates all strategies except misoprostol plus oxytocin. The estimated ICER for prevention with misoprostol plus oxytocin compared with carbetocin is £2480.19 per case of PPH blood loss of ≥ 500 ml avoided. This means that every additional case of PPH blood loss of ≥ 500 ml avoided by using misoprostol plus oxytocin over carbetocin costs an extra £2480.19. Following the intuition described *Analysis 2: vaginal birth with adverse events*, for misoprostol plus oxytocin to be considered cost-effective compared with carbetocin for preventing PPH blood loss of ≥ 500 ml, having an outcome of PPH blood loss of ≥ 500 ml must be equivalent to losing 30 days of full health. Therefore, it is doubtful that misoprostol plus oxytocin can be considered cost-effective.

For outcome measures of cost per case of PPH blood loss of ≥ 1000 ml avoided, and cost per major outcome averted, carbetocin is the dominant strategy, being less costly and more effective than all other prevention strategies.

Analysis 5: birth by caesarean section including ergometrine and ergometrine plus oxytocin, and with no adverse events

Including ergometrine and ergometrine plus oxytocin in this analysis changes the dominant strategy. In this case, the results show the prevention strategy of ergometrine plus oxytocin to be the only dominant strategy, being less costly and more effective than all other strategies.

Analysis 6: birth by caesarean section including ergometrine and ergometrine plus oxytocin, and with adverse events

Similar to analysis 5, the results of analysis 6 show that the prevention strategy of ergometrine plus oxytocin to be the only dominant strategy. The UK current practice of oxytocin is dominated by ergometrine plus oxytocin and carbetocin, as both ergometrine plus oxytocin and carbetocin are less costly and more effective than oxytocin for all outcome measures. The CEAC (see *Figure 111*) shows that for any given WTP threshold greater than zero, ergometrine plus oxytocin is the optimal strategy compared with the UK's current practice oxytocin for preventing PPH blood loss of ≥ 500 ml. The CEAC for ergometrine plus oxytocin compared with carbetocin shows less certainty in ergometrine plus oxytocin being the optimal strategy compared with carbetocin in preventing PPH blood loss of ≥ 500 ml for all WTP thresholds.

Strengths and limitations

Strengths

The strength of this model-based economic evaluation is that it is the first model-based economic evaluation to compare the cost-effectiveness of six different active strategies for preventing PPH. Previous cost-effectiveness studies have compared only two interventions. Being able to directly compare six active interventions and to rank them in terms of cost and effectiveness is especially helpful for policy-makers.

Second, by using effectiveness data from the NMA, it ensures that the pooled effectiveness data are a good reflection of the effectiveness of the prevention strategies. As opposed to a randomised control trial, which may have several biases attached and may be limited to specific countries or health-care settings, pooling the effectiveness data over so many trials from all over the world is intended to create more accurate data on the effectiveness of the uterotonic drugs.

Limitations

The main limitation in this economic evaluation was accurately accounting for missing data in the model. In the NMA, no studies had analysed the effect of ergometrine plus oxytocin or ergometrine for prevention of PPH for caesarean section, and so assumptions had to be made around these estimates in order to analyse their cost-effectiveness (analyses 5 and 6). Similarly, there were multiple data missing for adverse events from the uterotonic drugs in the model. This meant that several assumptions had to be made about the probability of certain adverse events resulting from different prevention strategies. Attempts were made to make missing probabilities as accurate as possible, and the probability of adverse events was explored in the PSA in an attempt to rectify this limitation. However, another method of including adverse events in the model, such as quality of life immediately post partum, may be more appropriate to capture the effect adverse events have on the women.

For analyses 5 and 6, ergometrine plus oxytocin results as the only dominant strategy for caesarean section for all outcome measures. However, the widely known risk factors associated with ergometrine were not addressed specifically in the model. For example, in the UK, under current guidelines,[197] ergometrine plus oxytocin is not to be given to hypertensive women as this can worsen hypertension and put the women at risk of more serious adverse events, such as stroke. The model does not address any further risks attached to the women other than the nine adverse events discussed in *Adverse events*.

The model-based economic evaluation makes no comparisons for different dosages of uterotonic or different routes of administration. Comparing the effects of different dosages and routes of administration for the dominant strategies may be useful for future research.

The model-based economic evaluation also includes only UK guidelines for model pathways, and attaches UK costs to resource use. It therefore does not consider different model pathways taken to treat PPH in developing countries where resources may be unavailable. It also fails to consider the costs and resources needed to store the uterotonic drugs. For example, oxytocin is required to be refrigerated, which may not be possible in some health-care settings.

Recommendations for practice

The findings of the health economic evaluation are insufficient on their own to dictate changes in practice, because of the varied results and uncertainty caused by missing data. However, the results do suggest that uterotonic drugs for the prevention of PPH, other than current UK practice, may be more effective and cost-effective for preventing PPH blood loss of $\geq$ 500 ml and PPH blood loss of $\geq$ 1000 ml.

Chapter 5 Discussion

Key findings

Key findings of the effectiveness network meta-analysis

A systematic review and NMA, using Cochrane methods, were performed to identify the most effective uterotonic drug for the prevention of PPH. The study included 137 randomised trials involving 87,466 women and compared six active drugs between them and with placebo or the control for prevention of PPH. Most trials were performed in the hospital setting and included women undergoing a vaginal birth, who were at either high or low risk for PPH. The study found that 29% of included trials were rated at being at a low overall risk of bias, but for most trials bias was uncertain because of insufficient reporting.

The strategies that were most effective for prevention of PPH blood loss of ≥ 500 ml were ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin, and all three strategies were found to reduce the risk of PPH blood loss of ≥ 500 ml compared with the current WHO-recommended drug, oxytocin (ergometrine plus oxytocin: RR 0.69, 95% CI 0.57 to 0.83; carbetocin: RR 0.72, 95% CI 0.52 to 1.00; misoprostol plus oxytocin: RR 0.73, 95% CI 0.6 to 0.9). These three strategies had an almost 100% probability of being ranked the first, second or third most effective strategy. Oxytocin was ranked fourth, with an almost 0% probability of being ranked in the top three. A similar performance of these three strategies was noted for the reduction of PPH blood loss of ≥ 1000 ml [ergometrine plus oxytocin: RR 0.77, 95% CI 0.61 to 0.95; carbetocin: RR 0.70, 95% CI 0.38 to 1.28; misoprostol plus oxytocin: RR 0.90, 95% CI 0.72 to 1.14), but the CIs were wider as this outcome is more rare. However, these three strategies had an almost 80% probability of being ranked the first, second or third most effective strategy. Oxytocin was ranked fourth, with an approximately 20% probability of being ranked in the top three strategies for this outcome.

For our secondary outcomes, including requirement for additional uterotonics, transfusion, change in Hb level and blood loss as a continuous outcome, again ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were the three most effective strategies. Oxytocin was consistently ranked fourth behind these three strategies. For some outcomes, such as maternal death, the composite outcome of maternal death or severe morbidity and manual removal of placenta, the study found that there were too few events to make analysis useful. For the duration of the third stage there was no clear ranking that emerged from this analysis. For the outcome of clinical signs of excessive blood loss, neonatal unit admissions and breastfeeding at discharge, there were too few studies to make the analysis useful.

In terms of side effects, ergometrine and ergometrine plus oxytocin are the lowest-ranked drugs for nausea, vomiting, hypertension and headache. Misoprostol and misoprostol plus oxytocin are the lowest-ranked drugs for fever and shivering. Misoprostol plus oxytocin and ergometrine plus oxytocin are the lowest-ranked drugs for causing abdominal pain. For hypotension and tachycardia, there were too few studies to make the analysis useful. Carbetocin, oxytocin and placebo or the control had a similar side-effect profile and were the highest-ranked drugs for all side effects. There were no serious adverse effects noted with any of the drugs in the included trials.

Subgroup analyses were carried out according to mode of birth, prior risk of PPH, health-care setting and dose and route of administration of the drugs. The study found that the results were, as expected, less powered and more unstable, but generally in agreement with the overall results. Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were the highest-ranked drug strategies, with oxytocin being consistently fourth. However, no studies have used ergometrine plus oxytocin or ergometrine alone for women undergoing caesareans and effectiveness estimates could not be provided for these drug strategies. Interestingly, in the subgroup including only oxytocin trials in which the drug was administered intramuscularly

or intravenously via a bolus as currently recommended, the ranking did not change. Similarly, restricting the analysis to high- or low-dose misoprostol trials did not alter the ranking of this drug.

In our sensitivity analyses, when we restricted the analysis to high-quality studies or studies rated as being at low risk of bias in terms of their funding, carbetocin lost its ranking and was comparable to oxytocin, but ergometrine plus oxytocin and misoprostol plus oxytocin were still ranked higher than oxytocin. When the analysis was restricted to studies that assessed the blood loss objectively, it was found that ergometrine plus oxytocin was ranked the highest, but there was no clear ranking hierarchy for the rest of the drugs or drug combinations. When the analysis was restricted to large studies we found that there were no studies investigating carbetocin and, again, ergometrine plus oxytocin and misoprostol plus oxytocin were ranked higher than oxytocin.

Key findings of the cost-effectiveness analysis

Alongside the NMA, the study aimed to discover the most cost-effective uterotonic drug for the prevention of PPH. The analyses took the perspective of the NHS, and costs were presented in Great British pounds. The results were presented as ICERs, with a primary outcome measure of cost per case of PPH blood loss of ≥ 500 ml avoided. Secondary outcome measures were cost per case of PPH blood loss of ≥ 1000 ml avoided and cost per major adverse outcome averted. The analysis was carried out separately for vaginal birth and caesarean section birth.

The results of the cost-effectiveness for vaginal birth, excluding adverse events, show ergometrine plus oxytocin and carbetocin to be the leading strategies. Ergometrine plus oxytocin is the least costly strategy, and carbetocin is the most-effective strategy. The estimated ICER for prevention with carbetocin compared with ergometrine plus oxytocin is £1888.75 per case of PPH blood loss of ≥ 500 ml avoided. This means that every additional case of PPH blood loss of ≥ 500 ml avoided by using carbetocin over oxytocin costs an extra £1888.75 (see *Table 4*). When adverse events were included in the analysis, the dominant strategies were carbetocin and oxytocin. Oxytocin is the least costly strategy, and carbetocin is the most effective. The estimated ICER for prevention with carbetocin compared with oxytocin is £927.65 per case of PPH blood loss of ≥ 500 ml avoided. This means that taking into account side effects, every additional case of PPH blood loss of ≥ 500 ml avoided by using carbetocin over oxytocin costs an extra £927.65. There is a case for carbetocin being considered cost-effective compared with oxytocin, particularly in a community setting, where treatment for PPH may not be as easily accessible.

The results for birth by caesarean section were mixed because of a large number of missing data. The probabilities of PPH blood loss of ≥ 500 ml and of ≥ 1000 ml for ergometrine and ergometrine plus oxytocin were unavailable from the NMA, so the strategies were initially excluded from the analysis. These results showed misoprostol plus oxytocin and carbetocin to be the leading strategies. Including ergometrine and ergometrine plus oxytocin in the analysis, by making assumptions about the effectiveness of these strategies, shows ergometrine plus oxytocin to dominate all other strategies.

The results of the PSA show moderate uncertainty in the input parameters. This reflects the differing results shown in the principal analysis.

Strengths and limitations

Strengths and limitations of the effectiveness network meta-analysis

Strengths

The systematic review answers a defined question through a comprehensive literature search using Cochrane methods. The study excluded quasi-randomised trials to improve the quality of the included evidence. Study selection and extraction of relevant quantitative and quality assessment data were performed by three reviewers (IG, HW, AM, OT, HG or DL) for all randomised trials. The NMA provides the

relative effectiveness of all drugs used for the prevention of PPH in a coherent and methodologically robust way across important clinical outcomes by combining both direct and indirect evidence increasing the power and confidence in the results.

The study found that most of the included trials reported the primary outcomes, most of the secondary outcomes and often side effects. This increased the power across most of the analyses and underpins the consistency in the ranking across all blood loss outcomes, which also increases the confidence in the results.

The NMA is valid only assuming that all drugs in the network were suitable for all included women. We were thorough in the evaluation of the six important potential treatment effect modifiers (mode of birth, prior risk of PPH, health-care setting, dose, route and regimen of the drugs) and found no clinically important differences in the distribution of these potential effect modifiers across the interventions with a ranking in each of the subgroups comparable to the overall ranking. The results of the NMAs were mostly consistent, and when there was significant inconsistency this was normally because of unstable estimates from single studies. Through the sensitivity analyses, it was possible to identify that the research underpinning the carbetocin effectiveness is based on small studies of low quality.

Limitations

Included studies were rated as being at a low risk of bias when the quality domains were reported, but around half of the quality domains were not reported. The most common reason for concerns regarding selective reporting was insufficient information regarding protocol publication to confidently judge if the trial has selectively reported results. This is affected by the fact that protocol publication only became common practice recently. Often studies did not report their sources of funding or their methods for measuring the blood loss. This latter outcome was particularly inconsistent because some trials measured blood loss objectively by weighing swabs and drapes and others subjectively by visual estimation. Around half of the studies used adequate concealment and blinded professionals and participants.

Patients identified the clinical signs of excessive blood loss, neonatal unit admissions and breastfeeding at discharge as important. These were not reported often enough in the trials to make conclusions based on their analyses.

Heterogeneity in the analyses may have been caused by the fact that trials were carried out over a long time period, during which the clinical response to PPH may have improved. These temporal changes could have contributed to heterogeneity and increased uncertainty of findings. As objective methods of measuring blood loss become increasingly available this could perhaps have also led to apparent increases in reported blood loss. However, a sensitivity analysis was carried out removing trials published before 1990, and this did not vary the ranking of the drugs.

The trials included in the review recruited women with varied clinical characteristics, and it is important to bear this in mind when interpreting results. The inclusion criteria were not always reported in detail and, when they were, these varied across trials. Many trials excluded women with significant comorbidities and at very high risk of PPH. Predominantly, women recruited to trials were > 37 weeks of gestation. Most of the trials were carried out in hospital settings and for women having a vaginal birth.

Clinical heterogeneity was encountered in settings and inclusion criteria, as described in *Chapter 3, Study characteristics*. However, some heterogeneity may also be present in the overall analysis related to the dose, route of drug administration or regimen of the drugs. Even though subgroup effects were not observed when the dose of misoprostol or regimen of oxytocin administration were varied, it was felt that they were most relevant. Subgroup analyses was not performed for every single increment in dosage or change in route or regimen of drug administration. Studies comparing exclusively different doses, routes or regimens of the drugs were excluded, as this was not the aim of this analysis.

Limitations in the cost-effectiveness analysis were mostly because of the missing data needed for the model. Several assumptions had to be made to impute probabilities for missing data, but there were uncertainties around these estimates. Attempts were made to make missing probabilities as accurate as possible, and the probability of adverse events was explored in the PSA in an attempt to rectify this limitation. Furthermore, the model does not address any further risks attached to the women other than the nine adverse events discussed in the methods. This includes serious adverse events, such as strokes, that can be more likely to occur when ergometrine plus oxytocin is given to hypertensive women.

The model-based economic evaluation includes only UK guidelines for model pathways, and attaches UK costs to resource use. It therefore does not consider different model pathways taken to treat PPH in developing countries where resources may be unavailable. It also fails to consider the costs and resources needed to store the uterotonic drugs.

Clinical implications of findings

This NMA found that ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin are more effective uterotonic drugs for preventing PPH than the standard drug recommendation of oxytocin. However, ergometrine plus oxytocin and misoprostol plus oxytocin cause significant side effects. Carbetocin has a favourable side-effect profile similar to oxytocin and placebo or the control. However, carbetocin trials are small and of poor quality, and when the analysis is restricted to high-quality trials, carbetocin loses its top ranking and does not appear to be more effective than oxytocin, but there is significant uncertainty around the effect estimate.

The ranking of the available drugs was similar in the subgroups including trials only of women having a vaginal birth or undergoing a caesarean. However, there are no trials that have used ergometrine plus oxytocin or ergometrine alone for prevention of PPH at caesarean section and these strategies cannot be recommended in this circumstance. However, these strategies are often used for treatment of PPH at the time of a caesarean section and should also be effective for prevention. The ranking is relevant to women at high or low risk of PPH in the hospital setting. There were not enough trials to be able to recommend a ranking in the community setting, even though a similar ranking in terms of effectiveness can be expected.

The advantages of carbetocin over existing practice using oxytocin as the agent of choice are evident. Carbetocin is always found to be more effective than oxytocin. Overall, carbetocin is also less costly than oxytocin, being the least costly in all but one of the analyses, despite the unit cost for carbetocin being relatively more expensive. Carbetocin, like oxytocin, has a relatively favourable side-effect profile, making it more appealing than uterotonic drugs, such as ergometrine plus oxytocin and misoprostol plus oxytocin, in which adverse events are more likely and the risks are less clear.

The current recommendation from NICE,[23] RCOG[174] and WHO[6] is for 10 IU of intramuscular or intravenous oxytocin for the prevention of PPH. However, several studies have demonstrated that oxytocin loses potency if not stored at room temperature (i.e. ≤ 25 °C) for a restricted amount of time or refrigerated (at 2–8 °C), making its use difficult in low-income countries.[198] The manufacturer of carbetocin, Ferring Pharmaceuticals (Saint-Prex, Switzerland), has recently developed a room temperature-stable (RTS) formulation (i.e. carbetocin RTS), which makes it an attractive option for countries where maintaining cold storage is problematic.[199] As oxytocin is ranked fourth in terms of effectiveness and carbetocin is more cost-effective with a similar side-effect profile, our results can have important implications for clinical practice. However, when the analysis is restricted to high-quality trials it changes the ranking of carbetocin and it does not appear to be more effective than oxytocin in this analysis. The conclusion from this is that there is an urgent need for a high-quality large trial, comparing carbetocin with the current standard of oxytocin, to confirm or reject the findings of the current small and poor-quality trials that involve carbetocin.

There are two key studies that will inform a future update of this review. The first one is a WHO-led multicentre Phase III clinical study[200] comparing the effectiveness of carbetocin RTS and oxytocin (administered intramuscularly) in the prevention of PPH for women having a vaginal birth. This study was recently published[201] and included approximately 30,000 women from 10 countries: Argentina, Egypt, India, Kenya, Nigeria, Singapore, South Africa, Thailand, Uganda and the UK. Carbetocin RTS was found to be non-inferior to oxytocin and the aim of the collaborating organisations is to now provide access to heat-stable carbetocin to public sector providers in low-income countries, with a high burden of maternal mortality, at an affordable and sustainable price. This is particularly important for low-resource countries where cold storage is difficult to achieve and maintain. Another trial,[202] based in the UK, is recruiting > 6000 women to a three-arm trial comparing carbetocin, ergometrine plus oxytocin and oxytocin. This trial is also expected to report in due course. These trials aim to provide the high-quality evidence to support a change in practice, if the effectiveness of carbetocin is confirmed.

Recommendations for research

This NMA and cost-effectiveness analysis will require further updates in the future, especially as new evidence from randomised trials becomes available. An updated search in October 2017 identified a further 85 trial reports listed under studies awaiting classification. The priority is to update this analysis once the WHO-led trial mentioned in *Clinical implications of findings* is complete. If such a large and high-quality trial confirms the effectiveness of carbetocin, this updated report is likely to support a change in clinical practice. If such a recommendation is issued, then future research should focus on the implementation of such a policy in different settings.

More research into patient-reported outcomes, such as women's views about the drugs, is important. After our consultation with the PPI group of this study, it was clear that preventing PPH is a top priority for preserving maternal well-being, and the group considered it important to evaluate additional outcomes, including women's views regarding the drugs used, clinical signs of excessive blood loss, neonatal unit admissions and breastfeeding at discharge. However, existing trials rarely investigated these outcomes. Side effects of the drugs are also considered equally important and these were often not reported. All triallists should consider reporting these outcomes and side effects for each drug in all future randomised trials.

Additionally, future evidence synthesis research should compare the effects of different dosages and routes of administration for the dominant strategies. Attaching other developed, and also developing, country costs and model pathways should also be explored, as this may change the ranking order of cost-effective uterotonics.

Chapter 6 Other information

Trial registration

HTA reference number: 14/139/17.

PROSPERO reference number: CRD42015020005.

Cochrane Pregnancy and Childbirth Group (substudy) reference number: 0871.

PROSPERO Cochrane (substudy) reference number: CRD42015026568.

Sponsor's reference number: ERN_13–1414.

Protocol versions

Preliminary protocol development

26 February 2014
Meta-analytic title registration (not including cost-effectiveness analysis) with the Cochrane Collaboration.

5 September 2014
Submission of our initial study proposal including cost-effectiveness analysis to the NIHR HTA programme.

10 January 2015
Submission of a more-detailed study proposal including cost-effectiveness analysis to the NIHR HTA programme (recommendation for funding 5 February 2015).

Publication of protocol

22 April 2015
Finalisation of our comprehensive study protocol including cost-effectiveness analysis for the NIHR Journals Library version 1.0.

30 April 2015
Typographic corrections only to the comprehensive study protocol, including cost-effectiveness analysis for the NIHR Journals Library version 1.1.

18 May 2015
Publication of meta-analytic protocol (not including the cost-effectiveness analysis) by the Cochrane Collaboration.

Changes post publication

November 2016
Submission of the NMA and cost-effectiveness analysis to the NIHR HTA programme, with meta-analysis performed in Stata rather than WinBUGS for reasons of future reproducibility.

Acknowledgements

Contributions of authors

All of the following named authors contributed substantially to the development of the research question and study design, implementation, analysis and/or interpretation of data and submission of the final report.

Particular contributions are denoted below.

Ioannis Gallos (Clinician Scientist and Honorary Consultant in Obstetrics and Gynaecology) conceived the idea for the project and contributed to protocol development, management of the project, design of electronic data collection forms, data collection and quality assessment for the systematic review, clinical interpretation of findings and co-ordination of the initial draft of the final report.

Helen Williams (Research Associate, Women's Health) was responsible for the completion of data gathering, providing data quality assurance, co-ordination of the analysis and the writing groups, and co-ordination of the initial draft of the final report.

Malcolm Price (Clinical Lecturer in Statistics) contributed to protocol development, conducted statistical analyses and drafted and edited the report.

Karen Pickering (Research Associate) conducted the economic analysis and modelling, and drafted and edited the report.

Abi Merriel (Research Fellow) contributed to data collection, data set management and quality assessment, and commented on drafts of the report.

Aurelio Tobias (Statistician) conducted statistical analyses and drafted and edited the report.

David Lissauer (Clinical Lecturer in Obstetrics and Gynaecology) contributed to data collection, data set management and quality assessment, and commented on drafts of the report.

Harry Gee (Retired Consultant in Obstetrics) contributed to data collection, data set management and quality assessment, and commented on drafts of the report.

Ôzge Tunçalp (Research Fellow) contributed to data collection, data set management and quality assessment, and commented on drafts of the report.

Gillian Gyte (Consumer Representative) co-ordinated consumer groups, contributed to protocol development, commented on drafts of all project documentation and commented on drafts of the report.

Vidhya Moorthy (Obstetrician) contributed to data collection, data set management and quality assessment and commented on drafts of the report.

Tracy Roberts (Professor of Health Economics) contributed to protocol development, supervised the economic analysis and modelling and drafted and edited the report.

Jonathan Deeks (Professor of Statistics) contributed to protocol development and commented on drafts of the report.

Justus Hofmeyr (Professor of Obstetrics) contributed to protocol development, drafted and edited the report.

Metin Gülmezoglu (WHO Co-ordinator for Maternal and Perinatal Health) contributed to protocol development, drafted and edited the report.

Arri Coomarasamy (Professor of Gynaecology) conceived the project and contributed to protocol development, and drafted and edited the report.

The Cochrane Collaboration

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

Other researchers

We are grateful to the investigators of the Postpartum Haemorrhage Core Outcome Sets Project, and particularly to Shireen Meher, Anna Cuthbert, Zarko Alfirevic, Jamie Kirkham and Paula Williamson, for discussing the progress of their work with us.

Publications

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Search strategy: Cochrane Pregnancy and Childbirth Group

ClinicalTrials.gov and the WHO'S International Clinical Trials Registry Platform (ICTRP).

Search strategy

Third stage AND labo(u)r AND oxytocin.

Third stage AND labo(u)r AND misoprostol.

Third stage AND labo(u)r AND carbetocin.

Third stage AND labo(u)r AND ergometrine.

uterotonic* AND oxytocin.

uterotonic* AND misoprostol.

uterotonic* AND carbetocin.

uterotonic* AND ergometrine.

uterotonic* AND labo(u)r.

uterotonic* AND h(a)emorrhage.

h(a)emorrhage AND postpartum AND ergometrine.

h(a)emorrhage AND postpartum AND oxytocin.

h(a)emorrhage AND postpartum AND carbetocin.

h(a)emorrhage AND postpartum AND misoprostol.

Appendix 2 Description of included studies

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Abdel-Aleem *et al.*, 2010[37]	Three-arm controlled randomised trial	There were 1964 parturients randomised in a hospital setting in Egypt and South Africa The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with medical complications, such as hypertension and diabetes mellitus, previous caesarean section, or an abdominal wall that was not thin enough to allow easy palpation of the uterus after delivery	10 IU of i.m. oxytocin vs. no treatment	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death	High risk of bias
Acharya *et al.*, 2001[38]	Two-arm active-controlled randomised trial	There were 60 parturients randomised in a hospital setting in the UK The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria were not specified	10 IU of i.v. oxytocin (bolus) vs. 400 µg of p.o. misoprostol	• PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels • Vomiting • Shivering	High risk of bias
Adanikin *et al.*, 2012[39]	Two-arm active-controlled double-dummy randomised trial	There were 218 parturients randomised in a hospital setting in Nigeria The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients with altered serum electrolyte levels, peritonitis, sepsis, previous bowel surgery, thyroid disease, inflammatory bowel disease or chronic constipation	25 IU of i.v. oxytocin (bolus plus infusion) vs. 600 µg of p.r. misoprostol plus 5 IU of i.v. oxytocin (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Blood loss (ml) • Nausea • Vomiting • Fever • Shivering	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Afolabi *et al.*, 2010[40]	Two-arm active-controlled randomised trial	There were 200 parturients randomised in a hospital setting in Nigeria The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction of labour or caesarean section, or those with haematocrit of < 30%, pre-eclampsia/eclampsia, grand multiparity (five or more), multiple pregnancy, coagulopathy or medical disorders	10 IU of oxytocin i.m. vs. 400 µg of p.o. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Fever • Shivering	High risk of bias
Ahmed *et al.*, 2014[41]	Two-arm active-controlled randomised trial	There were 80 parturients randomised in a hospital setting in Egypt The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean Exclusion criteria comprised parturients with risk factors for excessive blood loss, for example those women with placenta praevia or placental abruption	100 µg of i.v. carbetocin (bolus) vs. 10 IU of i.v. oxytocin (bolus)	• Blood loss (ml)	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Al-Sawaf *et al.*, 2013[42]	Three-arm controlled randomised trial	There were 120 parturients randomised in a hospital setting in Egypt The population comprised women of parity ≤ 4, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction of labour or instrumental delivery, or those with previous caesarean section, extensive perineal, vaginal or cervical lacerations, bleeding disorders, a Hb level of < 100 g/l, uterine malformations, grand multiparity, multiple pregnancy, polyhydramnios, intrauterine fetal death, medical problems such as pre-eclampsia, diabetes mellitus, cardiopulmonary problems, bowel disease or allergy to prostaglandins	200 µg of s.l. misoprostol vs. 5 IU of i.m. oxytocin vs. no treatment	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels	High risk of bias
Amant *et al.*, 1999[43]	Two-arm active-controlled double-dummy randomised trial	There were 213 parturients randomised in a hospital setting in Belgium The population comprised women of unspecified parity, either singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with hypertensive disorders, gestational age of < 32 weeks, intrauterine fetal death, uterine malformations, inflammatory bowel disease, obliterative vascular or coronary disease, sepsis or allergy to prostaglandins or alkaloids	600 µg of p.o. misoprostol vs. 200 µg of i.v. ergometrine (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual remote placenta • Nausea • Vomiting • Headache • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Amin, 2014[44]	Two-arm active-controlled randomised trial	There were 200 parturients randomised in a hospital setting in Pakistan The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with traumatic PPH, bleeding disorders, prolonged labour, placenta praevia, placental abruption, multiple pregnancy, a BMI of > 30 kg/m^2 or previous PPH	5 IU of i.v. oxytocin (bolus) vs. 800 µg of p.r. misoprostol	• PPH blood loss of ≥ 500 ml • Morbidity • Manual removal of placenta • Death • Blood loss (ml) • Third-stage duration (minutes) • Vomiting • Fever • Shivering	High risk of bias
Askar *et al.*, 2011[45]	Two-arm active-controlled double-blind randomised trial	There were 240 parturients randomised in a hospital setting in Kuwait The population comprised women of parity ≤ 5, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients < 18 years old and those with known or suspected coagulopathy, grand multiparity (≥ 5), uterine fibroids, polyhydramnios, multiple pregnancy, fetal macrosomia, severe anaemia, cervical tears or who required prophylactic oxytocin infusion The presence of contraindications to the use of either Syntometrine or carbetocin that include pre-existing hypertension, pre-eclampsia, asthma, cardiac, renal or liver diseases, epilepsy, or history of hypersensitivity to Syntometrine or carbetocin	100 µg of i.m. carbetocin vs. 500 µg of ergometrine plus 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Hypertension • Headache • Abdominal pain	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Attilakos *et al.*, 2010[46]	Two-arm active-controlled double-blind randomised trial	There were 377 parturients randomised in a hospital setting in the UK The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean Exclusion criteria comprised parturients undergoing caesarean section with general anaesthesia, gestational age of < 37 weeks performed for fetal or maternal distress where, because of time constraints, it was not possible to recruit or randomise, or those with multiple pregnancy, placenta praevia or placental abruption	100 µg of i.v. carbetocin (bolus) vs. 5 IU of i.v. oxytocin (bolus)	• PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Headache • Tachycardia • Hypotension • Shivering • Abdominal pain	Low risk of bias
Atukunda *et al.*, 2014[47]	Two-arm active-controlled double-dummy randomised trial	There were 1140 parturients randomised in a hospital setting in Uganda The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction or augmentation of labour or elective caesarean section, or those with intrauterine fetal death, heart disease, severe malaria or acute bacterial infection, multiple pregnancy, antepartum haemorrhage, altered cognitive status or reported hypersensitivity to prostaglandins	10 IU of oxytocin i.m. vs. 600 µg of s.l. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Headache • Fever • Shivering • Abdominal pain	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Badejoko *et al.*, 2012[48]	Two-arm active-controlled double-dummy randomised trial	There were 264 parturients randomised in a hospital setting in Nigeria The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients in the second or third stage of labour, or those women with cervical lacerations or coagulopathy	30 IU of i.v. oxytocin (bolus and infusion) vs. 600 µg of p.r. misoprostol plus 20 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Vomiting • Fever • Shivering	Low risk of bias
Balki *et al.*, 2008[49]	Two-arm active-controlled double-blind randomised trial	There were 48 parturients randomised in a hospital setting in Canada The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by emergency caesarean section Exclusion criteria comprised parturients requiring general anaesthesia, or those with cardiac disease, hypertension or any condition predisposing to uterine atony and PPH, such as placenta praevia, multiple pregnancy, pre-eclampsia, macrosomia, polyhydramnios, uterine fibroids, bleeding disorders, chorioamnionitis, previous uterine atony, previous PPH or allergy/hypersensitivity to oxytocin or ergot derivatives	250 µg of ergometrine plus 20 IU of i.v. oxytocin (bolus and infusion) vs. 20 IU of i.v. oxytocin (bolus and infusion)	• Additional uterotonics • Transfusion • Blood loss (ml) • Nausea • Vomiting • Hypertension • Tachycardia • Hypotension	Low risk of bias
Bamigboye *et al.*, 1998[50]	Two-arm placebo-controlled randomised trial	There were 550 parturients randomised in a hospital setting in South Africa The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	400 µg of p.r. misoprostol vs. placebo	• PPH blood loss of ≥ 1000 ml • Additional uterotonics • Manual removal of placenta • Third-stage duration (minutes) • Vomiting • Shivering • Abdominal pain	High risk of bias

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Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Bamigboye *et al.*, 1998[51]	Two-arm active-controlled randomised trial	There were 491 parturients randomised in a hospital setting in South Africa The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	400 µg of p.r. misoprostol vs. 500 µg of ergometrine plus 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes)	High risk of bias
Barton and Jackson, 1996[52]	Two-arm placebo-controlled randomised trial	There were 119 parturients randomised in a hospital setting in the USA The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria were not specified	100 µg of i.v. carbetocin (bolus) vs. placebo	• Additional uterotonics	High risk of bias
Baskett *et al.*, 2007[53]	Two-arm active-controlled double-dummy randomised trial	There were 622 parturients randomised in a hospital setting in Canada The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with placenta previa, placental abruption, coagulopathy or unstable asthma	5 IU of i.v. oxytocin (bolus) vs. 400 µg of p.o. misoprostol	• PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Fever • Shivering	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Begley, 1990[54]	Two-arm controlled randomised trial	There were 1429 parturients randomised in a hospital setting in Ireland The population comprised women of parity ≤ 5, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, vaginal breech or instrumental delivery, or those with hypertension, epidural anaesthesia, antepartum haemorrhage, placenta praevia, placental abruption, first stage of labour > 15 hours, 'quick' delivery or needing resuscitation	500 µg of i.v. ergometrine (bolus) vs. no treatment	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Hypertension • Headache • Abdominal pain	High risk of bias
Bellad *et al.*, 2012[55]	Two-arm active-controlled double-dummy randomised trial	There were 652 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section or instrumental delivery, or those with medical disorders, in active labour with > 4-cm dilatation or stillbirths	400 µg of s.l. misoprostol vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Third-stage duration (minutes) • Nausea • Vomiting • Fever • Shivering • Abdominal pain	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Benchimol *et al.*, 2001[56]	Three-arm controlled randomised trial	There were 602 parturients randomised in a hospital setting in France The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with gestational age of < 32 weeks, previous PPH, intrauterine fetal death, previous uterine scar, multiple pregnancy or pre-eclampsia	2.5 IU of i.m. oxytocin vs. 600 µg of p.o. misoprostol vs. no treatment	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Blood loss (ml) • Change in Hb levels • Vomiting • Fever • Shivering	High risk of bias
Bhullar *et al.*, 2004[57]	Two-arm placebo-controlled randomised trial	There were 756 parturients randomised in a hospital setting in the USA The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with a bleeding disorder	200 µg of s.l. misoprostol plus 20 IU of i.v. oxytocin (infusion) vs. 20 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Vomiting • Shivering	High risk of bias
Borruto *et al.*, 2009[58]	Two-arm active-controlled randomised trial	There were 104 parturients randomised in a hospital setting in France and Italy The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean Exclusion criteria comprised parturients with toxaemia, eclampsia or epilepsy	100 µg of i.v. carbetocin (bolus) vs. 10 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Blood loss (ml) • Vomiting • Headache • Hypotension • Shivering • Abdominal pain	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Boucher *et al.*, 1998[59]	Two-arm active-controlled double-dummy randomised trial	There were 60 parturients randomised in a hospital setting in Canada The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients with heart disease or cardiac arrhythmia, hypertension or liver/renal/endocrine disease	100 µg of i.v. carbetocin (bolus) vs. 32.5 IU of i.v. oxytocin (bolus and infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Nausea • Vomiting • Headache • Fever • Shivering • Abdominal pain	High risk of bias
Boucher *et al.*, 2004[60]	Two-arm active-controlled double-dummy randomised trial	There were 164 parturients randomised in a hospital setting in Canada The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients < 18 years old, or those without known PPH risk, known or suspected coagulopathy, heart disease or cardiac arrhythmia, chronic liver/renal/endocrine disease or hypersensitivity to study drugs	100 µg of i.m. carbetocin vs. 10 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Headache • Shivering • Abdominal pain	High risk of bias
Bugalho *et al.*, 2001[61]	Two-arm active-controlled double-dummy randomised trial	There were 700 parturients randomised in a hospital setting in Mozambique The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction or augmentation of labour	400 µg of p.r. misoprostol vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Third-stage duration (minutes) • Vomiting • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Butwick *et al.*, 2010[62]	Five-arm placebo-controlled randomised trial	There were 75 parturients randomised in a hospital setting in the USA The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients with active labour, ruptured membranes, drug allergy, multiple pregnancy, significant obstetric disease, risk factors for PPH (abnormal placentation, fibroids, previous PPH, previous classical uterine incision), coagulopathy or thrombocytopenia	5, 3, 1 or 0.5 IU of i.v. oxytocin (bolus) vs. placebo	• Additional uterotonics • Transfusion • Blood loss (ml) • Nausea • Vomiting • Tachycardia • Hypotension	High risk of bias
Calişkan *et al.*, 2003[64]	Four-arm active-controlled double-dummy randomised trial	There were 1800 parturients randomised in a hospital setting in Turkey The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with gestational age of < 32 weeks or hypersensitivity to prostaglandins	400 µg of p.o. misoprostol plus 10 IU of i.v. oxytocin (infusion) vs. 400 µg of p.o. misoprostol vs. 10 IU of i.v. oxytocin (infusion) vs. 200 µg of i.m. ergometrine plus 10 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Vomiting • Fever • Shivering	High risk of bias
Calişkan *et al.*, 2002[63]	Four-arm active-controlled double-dummy randomised trial	There were 1633 parturients randomised in a hospital setting in Turkey The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with a gestational age of < 32 weeks or hypersensitivity to prostaglandins	400 µg of p.r. misoprostol plus 10 IU of i.v. oxytocin (infusion) vs. 400 µg of p.r. misoprostol vs. 10 IU of i.v. oxytocin (infusion) vs. 200 µg of i.m. ergometrine plus 10 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Change in Hb levels • Third-stage duration (minutes) • Vomiting • Fever • Shivering	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Carbonell I Esteve *et al.*, 2009[65]	Two-arm active-controlled randomised trial	There were 1410 parturients randomised in a hospital setting in Spain The population comprised women of parity ≤ 4, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section or instrumental delivery, or those with a gestational age of < 32 weeks, coagulopathy, a Hb level < 80 g/l, liver or kidney disorder, grand multiparity (five or more), hypersensitivity or any contraindication for use of prostaglandins	400 µg of s.l. misoprostol plus 200 µg of p.r. misoprostol plus 10 IU of i.m. oxytocin vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • NNU admissions • Nausea • Vomiting • Fever • Shivering	High risk of bias
Cayan *et al.*, 2010[66]	Four-arm controlled randomised trial	There were 160 parturients randomised in a hospital setting in Turkey The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean section Exclusion criteria comprised parturients with thyroid disorder, inflammatory bowel disease or other bowel diseases, previous bariatric surgery or hypersensitivity to prostaglandins	200, 400 or 600 µg of p.r. misoprostol plus 10 IU of i.v. oxytocin (infusion) vs. 10 IU of i.v. oxytocin (infusion)	• Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Chaudhuri *et al.*, 2010[67]	Two-arm active-controlled double-dummy randomised trial	There were 200 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean Exclusion criteria comprised parturients undergoing caesarean section for cord prolapse or bradycardia, or those with cardiovascular, respiratory, liver or haematological disorders or known hypersensitivity to prostaglandins	800 µg of p.r. misoprostol vs. 40 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Change in Hb levels • Vomiting • Fever • Shivering	Low risk of bias
Chaudhuri *et al.*, 2012[68]	Two-arm active-controlled double-dummy randomised trial	There were 530 parturients randomised in a hospital setting in India The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing augmentation of labour, caesarean section or instrumental delivery, or those with risk factors for PPH, including a BMI of > 30 kg/m^2, grand multiparity (five or more), polyhydramnios, fetal macrosomia, antepartum haemorrhage, prolonged labour, previous PPH, a Hb level of < 80 g/l, severe pre-eclampsia, asthma or coagulopathy	400 µg of s.l. misoprostol vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Fever • Shivering	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Chaudhuri and Majumdar, 2015[69]	Two-arm active-controlled double-dummy randomised trial	There were 396 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by emergency caesarean section Exclusion criteria comprised parturients requiring conversion to general anaesthesia, or those with cardiovascular, hepatic, or haematological disorders or any contraindication for the use of misoprostol or oxytocin	400 µg of s.l. misoprostol plus 20 IU of i.v. oxytocin (bolus and infusion) vs. 20 IU of i.v. oxytocin (bolus and infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Change in Hb levels • Nausea • Fever • Shivering	Low risk of bias
Chhabra and Tickoo, 2008[70]	Three-arm active-controlled randomised trial	There were 300 parturients were randomised in a hospital setting in India The population comprised women of parity ≤ 5, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing augmentation of labour, caesarean section or instrumental delivery, or those with grand multiparity (more than five), multiple pregnancy, pregnancy-induced hypertension, antepartum haemorrhage, previous caesarean, a Hb level of < 80 g/l, other obstetric problems or known hypersensitivity to prostaglandins	100 or 200 µg of s.l. misoprostol vs. 200 µg of i.v. ergometrine (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Headache • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Choy *et al.*, 2002[71]	Two-arm active-controlled randomised trial	There were 991 parturients randomised in a hospital setting in Hong Kong The population comprised women of parity ≤ 3, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with medical conditions that precluded the use of ergometrine, such as pre-eclampsia, cardiac disease or conditions that required prophylactic oxytocin infusion after delivery such as grand multiparity (four or more) or presence of uterine fibroids	500 µg ergometrine plus 5 IU of i.m. oxytocin vs. 10 IU of i.v. oxytocin (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Hypertension • Headache	High risk of bias
Cook *et al.*, 1999[72]	Three-arm active-controlled randomised trial	There were 930 parturients randomised in a hospital setting in Australia, Papua New Guinea and China The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing elective caesarean section, or those with coagulopathy, asthma, heart disease, severe renal disease, epilepsy or hypertension	400 µg of p.o. misoprostol vs. 500 µg plus 5 IU of ergometrine plus i.m. oxytocin vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes)	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Dansereau *et al.*, 1999[73]	Two-arm active-controlled double-blind randomised trial	There were 694 parturients randomised in a hospital setting in Canada The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients undergoing general anaesthesia or requiring a classical uterine incision, or those with heart disease, chronic hypertension requiring treatment, liver/renal/endocrine disorders, coagulopathy, placenta praevia or placental abruption	100 µg of i.v. carbetocin (bolus) vs. 25 IU of i.v. oxytocin (bolus and infusion)	• Additional uterotonics • Transfusion • Change in Hb levels • Nausea • Vomiting • Headache • Shivering • Abdominal pain	High risk of bias
Dasuki *et al.*, 2002[74]	Two-arm active-controlled randomised trial	There were 196 parturients randomised in a hospital setting in Indonesia The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at unspecified for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	600 µg of p.o. misoprostol vs. 10 IU of i.m. oxytocin	• Blood loss (ml) • Third-stage duration (minutes) • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
de Groot *et al.*, 1996[75]	Three-arm placebo-controlled randomised trial	There were 371 parturients randomised in a hospital and community setting in the Netherlands The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction or augmentation of labour or instrumental delivery, requiring tocolysis or those who refuse to take part or with cardiac disease, multiple pregnancies, non-cephalic presentation, polyhydramnios, coagulopathy, stillbirth, antepartum haemorrhage, a Hb level of < 4.8 mmol/l or previous complication in third stage	5 IU of i.m. oxytocin vs. placebo	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml)	High risk of bias
Derman *et al.*, 2006[76]	Two-arm placebo-controlled randomised trial	There were 1620 parturients randomised in a community setting in India The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients at high risk and inappropriate for home or community births according to India's Ministry of Health guidelines including those women undergoing elective caesarean section or breech vaginal delivery, or those women who have had a caesarean section previously, a Hb level of < 80 g/l, antepartum haemorrhage, hypertension, multiple pregnancy, history of previous antepartum or PPH, retained placenta, uterine inversion, diabetes mellitus, heart disease, seizures, placenta praevia, asthma or contraindications to misoprostol	600 µg of p.o. misoprostol vs. placebo	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Nausea • Vomiting • Fever • Shivering	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Dhananjaya and Charishma, 2014[77]	Two-arm active-controlled randomised trial	There were 100 parturients randomised in a hospital setting in India The population comprised women of parity ≤ 4, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with grand multiparity (not defined), rhesus-negative blood group, cardiac disease, diabetes mellitus, bleeding disorder, precipitated labour, overdistended uterus, traumatic PPH, PROM/chorioamnionitis, intrauterine death, previous caesarean section/ scar on uterus or inability to obtain the informed consent	10 IU of i.m. oxytocin vs. 200 µg of i.m. ergometrine	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Headache	High risk of bias
Docherty *et al.*, 1981[78]	Two-arm active-controlled randomised trial	There were 50 parturients randomised in a hospital setting in UK The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at unspecified for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	10 IU of i.m. oxytocin vs. 500 µg ergometrine plus 5 IU of i.m. oxytocin	• Blood loss (ml)	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Eftekhari *et al.*, 2009[79]	Two-arm active-controlled randomised trial	There were 100 parturients randomised in a hospital setting in Iran The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients with multiple pregnancy, prolonged labour > 12 hours, two or more previous caesarean sections, previous uterine rupture, a Hb level of < 80 g/l, who had a history of heart/renal/liver disorders or had a coagulopathy did not enter the study	400 µg of s.l. misoprostol vs. 20 IU of i.v. oxytocin (infusion)	• Additional uterotonics • Blood loss (ml) • Change in Hb levels	High risk of bias
El Behery *et al.*, 2016[80]	Two-arm active-controlled double-dummy randomised trial	There were 180 parturients randomised in a hospital setting in Egypt The population comprised women of nulliparous, a singleton pregnancy, at high risk for PPH, who delivered by emergency caesarean section Exclusion criteria comprised parturients undergoing elective caesarean section, vaginal delivery or general anaesthesia, those women who were multigravida, or with malpresentation, fetal anomalies, placenta praevia, diabetes mellitus, hypertension, pre-eclampsia or cardiac disease	100 µg of i.v. carbetocin (bolus) vs. 20 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Change in Hb levels • Nausea • Headache • Fever	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
El Tahan *et al.*, 2012[81]	Two-arm placebo-controlled randomised trial	There were 382 parturients randomised in a hospital setting in Egypt The population comprised women of parity ≤ 3, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients with asthma, anaemia, bleeding disorders, cardiac disease, inflammatory disease, bowel disease, multiple pregnancy, pre-eclampsia, placenta praevia, placental abruption, previous APH, previous PPH, grand multiparity (not defined), fibroids, growth restriction, fetal malformations or allergy to prostaglandins	400 µg of s.l. misoprostol plus 10 IU of i.v. oxytocin (bolus) vs. 10 IU of i.v. oxytocin (bolus)	• Morbidity • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Vomiting • Fever • Shivering • Abdominal pain	Low risk of bias
Elgafor el Sharkwy, 2013[83]	Two-arm active-controlled double-dummy randomised trial	There were 380 parturients randomised in a hospital setting in Egypt The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients undergoing general anaesthesia, or those with coagulopathy, coronary artery disease, hypertension, PPH due to causes other than uterine atony or hypersensitivity to carbetocin	400 µg s.l. misoprostol plus 20 IU of s.l. i.v. oxytocin (infusion) vs. 100 µg of i.v. carbetocin (bolus)	• Morbidity • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Headache • Hypotension • Fever • Shivering	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
El-Refaey *et al.*, 2000[82]	Two-arm active-controlled randomised trial	There were 1000 parturients randomised in a hospital setting in UK The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section or water birth, or those women with severe asthma	500 µg of p.o. misoprostol vs. 500 µg of ergometrine plus 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Headache • Fever • Shivering • Abdominal pain	High risk of bias
Elsedeek *et al.*, 2012[84]	Two-arm placebo-controlled randomised trial	There were 400 parturients randomised in a hospital setting in Egypt The population comprised women of parity ≤ 4, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients undergoing their first elective caesarean section, those unsure of gestation or with hypertension, diabetes mellitus, oligohydramnios, abnormal placenta or abnormal laboratory investigations	400 µg p.r. misoprostol plus 10 IU of i.v. oxytocin (infusion) vs. 10 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels • NNU admissions • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Enakpene *et al.*, 2007[85]	Two-arm active-controlled randomised trial	There were 864 parturients randomised in a hospital setting in Nigeria The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with pre-eclampsia, hypertension, cardiac disease, severe anaemia, asthma, renal/hepatic disorders, grand multiparity (not defined), multiple pregnancy, polyhydramnios, previous PPH, fibroids or contraindications to misoprostol or ergometrine	400 µg of p.o. misoprostol vs. 500 µg of i.m. ergometrine	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Headache • Fever • Shivering	High risk of bias
Ezeama *et al.*, 2014[86]	Two-arm active-controlled double-dummy randomised trial	There were 300 parturients randomised in a hospital setting in Nigeria The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with premature labour (i.e. < 28 weeks' gestation), multiple pregnancy, antepartum haemorrhage, hypertension in pregnancy, severe anaemia or haemoglobinopathy	10 IU of i.m. oxytocin vs. 500 µg of i.m. ergometrine	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Third-stage duration (minutes) • Nausea • Vomiting • Hypertension • Headache	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Fararjeh *et al.*, 2003[87]	Two-arm active-controlled randomised trial	There were 97 parturients randomised in a hospital setting in Turkey The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing elective caesarean section or instrumental delivery, or those with premature labour (i.e. < 37 weeks' gestation), post maturity (i.e. > 43 weeks' gestation), grand multiparity (more than four), twin pregnancy, growth restriction, macrosomia, a Hb level of < 100 g/l, systemic disorder, prolonged third stage, manual removal of placenta or additional lacerations due to episiotomy or where it took > 30 minutes to repair lacerations after episiotomy	400 µg of p.r. misoprostol vs. 200 µg of ergometrine plus 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Blood loss (ml) • Change in Hb levels	High risk of bias
Fazel *et al.*, 2013[88]	Two-arm active-controlled randomised trial	There were 100 parturients randomised in a hospital setting in Iran The population comprised women of parity ≤ 3, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients with twin pregnancy, fetal distress, pregnancy-induced hypertension, oligohydramnios, polyhydramnios, macrosomia, grand multiparity (≥ 4), HELLP syndrome, coagulopathy, asthma, heart/lung/liver disease, previous more than one caesarean section, previous myomectomy, previous other abdominal operations, febrile diseases or sensitivity to prostaglandins	400 µg of p.r. misoprostol vs. 10 IU of i.v. oxytocin (infusion)	• Transfusion • Blood loss (ml) • Nausea • Vomiting • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Fekih *et al.*, 2009[89]	Two-arm active-controlled randomised trial	There were 250 parturients randomised in a hospital setting in Tunisia The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean section Exclusion criteria comprised parturients undergoing caesarean section with general anaesthesia, or those with placenta praevia, retroplacental clot, multiple pregnancy, premature labour (i.e. < 32 weeks' gestation), intrauterine death, a Hb level of < 80 g/l, coagulopathy, HELLP syndrome, antepartum haemorrhage, ruptured uterus, previous more than two caesareans or other uterine scar, prolonged labour (i.e. > 12 hours) or pyrexia	200 µg s.l. misoprostol plus 20 IU of i.v. oxytocin (bolus plus infusion) vs. 20 IU of i.v. oxytocin (bolus plus infusion)	• PPH blood loss of ≥ 1000 ml • Transfusion • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Headache • Fever • Shivering	High risk of bias
Fenix, 2012[90]	Two-arm active-controlled double-dummy randomised trial	There were 75 parturients randomised in a hospital setting in the Philippines The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with pre-existing hypertension, pre-eclampsia, diabetes mellitus, asthma, cardiac/renal diseases, coagulopathy, abnormal laboratory tests or allergy to the study medication	100 µg of i.v. carbetocin (bolus) vs. 10 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Headache • Tachycardia • Abdominal pain	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Fu *et al.*, 2003[91]	Two-arm controlled randomised trial	There were 156 parturients randomised in a hospital setting in China The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	400 µg of p.o. misoprostol vs. no treatment	• PPH blood loss of ≥ 500 ml • Blood loss (ml)	High risk of bias
Garg *et al.*, 2005[92]	Two-arm active-controlled randomised trial	There were 200 parturients randomised in a hospital setting in India The population comprised women who were primigravid, of a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	600 µg of p.o. misoprostol vs. 200 µg of i.v. ergometrine (bolus)	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Manual removal of placenta • Third-stage duration (minutes) • Nausea • Vomiting • Headache • Fever • Shivering	High risk of bias
Gavilanes *et al.*, 2015[93]	Two-arm active-controlled randomised trial	There were 100 parturients randomised in a hospital setting in Ecuador The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients with a Hb level of < 80 g/l, multiple pregnancy, polyhydramnios, previous uterine rupture, bleeding disorders, intrauterine death or hyperthermia (i.e. > 38.5 °C)	400 µg of s.l. misoprostol vs. 10 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Blood loss (ml) • Nausea • Vomiting • Headache • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Gerstenfeld and Wing, 2001[94]	Two-arm placebo-controlled randomised trial	There were 400 parturients randomised in a hospital setting in USA The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with multiple pregnancy, coagulopathy, a Hb level of < 70 g/l, indication for caesarean section or contraindication to prostaglandin or oxytocin use	400 µg of p.r. misoprostol vs. 20 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Nausea • Vomiting • Shivering	High risk of bias
Gülmezoglu *et al.*, 2001[95]	Two-arm active-controlled double-blind randomised trial	There were 18,530 parturients randomised in hospital settings in Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand and Vietnam The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing elective or emergency caesarean section after randomisation, or those with asthma, severe chronic allergic conditions, abortion, pyrexia (i.e. > 38 °C) or inability to give consent	600 µg of p.o. misoprostol vs. 10 IU of i.m. oxytocin or i.v. (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Third-stage duration (minutes) • Nausea • Vomiting • Fever • Shivering	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Gupta *et al.*, 2006[96]	Two-arm active-controlled double-blind randomised trial	There were 200 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	600 µg of p.r. misoprostol vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Fever • Shivering	High risk of bias
Hamm *et al.*, 2005[97]	Two-arm placebo-controlled randomised trial	There were 352 parturients randomised in a hospital setting in the USA The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean Exclusion criteria were not specified	200 µg of s.l. misoprostol plus 20 IU of i.v. oxytocin (infusion) vs. 20 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels	Low risk of bias
Harriott *et al.*, 2009[98]	Two-arm active-controlled randomised trial	There were 140 parturients randomised in a hospital setting in the West Indies The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with previous PPH, hypertension, previous caesarean, intrauterine death, sepsis/pyrexia (i.e. > 38 °C), antepartum haemorrhage or a Hb level of < 80 g/l	500 µg of ergometrine plus 10 IU of i.m. oxytocin vs. 400 µg of p.r. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Hypertension • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Hofmeyr *et al.*, 1998[99]	Two-arm placebo-controlled randomised trial	There were 500 parturients randomised in a hospital setting in South Africa The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing augmentation of labour, or those with hypertension, diabetes mellitus or previous caesarean	400 µg of p.o. misoprostol vs. placebo	• PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Shivering • Abdominal pain	High risk of bias
Hofmeyr *et al.*, 2001[100]	Two-arm placebo-controlled randomised trial	There were 600 parturients randomised in a hospital setting in South Africa The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at unspecified for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	600 µg of p.o. misoprostol vs. placebo	• PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Nausea • Vomiting • Fever • Shivering • Abdominal pain	High risk of bias
Hofmeyr *et al.*, 2011[101]	Two-arm placebo-controlled randomised trial	There were 1103 parturients randomised in a hospital setting in South Africa, Uganda and Nigeria The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section or instrumental delivery, or those who declined participation or were unable to consent, were too ill or distressed to participate or with an unviable pregnancy	400 µg of s.l. misoprostol plus 10 IU of i.m. oxytocin vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Manual removal of placenta • Death • Blood loss (ml) • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Høj *et al.*, 2005[102]	Two-arm placebo-controlled randomised trial	There were 661 parturients randomised in a community setting in Guinea-Bissau The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	600 µg of s.l. misoprostol vs. placebo	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Fever • Shivering	Low risk of bias
Hong *et al.*, 2007[103]	Two-arm placebo-controlled randomised trial	There were 214 parturients randomised in a hospital setting in Korea The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by caesarean (unspecified whether elective or emergency) Exclusion criteria were not specified	20 IU of i.v. oxytocin (infusion) vs. 400 µg of p.r. misoprostol plus 10 IU of i.v. oxytocin (infusion)	• Additional uterotonics • Transfusion • Change in Hb levels • Fever • Shivering	High risk of bias
Is *et al.*, 2012[104]	Two-arm active-controlled randomised trial	There were 200 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	400 µg of p.r. misoprostol vs. an unspecified dose of i.m. ergometrine	• Third-stage duration (minutes) • Nausea • Vomiting • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Jago *et al.*, 2007[105]	Two-arm active-controlled randomised trial	There were 510 parturients randomised in a hospital setting in Nigeria The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction or augmentation of labour or instrumental delivery, or those requiring epidural analgesia or with hypertension in pregnancy, existing hypertension, chronic renal disease, diabetes mellitus, vascular diseases, cardiac disease, anticoagulation therapy or allergy to ergometrine or oxytocin	500 µg of i.m. ergometrine vs. 10 IU of i.v. oxytocin (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Blood loss (ml) • Hypertension	High risk of bias
Jangsten *et al.*, 2011[106]	Two-arm controlled randomised trial	There were 1802 parturients randomised in a hospital setting in Sweden The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing elective caesarean section, or those who were non-Swedish speaking or with previous PPH, pre-eclampsia, grand multiparity (> four) or intrauterine death	10 IU of i.v. oxytocin (bolus) vs. no treatment	• PPH blood loss of ≥ 1000 ml • Transfusion • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes)	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Jerbi *et al.*, 2007[107]	Two-arm controlled randomised trial	There were 130 parturients randomised in a hospital setting in Tunisia The population comprised women of parity ≤ 5, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with placenta praevia, antepartum haemorrhage, non-cephalic presentation, intrauterine death, grand multiparity, (more than five), fibroids, anticoagulation therapy, previous PPH or previous caesarean section	5 IU of i.v. oxytocin (bolus) vs. no treatment	• PPH blood loss of ≥ 1000 ml • Transfusion • Manual removal of placenta • Death • Change in Hb levels • Third-stage duration (minutes)	High risk of bias
Jirakulsawas and Khooarmompattana, 2000[108]	Two-arm active-controlled randomised trial	There were 140 parturients randomised in a hospital setting in Thailand The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at unspecified for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	600 µg of p.o. misoprostol vs. 200 µg of i.m. ergometrine	• PPH blood loss of ≥ 500 ml • Blood loss (ml)	High risk of bias
Karkanis *et al.*, 2002[109]	Two-arm active-controlled randomised trial	There were 238 parturients randomised in a hospital setting in Canada The population comprised women of parity ≤ 5, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with coagulopathy, anticoagulation therapy, previous PPH or previous caesarean section	400 µg of p.r. misoprostol vs. 5 IU of i.v. oxytocin (bolus) or i.m.	• Additional uterotonics • Transfusion • Manual removal of placenta • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Headache • Fever • Shivering • Abdominal pain	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Kerekes and Domokos, 1979[110]	Three-arm controlled randomised trial	There were 140 parturients randomised in a hospital setting in Hungary The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at unspecified for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	200 µg of i.v. ergometrine (bolus) vs. no treatment	• Third-stage duration (minutes)	High risk of bias
Khan *et al.*, 1995[111]	Two-arm active-controlled double-blind randomised trial	There were 2040 parturients randomised in a hospital setting in the United Arab Emirates The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction or augmentation of labour, caesarean section or instrumental delivery, or requiring general anaesthesia, epidural or diazepam, or those with antenatal hypertension (≥ 160/100 mmHg), hypertension on antihypertensive drugs, multiple pregnancy, cardiac disease or a Hb level of ≤ 90 g/l	10 IU of i.m. oxytocin vs. 500 µg of ergometrine plus 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Transfusion • Manual removal of placenta • Vomiting • Headache	High risk of bias
Kumru *et al.*, 2005[112]	Two-arm active-controlled randomised trial	There were 55 parturients randomised in a hospital setting in Turkey The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean section Exclusion criteria comprised parturients with multiple pregnancy, hypertension or vascular diseases	10 IU of i.v. oxytocin (bolus plus infusion) vs. 200 µg of ergometrine plus 10 IU of i.v. oxytocin (bolus plus infusion)	• Blood loss (ml)	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Kundodyiwa *et al.*, 2001[113]	Two-arm placebo-controlled randomised trial	There were 500 parturients randomised in a hospital setting in Zimbabwe The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing instrumental delivery, or those with previous PPH, antepartum haemorrhage, coagulopathy, multiple pregnancy, asthma or allergies to prostaglandins or oxytocin	400 µg of p.o. misoprostol vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Third-stage duration (minutes) • Nausea • Vomiting • Fever • Shivering	High risk of bias
Lam *et al.*, 2004[114]	Two-arm active-controlled randomised trial	There were 60 parturients randomised in a hospital setting in Hong Kong The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction or augmentation of labour, or those with antepartum haemorrhage, anaemia, two or more surgical terminations, previous manual removal of placenta, previous PPH or previous third-stage complications	500 µg of ergometrine plus 5 IU of i.v. oxytocin (bolus) vs. 600 µg of s.l. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Manual removal of placenta • Death • Fever	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Lapaire *et al.*, 2006[115]	Two-arm active-controlled double-blind randomised trial	There were 56 parturients randomised in a hospital setting in Switzerland The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients undergoing emergency caesarean section, or those with fetal distress, fetal malformations, pre-eclampsia, HELLP syndrome, coagulopathy, severe systemic disorders, an American Society of Anaesthetists physical status of ≥ III, severe asthma, previous myomectomy, pyrexia (i.e. > 38.5 °C) or hypersensitivity to prostaglandins	25 IU of i.v. oxytocin (bolus plus infusion) vs. 800 µg of p.o. misoprostol plus 5 IU of i.v. oxytocin (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Nausea • Headache • Shivering	High risk of bias
Leung *et al.*, 2006[116]	Two-arm active-controlled double-dummy randomised trial	There were 329 parturients randomised in a hospital setting in Hong Kong The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients requiring prophylactic oxytocin infusion, or those with pre-existing hypertension, pre-eclampsia, asthma, cardiac/renal/liver diseases, grand multiparity or fibroids	100 µg of i.m. carbetocin vs. 500 µg of ergometrine plus 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Hypertension • Headache • Tachycardia • Shivering	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Lokugamage *et al.*, 2001[117]	Two-arm active-controlled randomised trial	There were 40 parturients randomised in a hospital setting in UK The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean section Exclusion criteria comprised parturients with two or more previous caesarean sections or previous uterine rupture	10 IU of i.v. oxytocin (bolus) vs. 500 µg of p.o. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels • Fever • Shivering	High risk of bias
Lumbiganon *et al.*, 1999[118]	Three-arm active-controlled double-dummy randomised trial	There were 597 parturients randomised in a hospital setting in South Africa and Thailand The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing elective caesarean section or abortion, or those with asthma, other severe chronic allergic conditions a contraindication to the use of misoprostol or if they were not willing or able to give informed consent	600 µg or 400 µg of p.o. misoprostol vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Nausea • Vomiting • Fever • Shivering	Low risk of bias
Maged *et al.*, 2015[119]	Two-arm active-controlled double-dummy randomised trial	There were 200 parturients randomised in a hospital setting in Egypt The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with placenta praevia, coagulopathy, pre-eclampsia, cardiac/renal/liver disorders, epilepsy or known hypersensitivity to oxytocin or carbetocin	100 µg of i.m. carbetocin vs. 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Headache • Tachycardia • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
McDonald *et al.*, 1993[120]	Two-arm active-controlled double-blind randomised trial	There were 3497 parturients randomised in a hospital setting in Australia The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing emergency or elective caesarean section, or requiring general anaesthetic for instrumental delivery, or those with hypertension in labour (i.e. >150/100 mmHg), antenatal hypertension, maternal distress, advanced stage in labour, language barrier, fetal abnormality, intrauterine death or medical disorder	500 µg of ergometrine plus 5 IU of i.m. oxytocin vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • NNU admissions • Breastfeeding • Nausea • Vomiting	Low risk of bias
Mitchell *et al.*, 1993[121]	Two-arm active-controlled double-blind randomised trial	There were 461 parturients randomised in a hospital setting in the UK The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing elective caesarean section, or those with significant hypertension or cardiac disease	500 µg of ergometrine plus 5 IU of i.m. oxytocin vs. 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Manual removal of placenta • Blood loss (ml) • Third-stage duration (minutes)	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Mobeen *et al.*, 2011[122]	Two-arm placebo-controlled randomised trial	There were 1119 parturients randomised in a community setting in Pakistan The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with hypertension, non-cephalic presentation, polyhydramnios, previous caesarean section, multiple pregnancy, intrauterine death, antepartum haemorrhage or a Hb level of > 80 g/l	600 µg of p.o. misoprostol vs. placebo	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Headache • Fever • Shivering	Low risk of bias
Moertl *et al.*, 2011[123]	Two-arm active-controlled double-blind randomised trial	There were 84 parturients randomised in a hospital setting in Austria The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients requiring general anaesthesia, or those with placenta praevia, placental abruption, multiple pregnancy, pre-eclampsia, gestational diabetes mellitus, pre-existing insulin-dependent diabetes mellitus, cardiovascular/renal disorders, hypo/hyperthyroidism or women on cardiovascular system medications	100 µg of i.v. carbetocin (bolus) vs. 5 IU of i.v. oxytocin (bolus)	• Additional uterotonics • Change in Hb levels • Nausea • Headache	High risk of bias
Moir and Amoa, 1979[124]	Two-arm active-controlled randomised trial	There were 88 parturients randomised in a hospital setting in the UK The population comprised women who were primigravid, of a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	500 µg of i.v. ergometrine (bolus) vs. 10 IU of i.v. oxytocin (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Blood loss (ml) • Nausea	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Moodie and Moir, 1976[125]	Two-arm active-controlled randomised trial	There were 148 parturients randomised in a hospital setting in the UK The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	500 µg of i.v. ergometrine (bolus) vs. 5 IU of i.v. oxytocin (bolus)	• PPH blood loss of ≥ 500 ml • Blood loss (ml) • Nausea	High risk of bias
Mukta and Sahay, 2013[126]	Two-arm active-controlled randomised trial	There were 200 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing emergency or elective caesarean section, or those with eclampsia, asthma, epilepsy, cardiac/kidney disorder or coagulopathy	600 µg of p.o. misoprostol vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Nausea • Vomiting • Fever • Shivering • Abdominal pain	High risk of bias
Musa *et al.*, 2015[127]	Two-arm active-controlled double-dummy randomised trial	There were 235 parturients randomised in a hospital setting in Nigeria The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing planned instrumental birth, or those who received oxytocin and/or misoprostol other than in the third stage of labour, or those with grand multiparity (more than four), multiple pregnancy, fibroids, polyhydramnios, pre-eclampsia, eclampsia, hypertension, cardiac disorder, asthma, antepartum haemorrhage previous PPH, prolonged rupture of membranes or a Hb level of < 100 g/l	600 µg of p.o. misoprostol vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • Morbidity • Additional uterotonics • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Nasr *et al.*, 2009[128]	Two-arm active-controlled double-dummy randomised trial	There were 514 parturients randomised in a hospital setting in Egypt The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with antepartum haemorrhage, coagulopathy, hypertension in pregnancy or the need for anticoagulants	800 µg of p.r. misoprostol vs. 5 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Third-stage duration (minutes) • Nausea • Vomiting • Fever • Shivering	Low risk of bias
Ng *et al.*, 2001[129]	Two-arm active-controlled randomised trial	There were 2058 parturients randomised in a hospital setting in Hong Kong The population comprised women of parity ≤ 3, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients requiring oxytocin infusion in the third stage of labour, or those with pre-eclampsia, cardiac disorder, asthma, grand multiparity (> 3), fibroids or contraindications to the use of either misoprostol or Syntometrine	600 µg of p.o. misoprostol vs. 500 µg of ergometrine plus 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Hypertension • Headache • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Ng *et al.*, 2007[130]	Two-arm active-controlled double-dummy randomised trial	There were 360 parturients randomised in a hospital setting in Hong Kong The population comprised women of parity ≤ 3, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients requiring oxytocin infusion in the third stage, or those with pre-eclampsia, cardiac disorder, asthma, grand multiparity (> 3), fibroids or contraindications to the use of either misoprostol or Syntometrine	400 µg of p.o. misoprostol vs. 500 µg of ergometrine plus 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Hypertension • Headache • Fever • Shivering	Low risk of bias
Nirmala *et al.*, 2009[131]	Two-arm active-controlled randomised trial	There were 120 parturients randomised in a hospital setting in Malaysia The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients aged < 18 years, or those with cardiac disorder, hypertension requiring treatment, liver/renal/vascular/endocrine disorder (excluding gestational diabetes mellitus) or hypersensitivity to oxytocin or carbetocin	100 µg of i.m. carbetocin vs. 500 µg of ergometrine plus 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Hypertension • Headache • Shivering • Abdominal pain	High risk of bias
Nordström *et al.*, 1997[132]	Two-arm placebo-controlled randomised trial	There were 1000 parturients randomised in a hospital setting in Sweden The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	10 IU of i.v. oxytocin (bolus) vs. placebo	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Third-stage duration (minutes)	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Oboro and Tabowei, 2003[133]	Two-arm active-controlled double-dummy randomised trial	There were 496 parturients randomised in a hospital setting in Nigeria The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction or augmentation of labour, or those with previous caesarean, a Hb level of < 80 g/l, previous PPH, grand multiparity (not defined), multiple pregnancy, polyhydramnios, fibroids or precipitate labour	10 IU of i.m. oxytocin vs. 600 µg of p.o. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Fever • Shivering	Low risk of bias
Ogunbode *et al.*, 1979[134]	Three-arm active-controlled randomised trial	There were 144 parturients randomised in a hospital setting in Nigeria The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing instrumental delivery, or those with previous PPH, multiple pregnancy, polyhydramnios or vaginal lacerations	200 µg or 500 µg of i.m. ergometrine vs. 500 µg of ergometrine plus 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • Manual removal of placenta • Blood loss (ml)	High risk of bias
Orji *et al.*, 2008[135]	Two-arm active-controlled randomised trial	There were 600 parturients randomised in a hospital setting in Nigeria The population comprised women of parity ≤ 6, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with hypertension in pregnancy, a packed cell volume of < 30%, previous PPH, haemoglobinopathy or cardiac disorder	10 IU of i.v. oxytocin (bolus) vs. 250 µg of i.v. ergometrine (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Hypertension • Headache	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Ortiz-Gómez *et al.*, 2013[136]	Three-arm active-controlled randomised trial	There were 156 parturients randomised in a hospital setting in Spain The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients with comorbidities, refractory hypotension caused by neuraxial blockage, vasoactive drugs needed to control haemodynamic issues or multiple pregnancy	100 µg of i.v. carbetocin (bolus) vs. 61 IU of i.v. oxytocin (bolus plus infusion)	• Additional uterotonics • Nausea • Vomiting • Headache • Shivering	High risk of bias
Owonikoko *et al.*, 2011[137]	Two-arm active-controlled randomised trial	There were 100 parturients randomised in a hospital setting in Nigeria The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean Exclusion criteria comprised parturients requiring general anaesthesia, or those with multiple pregnancy, placenta praevia, antepartum haemorrhage, cardiac/renal/liver disorders, coagulopathy, asthma, glaucoma, pre-eclampsia, eclampsia, prolonged labour or contraindications to administration of prostaglandins	20 IU of i.v. oxytocin (infusion) vs. 400 µg of s.l. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Headache • Hypotension • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Parsons *et al.*, 2006[138]	Two-arm active-controlled randomised trial	There were 450 parturients randomised in a hospital setting in Ghana The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with asthma, epilepsy or contraindications to prostaglandins	10 IU of i.m. oxytocin vs. 800 µg of p.o. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Hypertension • Fever • Shivering	High risk of bias
Parsons *et al.*, 2007[139]	Two-arm active-controlled randomised trial	There were 450 parturients randomised in a hospital setting in Ghana The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with asthma, epilepsy or contraindications to prostaglandins	10 IU of i.m. oxytocin vs. 800 µg of p.r. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Hypertension • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Penaranda *et al.*, 2002[140]	Three-arm active-controlled randomised trial	There were 78 parturients randomised in a hospital setting in Colombia The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with asthma, multiple pregnancy, intrauterine death, coagulopathy, cervical tear or water in the blood collector	50 µg of s.l. misoprostol vs. 16 mIU/minute of i.v. oxytocin (infusion) vs. 200 µg of i.m. ergometrine	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Blood loss (ml) • Third-stage duration (minutes) • Vomiting • Shivering	High risk of bias
Prendiville *et al.*, 1988[141]	Two-arm controlled randomised trial	There were 1695 parturients randomised in a hospital setting in UK The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with cardiac disorder, antepartum haemorrhage, non-cephalic presentation, multiple pregnancy and intrauterine death, but after change in the protocol multiple other exclusion criteria were introduced	500 µg of ergometrine plus 5 IU of i.m. oxytocin vs. no treatment	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Change in Hb levels • NNU admissions • Breastfeeding • Vomiting • Headache	High risk of bias
Rajaei *et al.*, 2014[142]	Two-arm active-controlled double-dummy randomised trial	There were 400 parturients randomised in a hospital setting in Iran The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with placenta praevia, placental abruption, coagulopathy, previous caesarean section, macrosomia (i.e. > 4 kg), polyhydramnios or uncontrolled asthma	20 IU of i.v. oxytocin (infusion) vs. 400 µg of p.o. misoprostol	• Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels • Hypotension • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Rashid *et al.*, 2009[143]	Two-arm active-controlled randomised trial	There were 686 parturients randomised in a hospital setting in Saudi Arabia The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section or requiring oxytocin infusion in the third stage, or those with pre-eclampsia, cardiac disorder, hypertension on treatment, antepartum haemorrhage, pre-term labour (i.e. < 37 weeks' gestation), post maturity (i.e. > 42 weeks' gestation) or a Hb level of ≤ 90 g/l	500 µg of ergometrine plus 5 IU of i.m. oxytocin vs. 10 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Third-stage duration (minutes) • Nausea • Vomiting • Headache	High risk of bias
Ray *et al.*, 2001[144]	Two-arm active-controlled randomised trial	There were 200 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing elective caesarean section, or those with pre-term labour (i.e. > 32 weeks' gestation), prolonged labour, antepartum haemorrhage, pre-eclampsia, intrauterine death, multiple pregnancy, epilepsy, asthma, cardiac/kidney disorder, coagulopathy or anaemia	400 µg of p.o. misoprostol vs. an unspecified dose and route of ergometrine	• Additional uterotonics • Transfusion • Manual removal of placenta • Hypertension	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Reyes, 2011[145]	Two-arm active-controlled randomised trial	There were 144 parturients randomised in a hospital setting in Panama The population comprised women of parity ≥ 5, a singleton pregnancy, at high risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing emergency caesarean section, or those with coagulopathy, unknown parity or known allergy to carbetocin	100 µg of i.v. carbetocin (bolus) vs. 20 IU of i.v. oxytocin (infusion)	• Additional uterotonics • Transfusion • Manual removal of placenta • Breastfeeding • Nausea • Vomiting • Headache • Shivering • Abdominal pain	High risk of bias
Reyes and Gonzalez, 2011[146]	Two-arm active-controlled double-dummy randomised trial	There were 57 parturients randomised in a hospital setting in Panama The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by both caesarean section and vaginal delivery Exclusion criteria comprised parturients with HELLP syndrome, blood dyscrasia or multiple pregnancy	100 µg of i.v. carbetocin (bolus) vs. 10 IU of i.v. oxytocin (infusion)	• Additional uterotonics • Transfusion • Change in Hb levels • Third-stage duration (minutes) • Breastfeeding • Vomiting • Headache • Fever	Low risk of bias
Rogers *et al.*, 1998[147]	Two-arm controlled randomised trial	There were 1512 parturients randomised in a hospital setting in UK The population comprised women of parity ≤ 5, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing augmentation of labour or instrumental delivery or requiring epidural analgesia, or those with placenta praevia, previous PPH, antepartum haemorrhage, a Hb level of < 100 g/l or mean corpuscular volume of < 75 fl, non-cephalic presentation, multiple pregnancy, intrauterine death, grand multiparity (more than five), fibroids, anticoagulation therapy, pre-term labour (i.e. < 32 weeks' gestation) or contraindications to any of the drugs	Unspecified dose of ergometrine plus i.m. oxytocin vs. no treatment	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • NNU admissions • Breastfeeding • Nausea • Vomiting • Headache	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Rosseland *et al.*, 2013[148]	hree-arm placebo-controlled randomised trial	There were 76 parturients randomised in a hospital setting in Norway The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section Exclusion criteria comprised parturients with pre-eclampsia, placenta praevia, placenta accreta, von Willebrand disease or other bleeding disorder or a preoperative systolic arterial pressure of < 90 mmHg	5 IU of i.v. oxytocin (bolus) vs. 100 µg of i.v. carbetocin (bolus) vs. placebo	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Blood loss (ml) • Change in Hb levels • Headache	Low risk of bias
Rozenberg *et al.*, 2015[149]	Two-arm placebo-controlled randomised trial	There were 1721 parturients randomised in a hospital setting in France The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing emergency caesarean section, or those with known hypersensitivity to prostaglandins	400 µg of p.o. misoprostol plus 10 IU of i.v. oxytocin (bolus) vs. 10 IU of i.v. oxytocin (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Death • Fever • Shivering	High risk of bias
Sadiq *et al.*, 2011[150]	Two-arm active-controlled randomised trial	There were 1865 parturients randomised in a hospital setting in Nigeria The population comprised women of parity ≤ 6, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing instrumental delivery, or those with diabetes mellitus, non-cephalic presentation, anaemia, antepartum haemorrhage, multiple pregnancy, grand multiparity (> six) or known allergy	10 IU of i.v. oxytocin (bolus) vs. 600 µg of p.o. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Samimi *et al.*, 2013[151]	Two-arm active-controlled double-blind randomised trial	There were 216 parturients randomised in a hospital setting in Iran The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with hypertension, pre-eclampsia, uterine rupture, cervical tear, asthma, cardiovascular/renal/liver disorders, grand multiparity (not defined), fibroids or previous PPH	100 µg of i.m. carbetocin vs. 200 µg of ergometrine plus 5 IU of i.m. oxytocin	• Morbidity • Additional uterotonics • Death • Change in Hb levels • Nausea • Vomiting • Tachycardia • Hypotension • Shivering • Abdominal pain	High risk of bias
Shrestha *et al.*, 2011[152]	Two-arm active-controlled randomised trial	There were 200 parturients randomised in a hospital setting in Nepal The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with polyhydramnios, chorioamnionitis, preterm labour, previous caesarean, asthma, cardiac disorder or contraindication/hypersensitivity to the use of prostaglandin and uterotonics	1000 µg of p.r. misoprostol vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • Morbidity • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Fever • Abdominal pain	High risk of bias
Singh *et al.*, 2009[153]	Four-arm active-controlled double-dummy randomised trial	There were 300 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing augmentation of labour, or those with intrauterine death, antepartum haemorrhage, multiple pregnancy, malpresentation, cardiac disorder, Rhesus-negative mother, hypertension, a Hb level of < 70 g/l or hypersensitivity/contraindication to prostaglandins	400 µg or 600 µg of s.l. misoprostol vs. 5 IU of i.v. oxytocin (bolus) vs. 200 µg of i.v. ergometrine (bolus)	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Third-stage duration (minutes) • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Soltan *et al.*, 2007[154]	Four-arm active-controlled randomised trial	There were 1228 parturients randomised in a hospital setting in Egypt The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with traumatic PPH, blood disorders, chorioamnionitis, placenta praevia or placental abruption	200 µg of i.m. ergometrine vs. 600–1000 µg of s.l. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Vomiting • Fever • Shivering	High risk of bias
Sood and Singh, 2012[155]	Two-arm placebo-controlled randomised trial	There were 174 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean Exclusion criteria were not specified	400 µg of s.l. misoprostol plus 20 IU of i.v. oxytocin (infusion) vs. 20 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Change in Hb levels • Nausea • Vomiting • Fever • Shivering	Low risk of bias
Stanton *et al.*, 2013[156]	Two-arm cluster-controlled randomised trial	There were 1586 parturients randomised in a community setting in Ghana The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	10 IU of i.m. oxytocin vs. no treatment	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Death	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Su *et al.*, 2009[157]	Two-arm active-controlled double-blind randomised trial	There were 370 parturients randomised in a hospital setting in Singapore The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing elective caesarean section, or those with multiple pregnancy, previous PPH, coagulopathy, coronary artery disease, hypertension or hypersensitivity/ contraindications to the use of Syntometrine or carbetocin	100 µg of i.m. carbetocin vs. 500 µg of ergometrine plus 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Third-stage duration (minutes) • Nausea • Vomiting • Headache • Shivering • Abdominal pain	Low risk of bias
Sultana and Khatun, 2007[158]	Two-arm active-controlled randomised trial	There were 400 parturients randomised in a hospital setting in Bangladesh The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with previous caesarean	400 µg of p.o. misoprostol vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Shivering • Abdominal pain	High risk of bias
Surbek *et al.*, 1999[159]	Two-arm placebo-controlled randomised trial	There were 65 parturients randomised in a hospital setting in Switzerland The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with multiple pregnancy, pre-eclampsia, previous PPH or antepartum haemorrhage	600 µg of p.o. misoprostol vs. placebo	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • NNU admissions • Shivering	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Tewatia *et al.*, 2014[160]	Two-arm active-controlled randomised trial	There were 100 parturients randomised in a hospital setting in India The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with grand multiparity (> 4), anaemia, malpresentation, polyhydramnios, antepartum haemorrhage, liver/renal disorder, previous caesarean, previous PPH, uterine anomaly, traumatic PPH or contraindications to the use of misoprostol or oxytocin	10 IU of i.v. oxytocin (infusion) vs. 600 µg of s.l. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Fever • Shivering	High risk of bias
Thilaganathan *et al.*, 1993[161]	Two-arm controlled randomised trial	There were 193 parturients randomised in a hospital setting in the UK The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction or augmentation of labour or instrumental delivery, or those with grand multiparity (not defined), malpresentation, multiple pregnancy, previous caesarean, previous PPH, antepartum haemorrhage, hypertension in pregnancy, intrauterine death, preterm rupture of membranes, cervical lacerations or third-degree perineal tears	500 µg of ergometrine plus 5 IU of i.m. oxytocin vs. no treatment	• Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes)	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Ugwu *et al.*, 2014[162]	Two-arm active-controlled randomised trial	There were 120 parturients randomised in a hospital setting in Nigeria The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean Exclusion criteria comprised parturients requiring general anaesthesia, or those with multiple pregnancy, placenta praevia, pre-eclampsia, eclampsia, undiagnosed vaginal bleeding, prolonged labour, prolonged obstructed labour, cardiac/renal/liver disorders or fever	400 µg of s.l. misoprostol plus 20 IU of oxytocin (infusion) vs. 20 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Death • Blood loss (ml) • Change in Hb levels • Fever • Shivering	High risk of bias
Un Nisa *et al.*, 2012[163]	Two-arm active-controlled randomised trial	There were 100 parturients randomised in a hospital setting in India The population comprised women of parity 2–4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with previous PPH, multiple pregnancy, previous caesarean section, macrosomia, pre-eclampsia, diabetes mellitus, cardiac/lung/bleeding/clotting disorders or taking anticoagulants	10 IU of i.v. oxytocin (bolus) vs. 500 µg of ergometrine plus 5 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Uncu *et al.*, 2015[164]	Five-arm controlled randomised trial	There were 248 parturients randomised in a hospital setting in Turkey The population comprised women of parity ≤ 5, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those with placenta praevia, previous PPH, antepartum haemorrhage, non-cephalic presentation, multiple pregnancy, intrauterine death, grand multiparity (more than five), fibroids, pre-eclampsia or anticoagulation therapy	400–800 µg of p.o. misoprostol, p.v. or p.r. vs. no treatment	• Additional uterotonics • Transfusion • Third-stage duration (minutes) • Shivering • Abdominal pain	High risk of bias
Vagge *et al.*, 2014[165]	Two-arm active-controlled randomised trial	There were 200 parturients randomised in a hospital setting in India The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those women with cardiac disorder in pregnancy, uterine tumour in pregnancy, secondary PPH, grand multiparity (not defined), multiple pregnancy, polyhydramnios, anaemia, coagulopathy, antepartum haemorrhage, previous PPH, prolonged labour, precipitate labour or known allergic or hypersensitivity reaction to prostaglandins	10 IU of i.v. oxytocin (infusion) vs. 800 µg of p.r. misoprostol	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Blood loss (ml) • Nausea • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Vaid *et al.*, 2009[166]	Three-arm active-controlled randomised trial	There were 200 parturients randomised in a hospital setting in India The population comprised women of parity ≤ 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients with grand multiparity (> 4), multiple pregnancy, preterm labour (i.e. < 32 weeks' gestation), HELLP syndrome, polyhydramnios, coagulopathy, asthma, cardiac/renal disorder, epilepsy, hypertension, a Hb level of < 80 g/l or known drug allergy	400 µg of s.l. misoprostol vs. 200 µg of i.m. ergometrine	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Nausea • Vomiting • Fever • Shivering • Abdominal pain	High risk of bias
Verma *et al.*, 2006[167]	Two-arm active-controlled double-dummy randomised trial	There were 200 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria were not specified	400 µg of s.l. misoprostol vs. 200 µg of i.m. ergometrine	• PPH blood loss of ≥ 500 ml • Additional uterotonics • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Fever • Shivering	High risk of bias
Vimala *et al.*, 2004[168]	Two-arm active-controlled randomised trial	There were 120 parturients randomised in a hospital setting in India The population comprised women of parity < 5, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction or augmentation of labour or caesarean section, or those with preterm labour (i.e. < 37 weeks' gestation), grand multiparity (> 5), multiple pregnancy, hypertension in pregnancy, a Hb level of < 80 g/l or known hypersensitivity to prostaglandins	400 µg of s.l. misoprostol vs. 200 µg of i.v. ergometrine (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Headache • Fever • Shivering	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Vimala *et al.*, 2006[169]	Two-arm active-controlled randomised trial	There were 100 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective or emergency caesarean Exclusion criteria comprised parturients with multiple pregnancy, antepartum haemorrhage, polyhydramnios, prolonged labour (i.e. > 12 hours), more than one previous caesarean section, previous uterine rupture, cardiac/liver/renal disorder, coagulopathy or a Hb level of < 80 g/l	400 µg of s.l. misoprostol vs. 20 IU of i.v. oxytocin (infusion)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Blood loss (ml) • Change in Hb levels • Vomiting • Headache • Fever • Shivering	High risk of bias
Walley *et al.*, 2000[170]	Two-arm active-controlled double-dummy randomised trial	There were 401 parturients randomised in a hospital setting in Ghana The population comprised women of parity ≤ 5, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing induction or augmentation of labour or caesarean section, or those with grand multiparity (> 5), multiple pregnancy, preterm labour (i.e. < 32 weeks' gestation), hypertension in pregnancy, HELLP syndrome, polyhydramnios, previous PPH, coagulopathy, precipitate labour, chorioamnionitis, a Hb level of < 80 g/l or a known hypersensitivity to prostaglandins	400 µg of p.o. misoprostol vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Fever • Shivering	Low risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Whigham *et al.*, 2014[171]	Two-arm active-controlled double-blind randomised trial	There were 58 parturients randomised in a hospital setting in Australia The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by emergency caesarean section Exclusion criteria comprised parturients undergoing elective caesarean section or requiring general anaesthesia, or those with vascular/liver/renal disorders, preterm labour (i.e. < 37 weeks' gestation), placenta praevia, placental abruption, previously more than two caesarean sections or an adverse reaction to carbetocin or oxytocin	100 µg of i.v. carbetocin (bolus) vs. 5 IU of i.v. oxytocin (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Blood loss (ml) • Change in Hb levels	High risk of bias
Yuen *et al.*, 1995[172]	Two-arm active-controlled double-blind randomised trial	There were 1000 parturients randomised in a hospital setting in Hong Kong The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients requiring oxytocin infusion in the third stage of labour or those with pre-eclampsia or cardiac disorder	500 µg of ergometrine plus 5 IU of i.m. oxytocin vs. 10 IU of i.m. oxytocin	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Morbidity • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Change in Hb levels • Nausea • Vomiting • Headache	High risk of bias

Study (author and year of publication)	Methods	Participants	Interventions	Outcomes	Quality rating
Zachariah *et al.*, 2006[173]	Three-arm active-controlled randomised trial	There were 2023 parturients randomised in a hospital setting in India The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery Exclusion criteria comprised parturients undergoing caesarean section, or those women with asthma, cardiac disorder, rhesus factor incompatibility or hypertension	400 µg of p.o. misoprostol vs. 10 IU of i.m. oxytocin vs. 200 µg of i.v. ergometrine (bolus)	• PPH blood loss of ≥ 500 ml • PPH blood loss of ≥ 1000 ml • Additional uterotonics • Transfusion • Manual removal of placenta • Death • Blood loss (ml) • Change in Hb levels • Third-stage duration (minutes) • Nausea • Vomiting • Headache • Fever • Shivering	High risk of bias

APH, antepartum haemorrhage; BMI, body mass index; HELLP, complication of pregnancy characterised by Haemolysis, Elevated Liver enzymes and a Low Platelet count; i.m., intramuscular(ly); i.v., intravenous(ly); NNU, neonatal unit; p.o., per os (by mouth); p.r., per rectum; PROM, premature rupture of membranes; p.v., per vagina; s.l., sublingual.

Appendix 3 Reference list for excluded studies

Abdel-Aleem 1993

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Appendix 4 Characteristics of excluded studies

Author	Year	Reason for exclusion
Abdel-Aleem	1993	Not eligible intervention
Abdel-Aleem	1997	Not eligible intervention
Abdel-Aleem	1997a	Not eligible intervention
Abdel-Aleem	1997a	Not eligible intervention
Abdel-Aleem	2013	Not eligible intervention
Abdollahy	2000	Not eligible intervention
Al-Harazi	2009	Same drug intervention used in both arms and only different route of misoprostol administration
Anandakrishnan	2013	Same drug intervention used in both arms and only different dose of carbetocin administration
Anjaneyulu	1988	Not eligible intervention
Anvaripour	2013	Intervention given after the third stage of labour
Athavale	1991	Not eligible intervention
Ayedi	2011	Not eligible intervention
Ayedi	2011a	Same drug intervention used in both arms and only different dose of oxytocin administration
Aziz	2014	Quasi-randomised
Bader	2000	Not eligible intervention
Bader	2000a	Not eligible intervention
Badhwar	1991	Not eligible intervention
Bai	2014	Not eligible uterotonic
Balki	2005	Same drug intervention used in both arms and only different dose of oxytocin administration
Balki	2006	Same drug intervention used in both arms and only different dose of oxytocin administration
Banovska	2013	Not eligible intervention
Barbaro	1961	Not eligible intervention
Baumgarten	1983	Not eligible uterotonic
Bhattacharya	1988	Not eligible uterotonic
Bhavana	2013	Not eligible intervention
Bider	1991	Not eligible intervention
Bider	1992	Not eligible intervention
Bisri	2011	Same drug intervention used in both arms and only different route of oxytocin administration
Biswas	2007	Not eligible uterotonic
Bivins	1993	Not eligible uterotonic
Bivins	1993a	Not eligible uterotonic
Blum	2010	Intervention for treatment of PPH
Bonham	1963	Quasi-randomised
Bonis	2012	Quasi-randomised
Cappiello	2006	Not eligible intervention

Author	Year	Reason for exclusion
Carvalho	2004	Same drug intervention both arms and only different dose of oxytocin administration
Catanzarite	1990	Not eligible intervention
Chaplin	2009	Not eligible intervention
Chaudhuri	2014	Inappropriate population (excluded women who had PPH)
Chestnut	1987	Not eligible intervention
Chestnut	1987a	Not eligible intervention
Chou	1994	Not eligible intervention
Chua	1995	Not eligible intervention
Chukudebelu	1963	Quasi-randomised
Cooper	2004	Same drug intervention used in both arms and only different dose of oxytocin administration
Cordovani	2012	Same drug intervention used in both arms and only different dose of carbetocin administration
Dagdeviren	2014	Same drug intervention used in both arms and only different route of oxytocin administration
Dahiya	1995	Not eligible intervention
Daley	1951	Quasi-randomised
Daly	1999	Not able to extract outcomes
Dao	2009	Intervention for treatment of PPH
Davies	2005	Same drug intervention used in both arms and only different route of oxytocin administration
De bonis	2012	Quasi-randomised
Dennehy	1998	Same drug intervention used in both arms and only different route of oxytocin administration
Devi	1988	Not eligible intervention
Diab	1999	Quasi-randomised
Dickinson	2009	Not eligible population (terminations in second trimester)
Dommisse	1980	Not randomised
Dong	2011	Not eligible intervention
Durocher	2012	Quasi-randomised
Dutta	2000	Quasi-randomised
Dweck	2000	Not eligible intervention
Dzuba	2012	Same drug intervention used in both arms and only different route of oxytocin administration
Elati	2011	Same drug intervention used in both arms and only different route of misoprostol administration
Erkkola	1984	Not eligible intervention
Farber	2013	Not eligible intervention
Farber	2015	Not eligible intervention
Fatemeh	2011	Same drug intervention used in both arms and only different route of oxytocin administration
Fawole	2011	The intervention was oxytocin or ergometrine plus oxytocin and data were not given for each of the drugs separately
Fawzy	2012	Treatment (not prevention) of PPH

Author	Year	Reason for exclusion
Forster	1957	Quasi-randomised
Francis	1965	Quasi-randomised
Francis	1965a	Quasi-randomised
Friedman	1957	Quasi-randomised
Frye	2012	Study abandoned
Fugo	1958	Quasi-randomised
Gai	2004	Not eligible intervention
Gambling	1994	Duplicate (abstract of Dansereau 1999)
Gambling	1994a	Duplicate (abstract of Dansereau 1999)
Gawecka	2014	Duplicate (abstract of Rosseland 2013)
Geller	2004	Duplicate (abstract of Derman 2006)
Geller	2008	Duplicate (secondary analysis from Derman 2006)
George	2010	Same drug intervention used in both arms and only different route of oxytocin administration
Ghulmiyyah	2005	Not eligible intervention
Ghulmiyyah	2007	Not eligible intervention
Gobbur	2011	Not eligible intervention
Gohel	2007	Not eligible intervention
Goswami	2013	Not eligible intervention
Groeber	1960	Not eligible intervention
Gungorduk	2010	Not eligible intervention
Gungorduk	2010a	Same drug intervention used in both arms and only different route of oxytocin administration
Gungorduk	2011	Not eligible intervention
Gungorduk	2013	Not eligible intervention
Gupta	2014	Not eligible intervention
Habek	2007	Not eligible intervention
Hacker	1979	No available outcomes
Halder	2013	Not eligible intervention
Hoffman	2004	Not appropriate intervention (comparing timing of oxytocin)
Hoffman	2006	Not appropriate intervention (comparing timing of oxytocin)
Hofmeyr	1997	Duplicate (interim analysis from Hofmeyr 1998)
Hofmeyr	1998a	Duplicate (from Hofmeyr 1998 and 2001)
Hofmeyr	2000	Duplicate (abstract from Hofmeyr 2001)
Hofmeyr	2004	Intervention for treating PPH
Hofmeyr	2008	Duplicate (trial registration for Hofmeyr 2011)
Howard	1964	Not eligible intervention
Huh	2000	Same drug intervention used in both arms and only different regimen of oxytocin administration
Huh	2004	Same drug intervention used in both arms and only different route of oxytocin administration

Author	Year	Reason for exclusion
Hunt	2013	Not eligible intervention
Häivä	1994	Quasi-randomised
Ilancheran	1990	No outcome data
Irons	1994	No outcome data
Jackson	2001	Not eligible intervention
Jiang	2001	Same drug intervention used in both arms and only different route of oxytocin administration
Jin	2000	Not eligible intervention
Jolivet	1978	Not eligible outcomes
Jonsson	2009	Same drug intervention used in both arms and only different route of oxytocin administration
Jonsson	2010	Same drug intervention used in both arms and only different route of oxytocin administration
Kashanian	2010	Ineligible population (excluded women with PPH)
Kemp	1963	Quasi-randomised
Khan	1997	Not eligible intervention
Khan	2003	Same drug intervention used in both arms and only different route of misoprostol administration
Khan	2012	Same drug intervention used in both arms and only different route of oxytocin administration
Khanun	2011	Same drug intervention used in both arms and only different route of misoprostol administration
Khurshid	2010	Not eligible intervention
Kikutani	2003	Not eligible outcomes
Kikutani	2003a	Not eligible outcomes
Kikutani	2006	Data cannot be extracted
King	2006	Same drug intervention used in both arms and only different route of oxytocin administration
King	2007	Same drug intervention used in both arms and only different route of oxytocin administration
King	2010	Same drug intervention used in both arms and only different route of oxytocin administration
Kintu	2012	Same drug intervention used in both arms and only different dose of oxytocin administration
Kiran	2012	Same drug intervention used in both arms and only different dose of oxytocin administration
Kore	2000	Not eligible intervention
Kovacheva	2015	Same drug intervention used in both arms and only different route of oxytocin administration
Kovavisarach	1996	Not eligible intervention
Kovavisarach	1998	Not eligible intervention
Kumar	2011	Not available outcomes
Kushtagi	2006	Not eligible intervention (carboprost)
Lamont	2001	Not eligible intervention (carboprost)
Le	2000	Not eligible intervention
Leader	2002	Not eligible population (second trimester)

Author	Year	Reason for exclusion
Li	2002	Not eligible intervention
Li	2003	Not eligible intervention
Li	2011	Not eligible intervention
Li	2011a	Not eligible intervention
Lin	2009	Not eligible intervention
Liu	1997	Not eligible intervention
Liu	2002	Not eligible intervention
Luamprapas	1994	Not eligible intervention
Mangla	2012	Not eligible intervention
Mankuta	2006	Not eligible intervention
Mansouri	2011	Same drug intervention used in both arms and only different route of misoprostol administration
Martinez	2006	Not eligible intervention
McGinty	1956	Quasi-randomised
Miller	2009	Not eligible intervention
Mirghafourvand	2013	Not eligible intervention
Mirghafourvand	2015	Not eligible intervention
Mobeen	2006	Duplicate (trial registration for Mobeen 2011)
Mobeen	2009	Duplicate (abstract for Mobeen 2011)
Moertl	2008	Duplicate (abstract of Moertl 2011)
Mollitt	2009	Same drug intervention used in both arms and only different route of oxytocin administration
Moore	1956	Same drug intervention used in both arms and only different type of the same drug
Mortl	2008	Duplicate (abstract of Moertl 2011)
Movafegh	2011	Not eligible intervention
Muller	1996	Outcome data cannot be extracted
Munishankarappa	2009	Same drug intervention used in both arms and only different route of oxytocin administration
Munn	2001	Same drug intervention used in both arms and only different route of oxytocin administration
Munn	2001a	Same drug intervention used in both arms and only different route of oxytocin administration
Murphy	2008	Same drug intervention used in both arms and only different route of oxytocin administration
Murphy	2009	Same drug intervention used in both arms and only different route of oxytocin administration
Murphy	2009a	Same drug intervention used in both arms and only different route of oxytocin administration
Nankali	2013	Not eligible intervention
Nellore	2006	Not eligible intervention
NCT01710566	2012	Study withdrawn
Nelson	1983	Not eligible intervention
Newton	1961	Quasi-randomised

Author	Year	Reason for exclusion
Nguyen-Lu	2013	Same drug intervention used in both arms and only different dose of carbetocin administration
Nieminen	1964	Not eligible intervention
Norchi	1988	Not eligible intervention
Oberbaum	2005	Not eligible intervention
Oberbaum	2010	Not eligible intervention
Oguz	2014	Same drug intervention used in both arms and only different route and timing of oxytocin administration
Ozalp	2010	Not eligible intervention
Ozcan	1996	Not eligible intervention
Ozkaya	2005	Inappropriate population (excluded women who had PPH)
Padhy	2006	Not eligible intervention
Palacio	2011	Same drug intervention used in both arms and only different dose of oxytocin administration
Paull	1977	Same drug intervention used in both arms and only different doses of drug administration
Pei	1996	Not eligible outcomes
Perdiou	2009	Not eligible intervention
Perdiou	2009a	Not eligible intervention
Phromboot	2010	Not eligible intervention
Pierre	1992	Quasi-randomised
Pinder	2002	Same drug intervention used in both arms and only different doses of drug administration
Pisani	2012	Quasi-randomised
Poeschmann	1988	Duplicate (abstract of Poeschmann 1991)
Poeschmann	1991	Quasi-randomised
Poeschmann	1991a	Duplicate (abstract of Poeschmann 1991)
Porter	1991	Not eligible intervention
Porter	1991a	Not eligible intervention
Priya	2015	Ineligible outcomes (not measured blood loss in the third stage)
Puri	2012	Not eligible intervention
Qiu	1998	Not eligible population (second stage)
Qiu	1999	Not eligible population (second stage)
Quiroga	2009	Not eligible intervention
Rajwani	2000	Not eligible intervention
Ramirez	2001	No available data
Reddy	1989	Not eligible intervention
Reddy	2001	Not eligible intervention
Rooney	1985	Quasi-randomised
Rosales-Ortiz	2013	Quasi-randomised
Rouse	2011	Same drug intervention both arms and only different doses of drug administration
Sadeghipour	2013	Not eligible intervention
Saito	2007	Quasi-randomised

Author	Year	Reason for exclusion
Samuels	2005	Not eligible intervention
Sariganont	1999	Cannot extract data
Sarna	1997	Same drug intervention used in both arms and only different doses of drug administration
Sartain	2008	Same drug intervention used in both arms and only different doses of drug administration
Schaefer	2004	Same drug intervention used in both arms and only different timings of drug administration
Schemmer	2001	Same drug intervention used in both arms and only different timings of drug administration
Sekhavat	2009	Not eligible intervention
Sentilhes	2014	Not eligible intervention
Sentürk	2013	Not eligible intervention
Shahid	2013	Not eligible intervention
Sharma	2014	Not randomised
Sheehan	2009	Same drug intervention used in both arms and only different doses of drug administration
Sheehan	2011	Same drug intervention used in both arms and only different doses of drug administration
Sheehan	2011a	Same drug intervention used in both arms and only different doses of drug administration
Shirazi	2013	Not eligible intervention
Shrestha	2007	Not eligible intervention
Singh	2005	Not eligible intervention
Siriwarakul	1991	Not eligible intervention
Soiva	1964	Quasi-randomised
Sorbe	1978	Quasi-randomised
Soriano	1995	Quasi-randomised
Stearn	1963	Quasi-randomised
Svanstrom	2008	No eligible outcomes
Symes	1984	No eligible outcomes
Taj	2014	Not eligible intervention
Takagi	1976	Not eligible intervention
Tanir	2009	Not eligible intervention
Tarabrin	2012	Not eligible intervention
Tariq	2015	Not eligible intervention
Tariq	2015a	Administered for treatment of PPH
Tehseen	2008	Administered for treatment of PPH
Terry	1970	Not eligible intervention
Tessier	2000	Same drug intervention used in both arms and only different doses of drug administration
Tharakan	2007	Same drug intervention used in both arms and only different doses of drug administration
Tharakan	2008	Same drug intervention used in both arms and only different doses of drug administration
Thomas	2006	Same drug intervention used in both arms and only different doses of drug administration
Thomas	2007	Same drug intervention used in both arms and only different doses of drug administration
Thornton	1987	Quasi-randomised
Thornton	1988	Quasi-randomised

Author	Year	Reason for exclusion
Tita	2012	Same drug intervention used in both arms and only different doses of drug administration
Tripti	2006	Not eligible intervention
Tripti	2009	Not eligible intervention
Tudor	2006	Same drug intervention used in both arms and only different doses of drug administration
Van den	2009	Not eligible uterotonic
Van Selm	1995	Not randomised
Vasegh	2005	Quasi-randomised
Vaughan	1974	No effectiveness outcomes reported
Ventoskovskiy	1990	Not eligible intervention
Verghese	2008	Not eligible intervention
Vogel	2004	Not eligible outcomes
Wallace	2008	Same drug intervention used in both arms and only different regimen of oxytocin administration
Walraven	2005	Not eligible uterotonic (oral ergometrine)
Wang	2000	Not eligible intervention
Weeks	2013	Self-administered drug
Weihong	1998	Not eligible intervention
Weiss	1975	Not eligible outcomes
Wetta	2011	Same drug intervention used in both arms and only different doses of drug administration
Wetta	2013	Same drug intervention used in both arms and only different doses of drug administration
Winikoff	2012	Same drug intervention used in both arms and only different doses of drug administration
Wong	2006	Same drug intervention used in both arms and only different doses of drug administration
Wright	2006	Not eligible intervention
Wu	2007	Not eligible intervention
Xu	2003	Not eligible intervention
Xu	2013	Not eligible intervention
Yamaguchi	2011	Same drug used in intervention both arms and only different doses of drug administration
Yan	2000	Not eligible intervention
Yang	2001	Not eligible intervention
Young	1988	Not eligible intervention
Zamora	1999	Not eligible intervention
Zaporozhan	2013	Not eligible intervention
Zhao	1998	Not eligible intervention
Zhao	2003	Not eligible intervention or able to extract outcomes
Zhou	1994	Same drug intervention used in both arms and only different doses of drug administration

Appendix 5 Reference list for studies awaiting classification

Adanikin 2013

Adanikin AI, Orji E, Adanikin PO, Olaniyan O. Comparative study of rectal misoprostol to oxytocin infusion in preventing postpartum haemorrhage after caesarean section. *Nepal J Obstet Gynaecol* 2013;**8**:34–7.

Adhikari 2007

Adhikari S, Rana A, Bista KD. Active management of third stage of labour: comparison between prophylactic intramuscular methylergometrine and intramuscular oxytocin. *Nepal J Obstet Gynaecol* 2007;**2**:24–8.

Ahmed 2015

Ahmed MR, Sayed Ahmed WA, Madny EH, Arafa AM, Said MM. Efficacy of tranexamic acid in decreasing blood loss in elective caesarean delivery. *J Matern Fetal Neonatal Med* 2015;**28**:1014–18.

Akinaga 2016

Akinaga C, Uchizaki S, Kurita T, Taniguchi M, Makino H, Suzuki A, *et al.* Randomized double-blind comparison of the effects of intramyometrial and intravenous oxytocin during elective cesarean section. *J Obstet Gynaecol Res* 2016;**42**:404–9.

Ali 2012

Ali R, Hina F. Postpartum haemorrhage; comparison of efficacy of ergometrine with misoprostol in prophylaxis in cesarean section. *Prof Med J* 2012;**19**:360–4.

Alli 2013

Alli QO. Comparing effectiveness of sublingual misoprostol with oxytocin infusion to reduce blood loss at caesarean section: double blind, randomized study. *BJOG* 2013;**120**:77–8.

Alwani 2014

Alwani M, Singh S, Thakur R, Mishra S. A randomised study comparing rectally administered misoprostol after spinal anaesthesia versus intramuscular oxytocin for prevention of postpartum haemorrhage in caesarean section. *Int J Reprod Contracept Obstet Gynaecol* 2014;**3**:512–5.

Ashwal 2016

Ashwal E, Hiersch L, Wertheimer A, Krispin E, Aviram A, Dayan DB, *et al.* The effect of post-partum oxytocin regimen on haemoglobin decline – a randomized controlled trial. *Am J Obstet Gynaecol* 2016;**214**(Suppl.):197–8.

Asmat 2017

Asmat R, Ashraf T, Asmat F, Asmat S, Asmat N. Effectiveness of Per Rectal Misoprostol Versus Intramuscular Oxytocin for Prevention of Primary Postpartum Haemorrhage. *J Coll Physicians Surg Pak* 2017;**27**:13–17.

Ayedi 2012

Ayedi M. *Effects of Tranexamic Acid on Post Partum Haemorrhage by Uterine Atony After Cesarean Section Delivery: A Randomised, Placebo Controlled Trial.* ClinicalTrials.gov. 2012. URL: clinicaltrials.gov/ct2/show/NCT01599468 (accessed 28 March 2016).

Baig 2015

Baig FS, Shahzad N, Khurshid HN, Malik A. Postpartum haemorrhage; comparison of intra umbilical and intra venous injection of oxytocin on blood loss in third stage of labour. *Prof M J* 2015;**22**:793–7.

Begum 2015

Begum T, Yeasmin S, Chakma S. Sublingual misoprostol versus oxytocin infusion to reduce blood loss in caesarean section. *BJOG* 2015;**122**(Suppl. 1):258.

Beigi 2009

Beigi A, Tabarestani H, Moini A, Zarrinkoub F, Kazempour M, Hadian Amree A. [Sublingual misoprostol versus intravenous oxytocin in the management of postpartum haemorrhage.] *Tehran Univ Med J* 2009;**67**:556–61.

Bhatti 2014

Bhatti K, Mahar T, Hafeez R, Shoaib-u-Nisa. A randomised controlled trial on prevention of postpartum haemorrhage with sublingual misoprostol or oxytocin. *Med For Mon* 2014;**25**:10–2.

Boopathi 2014

Boopathi A, Nayak SR, Rao A, Rao B. Oxytocin versus methylergometrine in the active management of third stage of labour. *Open J Obstet Gynaecol* 2014;**4**:666–71.

Carrillo-Gaucín 2016

Carrillo-Gaucín S, Torres-Gómez LG. [Carbetocin and oxytocin: Prevention of postpartum hemorrhage in patients with risk factors for uterine atony.] *Rev Med Inst Mex Seguro Soc* 2016;**54**(Suppl. 3):284–90.

Chalermpolprapa 2010

Chalermpolprapa V. Efficacy of sublingual misoprostol in prevention of postpartum haemorrhage in cesarean section: a randomized double-blinded, placebo-controlled trial. *Regi 4–5 Med J* 2010;**29**:325–35.

Chandhiok 2006

Chandhiok N, Dhillon BS, Datey S, Mathur A, Saxena NC. Oral misoprostol for prevention of postpartum hemorrhage by paramedical workers in India. *Int J Gynaecol Obstet* 2006;**92**:170–5.

Chatterjee 2016

Chatterjee S, Sarkar A, Rao KD. Using misoprostol for primary versus secondary prevention of postpartum haemorrhage – do costs matter? *PLOS ONE* 2016;**11**:e0164718.

Chaudhuri 2016

Chaudhuri P, Majumdar A. A randomized trial of sublingual misoprostol to augment routine third-stage management among women at risk of postpartum haemorrhage. *Int J Gynaecol Obstet* 2016;**132**:191–5.

Chou 2015

Chou LT, Da AW, Murizah MZ1, Rushdan M, Rashid Z. A randomised controlled trial on low dose versus high dose oxytocin infusion in prevention of uterine atony at caesarean delivery. *J Obstet Gynaecol Res* 2015;**41**(Suppl. 1):44–5.

Cordovani 2011

Cordovani D, Farine D, Balki M, Seaward G, Carvalho JC. Carbetocin at elective cesarean delivery: A dose-finding study. *Can J Anaesth* 2011;**58**(Suppl. 1):90.

Dabbaghi 2012

Dabbaghi Gale T, Elmizadeh KH, Moradi SD, Rashvand Melli E. [Comparison of intravenous oxytocin and oral misoprostol in reduction of postpartum haemorrhage.] *J Zanjan Univ Med Sci* 2012;**20**:1–8.

Dagdeviren 2016

Dagdeviren H, Cengiz H, Heydarova U, Caypinar SS, Kanawati A, Guven E, Ekin M. Intramuscular versus intravenous prophylactic oxytocin for postpartum hemorrhage after vaginal delivery: a randomized controlled study. *Arch Gynecol Obstet* 2016;**294**:911–16.

Dell-Kuster 2016

Dell-Kuster S, Hoesli I, Lapaire O, Seeberger E, Steiner LA, Bucher HC, Girard T. Efficacy and safety of carbetocin applied as an intravenous bolus compared to as a short-infusion for caesarean section: study protocol for a randomised controlled trial. *Trials* 2016;**17**:155.

Dell-Kuster 2016a

Dell-Kuster S, Hoesli I, Lapaire O, Seeberger E, Steiner LA, Bucher HC, *et al.* Efficacy and safety of intravenous carbetocin as a bolus compared to a short infusion for caesarean section. *J Obstet Anaesth* 2016;**26**(Suppl. 1):7.

Dell-Kuster 2017

Dell-Kuster S, Hoesli I, Lapaire O, Seeberger E, Steiner LA, Bucher HC, *et al.* Efficacy and safety of carbetocin given as an intravenous bolus compared with short infusion for caesarean section – double-blind, double-dummy, randomised controlled non-inferiority trial. *Brit J Anaesth* 2017;**118**:772–80.

Deshpande 2016

Deshpande HG, Madkar CS, Patel KK. Comparative study between intravenous and intraumbilical oxytocin as active management of third stage in elective and emergency caesarean section. *Indian J Obstet Gynaecol Res* 2016;**3**:55–8.

Diop 2016

Diop A, Daff B, Sow M, Blum J, Diagne M, Sloan NL, *et al.* Oxytocin via Uniject (a prefilled single-use injection) versus oral misoprostol for prevention of postpartum haemorrhage at the community level: a cluster-randomised controlled trial. *Lancet Glob Health* 2016;**4**:e37–44.

Dutta 2016

Dutta BK, Gupta KR. A comparative study on rectal misoprostol versus intramuscular oxytocin to prevent postpartum haemorrhage. *New Indian J Obgyn* 2016;**2**:98–103.

Elbohoty 2016

Elbohoty AEH, Mohammed WE, Sweed M, Eldin AMB, Nabhan A, Abd-El-Maeboud KHI. Randomized controlled trial comparing carbetocin, misoprostol, and oxytocin for the prevention of postpartum haemorrhage following an elective cesarean delivery. *Int J Gynaecol Obstet* 2016;**134**:324–8.

Fahmy 2015

Fahmy AA, Fawzy M. Oxytocin infusion after oxytocin bolus and carbetocin bolus to reduce blood loss during and after cesarean section – a randomised clinical trial. *Med J Cairo Univ* 2015;**83**:79–83.

Fahmy 2016

Fahmy NG, Yousef HM, Zaki HV. Comparative study between effect of carbetocin and oxytocin on isoflurane-induced uterine hypotonia in twin pregnancy patients undergoing cesarean section. *Egypt J Anaesth* 2016;**32**:117–21.

Fakour 2013

Fakour F, Mirzayi M, Reza Naghipour M, Ebrahimi H, Mahdavi M. Comparison between sublingual misoprostol and intravenous oxytocin in management of third stage of labor. *Iran J Obstet Gynaecol Infert* 2013;**15**:7–14.

Frye 2012

Frye LJ, Diop AR, Kone Y. *Comparing Misoprostol and Oxytocin in UnijectTM for Postpartum Hemorrhage (PPH) Prevention in Mali.* ClinicalTrials.gov. 2012. URL: https://clinicaltrials.gov/ct2/show/NCT01487278 (accessed 28 March 2016).

Frye 2015

Frye L, Durocher J, Weeks A, Ditai J, Ononge S, Faragher B, *et al.* On the trail of misoprostol in the community: A secondary analysis of self-administered misoprostol for the prevention of postpartum haemorrhage in Uganda. *Int J Gynaecol Obstet* 2015;**131**(Suppl. 5):e354–5.

Fuks 2014

Fuks AM, Khanna P, Yusaf T, Aslian A, Kowalska D, Salafia CM. Use of prophylactic misoprostol in reduction of blood loss at vaginal delivery. *Obstet Gynaecol* 2014;**123**(Suppl.):144–5.

Ghulmiyyah 2017

Ghulmiyyah LM, Usta i.m., Ghazeeri G, Taher N, Abu-Ghannam G, Tamim H, Nassar AH. Intravenous oxytocin use to decrease blood loss during scheduled cesarean delivery: a randomized double-blinded controlled trial (OXYTRIAL). *Am J Perinatol* 2017;**34**:379–87.

Gülmezoglu 2015

Gülmezoglu M. The WHO champion trial. *Int J Gynaecol Obstet* 2015;**131**(Suppl. 5):E29–30.

Hernandez-Castro 2016

Hernandez-Castro F, Lopez-Serna N, Trevino-Salinas EM, Soria-Lopez JA, Sordia-Hernandez LH, Cardenas-Estrada E. Randomized double-blind placebo-controlled trial of buccal misoprostol to reduce the need for additional uterotonic drugs during cesarean delivery. *Int J Gynaecol Obstet* 2016;**132**:184–7.

Islam 2008

Islam A, Siraj A, Arif N. Post partum haemorrhage prophylaxis; comparison of the efficacy of misoprostol and ergometrine in cesarean delivery. *Prof Med J* 2008;**15**:323–7.

Jagielska 2015

Jagielska I, Kazdepka-Ziemińska A, Kaczorowska A, Madej A, Kolossa T, Grabiec M. [Evaluation of carbetocin and oxytocin efficacy in prevention of postpartum hemorrhage in women after cesarean section.] *Ginekol Pol* 2015;**86**:689–93.

Jans 2017

Jans S, Herschderfer KC, van Diem MT, Aitink M, Rijnders M, van der Pal-Bruin K, *et al. LENTE Study: Effectiveness of Prophylactic Intramuscular Oxytocin During Third Stage of Labour Among Low Risk Women. A Randomised Controlled Trial*. *Midwives – Making a Difference in the World*. Proceedings of the 31st International Confederation of Midwives Triennial Congress, Toronto, ON, Canada, 18–22 June 2017.

Javadi 2015

Javadi EHS, Sadeghipour Z, Barikani A, Javadi M. Tranexamic acid in the control of uterine atony during labor. *Biotech Health Sci* 2015;**2**:e26898.

Kabir 2015

Kabir N, Akter D, Daisy TA, Jesmin S, Razzak M, Tasnim S, *et al.* Efficacy and safety of carbetocin in comparison to oxytocin in the active management of third stage of labour following vaginal delivery: an open label randomized control trial. *Bangladesh J Obstet Gynaecol* 2015;**30**:3–9.

Khan 2013

Khan M, Balki M, Ahmed I, Farine D, Searward G, Carvalho JCA. *Carbetocin at Elective Cesarean Delivery: A Randomised Controlled Trial to Determine the Effective Dose, Part 3 Final.* Society for Obstetric Anaesthesia and Perinatology, 45th Annual Meeting, San Juan, Puerto Rico, 24–8 April 2013.

Koen 2016

Koen S, Snyman LC, Pattinson RC, Makin JA. A randomised controlled trial comparing oxytocin and oxytocin + ergometrine for prevention of postpartum haemorrhage at caesarean section. *S Afr Med J* 2016;**106**:55–6.

Liu 2015

Liu Y, Chen HX, Kang DL, Kuang XH, Liu WX, Ni J. Influence of dexmedetomidine on incidence of adverse reactions introduced by hemabate in postpartum hemorrhage during cesarean section. *Int J Clin Exp Med* 2015;**8**:13776–82.

Liu 2016

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Appendix 7 Additional data from triallists

First author and publication year	Additional data
Adanikin, 2012[39]	Additional data retrieved from: Adanikin A, Orji E, Adanikin P, Olaniyan O. Comparative study of rectal misoprostol to oxytocin in preventing postpartum haemorrhage post caesarean section. *Int J Gynaecol Obstet* 2012;**119**(Suppl. 3):S825
Al-Sawaf, 2013[42]	Response to e-mail queries

Trial arm	**Number of events**	**Number of participants in trial arm**
PPH blood loss of > 500 ml		
Control	8	39
Misoprostol	3	28
Oxytocin	2	37
PPH blood loss of > 1000 ml		
Control	6	39
Misoprostol	2	28
Oxytocin	1	37
Change in Hb levels after delivery (g/dl)		
Trial arm	**Mean Hb level (g/dl) change (SD)**	**Number of participants in trial arm**
Control	1.3 (0.6)	39
Misoprostol	1.3 (0.9)	28
Oxytocin	1.2 (0.9)	37

Amin, 2014[44]	Response to e-mail queries
	All patients included in the study were admitted through emergency and operations
	After a complete history and examination, women who had undergone a previous caesarean section or experienced a traumatic PPQ, bleeding disorders, prolonged difficult labour, placenta previa, placental abruption, PPH or multiple gestations, and women having a BMI of > 30 kg/m^2 were excluded
	However, all other women with a full-term pregnancy and who came to a labour room in spontaneous onset of labour resulting in spontaneous vaginal delivery without episiotomy were included in the study
	High-risk patients were not included in the study, so no death or major morbidity were noted

First author and publication year	Additional data		
Askar, 2011[45]	Response to e-mail queries		
	Hypertension		
	Trial arm	**Duration (minutes) of third stage of labour (number of women)**	
		30–60	**60–120**
	Intervention (carbetocin)	0	0
	Control (Syntometrine) (these are the same patients)	7	7
Attilakos, 2010[46]	Response to e-mail queries		
	Trial arm		
	Carbetocin (*n* = 22)	**Oxytocin (*n* = 26)**	
	Nausea, *n* = 1	Nausea, *n* = 2	
	Nausea and flushed, *n* = 2	Vomiting, *n* = 3	
	Nausea and headache, *n* = 1	Vomiting and trigeminy, *n* = 1	
	Nausea and abdominal pain, *n* = 1	Nausea and headache, *n* = 1	
	Nausea and vomiting, *n* = 2	Nausea and vomiting, *n* = 2	
	Nausea, vomiting and sweating, *n* = 1	Nausea, vomiting and shortness of breath, *n* = 1	
	Nausea, vomiting and tremors, *n* = 1	Nausea, vomiting and tremors, *n* = 1	
	Nausea, vomiting, flushed and hypotension, *n* = 1	Nausea, vomiting, flushed and tremors, *n* = 1	
	Tight throat, *n* = 1	Dizziness, *n* = 2	
	Dizziness, *n* = 2	Dizziness, flushed and sweating, *n* = 1	
	Flushed, *n* = 1	Hypotension, *n* = 2	
	Hypotension, *n* = 2	Tremors, *n* = 2	
	Hypotension and shortness of breath, *n* = 1	Shortness of breath, *n* = 1	

First author and publication year	Additional data		
	ST segment depression, *n* = 1	Blurred vision, *n* = 1	
	Tachycardia, *n* = 1	Metallic taste in mouth, *n* = 1	
	Tremors and tachycardia, *n* = 1	Pain in arm, *n* = 1	
	Metallic taste in mouth, shortness of breath and wheezing, *n* = 1	Abdominal pain and shortness of breath, *n* = 1	
	Metallic taste in mouth and pressure over forehead, *n* = 1	Backache, *n* = 1	
	Headache, *n* = 1	Headache, *n* = 1	
Atukunda, 2014[47]	Attachment to response to e-mail queries		
	Trial arm	**Events, *n* (%)**	**Number of participants in trial arm**
	Vomiting (generally)		
	Misoprostol	35 (6.1)	569
	Oxytocin	19 (3.3)	570
	Vomiting (severe)		
	Misoprostol	8 (1.4)	569
	Oxytocin	3 (0.5)	570
	Morbidity (extensive vaginal repair)		
	Misoprostol	11 (1.9)	570
	Oxytocin	8 (1.4)	570
Bamigboye, 1998[50]	Response to e-mail queries		
	The authors did not document the routine drugs used in the active management of labour in each case		
	At two sites in South Africa (East London and Dora Nginza, Port Elizabeth), and in Uganda the routine was 10 units of i.m. oxytocin		
	At the third site in South Africa (Rob Ferreira) 5 units of i.m. oxytocin was used in 60 out of 155 cases and oxytocin–ergometrine (5 units/0.5 mg) was used in 85 out of 155 cases		
	In Nigeria, either oxytocin or ergometrine was used, but the authors did not have the details		
	As this was a randomised trial, it was expected that the routine management be evenly distributed between the randomised groups		

First author and publication year	Additional data
Begley, 1990[54]	Response to e-mail queries Random number tables were used from the statistical textbook by Fleiss[203] The first number was selected from the table by a disinterested observer and the numbers were then allocated in blocks of 100, following in sequence

Trial arm	Duration (minutes) of third stage of labour (number of women)							Mean number of women (SD/CI)	Total number of women
	0–20	21–40	41–60	61–80	81–100	101–120	> 120		
Intervention (active)	674	11	4	0	2	8	6	11.26 (19.62)	705
Control (physiological)	670	41	7	1	4	1	0	11.56 (8.41)	724

Trial arm	Change in Hb levels (g/dl)	Total number of patients
	Mean change in Hb level (g/dl)	SD/CI (g/dl)
Intervention (active)	+ 0.91	1.19	618
Control (physiological)	+ 0.47	1.27	645

First author and publication year	Additional data
Bellad, 2012[55]	Response to e-mail queries
	Four women in the misoprostol group and none in the oxytocin group experienced fever (defined as a temperature of > 38 °C); this was entered onto the form as a dichotomous variable and the authors have no information regarding the actual temperature (or whether or not any woman experienced a temperature of > 40 °C)
	One woman in the oxytocin group had retained placenta and had a blood transfusion; this was the only case of transfusion and required intensive care unit admission for monitoring
	There were no other complications (e.g. organ failure) and no maternal deaths
	58/329 women receiving oxytocin (17.6%) had a second stage of labour of ≥ 30 minutes
	53/323 women receiving sublingual misoprostol (16.4%) had a second stage of labour of ≥ 30 minutes
	One woman receiving oxytocin and no women receiving sublingual misoprostol had a third stage of labour of ≥ 30 minutes
Bhullar, 2004[57]	Response to e-mail queries
	I do not have the raw data anymore, but I am certain we did not have any maternal deaths
Bugalho, 2001[61]	Additional data extracted from published Cochrane review(s)[17]
Chaudhuri, 2012[68]	Additional data extracted from published Cochrane review(s)[17]
Chhabra, 2008[70]	Response to e-mail queries
	This was a low-dose study in low-risk cases for prophylaxis
	The number of women (*n*/*N*) in each study group (if any) who needed major surgery: 0
	The number of women (*n*/*N*) in each study group (if any) who needed ICU admission: 0
	The number of women (*n*/*N*) in each study group (if any) who had hyperpyrexia (i.e. a temperature of > 40 °C): 0
	The number of women (*n*/*N*) in each study group (if any) who had vital organ failure: 0
	The number of women (*n*/*N*) in each study group (if any) who had an estimated blood loss of > 1000 ml: 0
	The number of women (*n*/*N*) in each study group (if any) who died: 0

First author and publication year	Additional data
Dansereau, 1999[73]	Response to e-mail queries The paper should have stated that: *. . . two patients in each group had a [severe] postpartum haemorrhage [requiring blood transfusion] . . .* Because of the difficulty in assessing estimated blood loss, the authors had decided – before the beginning of the study – to not use that variable but to use the judgment of the surgeon (blinded to the study drug), as to whether or not the patient needed additional oxytocic drugs (required in all cases of PPH) Clearly, more than two patients per group had a PPH blood loss of > 500 or even 1000 ml The exact number is not available though, as it was decided not to use this outcome of PPH in the study
El Behery, 2016[80]	Response to e-mail queries: **Trial arm** — **Number of events** *PPH > 500 ml* Carbetocin — 6 Oxytocin — 19 *Major morbidity or death* Carbetocin — 0 Oxytocin — 3 The authors excluded the following cases from their study: congenital fetal anomalies, placenta previa, diabetes mellitus, hypertension, preeclampsia, cardiac disorders and general anaesthesia
El Tahan, 2012[81]	Response to e-mail queries Any of the following: • Maternal deaths: no • Maternal ICU admissions: no • Hysterectomies: no • Maternal fever of > 40 °C: 16 out of 179 cases developed pyrexia of < 40 °C in the misoprostol group; none exceeded 40 °C • Blood loss of > 1000 ml: yes, some cases in the placebo group had a total perioperative blood loss of > 1000 ml

First author and publication year	Additional data
Enakpene, 2007[85]	Response to e-mail queries
	There were no deaths recorded in either group
	None of the study participants required additional surgery, such as hysterectomy or arterial ligation, to treat massive postpartum haemorrhage
	There was only one ICU admission in the misoprostol group for a non-haemorrhage-related condition but caused by postpartum eclampsia
	No participants in each study group developed hyperpyrexia with a temperature of > 40 °C
	No participants developed major organ failure
	Three participants from the oral misoprostol group had a massive PPH blood loss of > 1000 ml, whereas only one participant in the methylergometrine group developed a massive PPH
	However, all four women who developed a massive haemorrhage responded very well with additional oxytocic drugs and did not require surgical interventions
Fenix, 2012[90]	Additional data retrieved from an unpublished text entitled 'Double-blind randomized controlled trial comparing the effect of carbetocin with oxytocin for the prevention of postpartum haemorrhage among high risk women following vaginal delivery'[204]
	Results
	The study was conducted over a 4-month period (from May 2011 to August 2011)
	There was a total of 272 deliveries in our hospital during the study period, of which 111 delivered vaginally
	Seventy-five women were finally recruited into the study
	Nine women in the carbetocin group and six women in the oxytocin group failed to have a paired Hb test to measure the change in Hb level 24 hours after delivery because they refused further blood extraction
	These 15 women were excluded and, therefore, the study had 30 women each in the carbetocin and oxytocin arm in the analysis who were randomly assigned to receive either of the two different interventions
	There was no significant difference between the two groups in their demographic characteristics (*Table 1*)
	Most of the participants were college degree holders, with an average age of 30 years
	The average age of gestation was 38 weeks for the carbetocin group, whereas it was almost 39 weeks' gestation in the oxytocin group
	It was also observed that about two-thirds were multigravid women for both groups

First author and publication year	Additional data
	The average Hb count 24 hours after delivery of the participants for the oxytocin group (–1.1g/dl) seems to have a greater drop than those in the carbetocin group (–0.6g/dl)[204]
	Participants in the carbetocin group exhibited a relatively lower average estimated blood loss than those in the oxytocin group (296 cc and 493 cc, respectively)
	There was no case of PPH between the two trial groups
	The distribution of exposure to additional agents revealed that 9 out of 10 patients in the oxytocin group needed additional uterotonic agents
	In contrast, 90% of the participants in the carbetocin group did not need any additional agent after drug administration
	In addition, it was noted that almost all of the patients in the oxytocin group needed a uterine massage compared with a negligible number of those in the carbetocin group
	Meanwhile, none of the patients needed a blood transfusion[204]
	Carbetocin immediately (1 minute) took effect in the patients of the carbetocin group while those patients in the oxytocin group waited for some time (i.e. > 30 minutes) for oxytocin to take effect[204]
	Adverse effects are presented[204]
	The incidences of headache and hypogastric pain were similar in between trial groups
	There were no nausea, vomiting, facial flushing or pain in the injection site noted
	Twenty per cent or 6 out of 30 women in the carbetocin group had tachycardia (defined as a maternal pulse rate of ‡ 100 b.p.m.) within 60 minutes post delivery and were significantly higher than the 10% (3 out of 30) recorded in the oxytocin group; however, the difference was statistically insignificant
	The mean blood pressure values at different intervals after delivery of each group are also shown,[204] although no statistical difference was observed between the two trial interventions
	To determine if there is a significant difference between the two drugs, the authors will need to perform independent sample *t*-tests
	Prior to performing the test, we need to satisfy its assumptions which are as follows: • normality of the data • homogeneity/constancy of variance

First author and publication year	Additional data
	Based on the results, the authors can conclude that there was a significant difference between the carbetocin and oxytocin groups, as the *p*-values for the estimated mean blood loss and mean difference of the Hb count were approximately zero (i.e. a < LOS = 0.05)[204]
	Looking at the mean difference of the Hb count, having a value of 0.57 implies that carbetocin garnered a significantly lower change in the Hb count after 24 hours[204]
	The mean difference of the estimated blood loss, with value of –197.33 ml, denotes a statistically lower blood loss for women exposed to carbetocin than those who were exposed to oxytocin[204]
	Baseline characteristics of patients – see reference number 204
	Primary outcome (peripartum Hb concentration) – see reference number 204
	Secondary outcomes – see reference number 204
	Adverse reactions – see reference number 204
	t-test for independent samples means – see reference number 204
	Q–Q plot of estimated blood loss – see reference number 204
	Q–Q plot of difference of preoperative Hb count and 24-hour Hb count – see reference number 204
	Response to e-mail queries
	Thirty parturients received oxytocin with a mean blood loss of 493 ml, but there were no cases of blood loss of > 500 ml because the estimated blood loss during delivery was measured only through eyeballing of the gauzes used
	In the estimation, the authors did not include the bleeding coming from repair of the laceration
	One of the recommendations for future studies is to measure the actual blood loss using a more accurate device of measurement
	In addition, because the estimation of blood loss is often inaccurate during delivery, it was agreed that a fall in Hb level be used as a primary outcome assessing the efficacy of the uterotonic agents in reducing postpartum haemorrhage

First author and publication year	Additional data			
Gavilanes, 2015[93]	Response to e-mail queries			
	Trial group	**Number of events**	**Total**	
	PPH blood loss of 500–1000 ml			
	Misoprostol	33	50	
	Oxytocin	26	50	
	PPH blood loss of > 1000 ml			
	Misoprostol	12	50	
	Oxytocin	13	50	
	None of the women had major morbidity			
	There were no deaths either			
Gülmezoglu, 2001[95]	Additional data extracted from published Cochrane review(s)[17]			
Hofmeyr, 1998[99]	Response to e-mail queries			
	Dosage	**Trial arm, *n* (%)**	**Relative risk (95% CI)**	***p*-value**
		Misoprostol (*N* = 36)	**Placebo (*N* = 37)**	
	> 500 ml	8 (22)	15 (41)	0.55 (0.27 to 1.13)	0.15
	> 1000 ml	2 (5.6)	5 (14)	0.41 (0.09 to 1.98)	0.23
	Additional oxytocic drug	2 (5.6)	7 (19)	0.29 (0.07 to 1.32)	0.08

First author and publication year	Additional data
Hofmeyr, 2011[100]	Response to e-mail queries
	All nine pyrexias were between 39 and 39.9 °C, none was ≥ 40 °C
	The only severe morbidity that was recorded were the nine laparotomy patients, of whom one had a hysterectomy
	There was no overlap of data
	The Nigeria site in Hofmeyr 2011 was the University College Hospital, Ibadan
	Fawole 2011 included two other hospitals in Ibadan and other Nigerian sites
	The University College Hospital occurs in the title, as that is Bukola's base, but this was not a site
	Additional data also retrieved from:
	Hofmeyr GJ, Gülmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. *Bull World Health Organ* 2009;**87**:666–77
	Additional data were also retrieved from:
	Hofmeyr GJ, Ferreira S, Nikodem VC, Mangesi L, Singata M, Jafta Z, *et al.* Misoprostol for treating postpartum haemorrhage: a randomized controlled trial. *BMC Pregnancy Childbirth* 2004;**4**:167
Jerbi, 2007[107]	Response to e-mail queries
	No blood loss of > 1000 ml in any trial group
	No transfusion or maternal death in the two trial groups

First author and publication year	Additional data		
Lapaire, 2006[115]	Response to e-mail queries		
	Blood loss	**Trial arm (number of women)**	
		Misoprostol (*N* = 24)	**Oxytocin (*N* = 19)**
	Calculated		
	> 500 ml	18	15
	> 1000 ml	13	11
		Misoprostol (*N* = 28)	Oxytocin (*N* = 28)
	Estimated		
	> 500 ml	18	10
	> 1000 ml	1	14
Musa, 2015[127]	Response to e-mail queries		
	There was no postpartum blood loss of > 1000 ml in both trial groups		
	Range of blood loss was 20–790 ml in the misoprostol group and 40–790 ml in the oxytocin group		
	There were no maternal deaths recorded, though participants were followed up only in the early puerperium		
	There was no major morbidity		
	The only morbidity recorded was retained placenta that warranted a manual removal of placenta		
	The two cases occurred in the oxytocin group and none in the misoprostol group		
Nasr, 2009[128]	Response to e-mail queries		
	No women in either group needed major surgery or ICU admission, nor did any have hyperpyrexia, massive bleeding of > 1000 ml or major organ failure		
Ortiz-Gómez, 2013[136]	Response to e-mail queries		
	The method of randomisation was made by the statistical department, and it was believed that it was a computer-generated sequence		

First author and publication year	Additional data			
Owonikoko, 2011[137]	Response to e-mail queries			
	Trial arm	**Number of women**		
	PPH > 500 ml			
	s.l. misoprostol	34		
	i.v. oxytocin	27		
	PPH > 1000 ml			
	s.l. misoprostol	4		
	i.v. oxytocin	5		
	Blood loss (ml), mean (SD/CI)		*Total*	
	s.l. misoprostol	667.12 (213.38)	50	
	i.v. oxytocin	649.90 (251.15)	50	
	Change in Hb levels (%), mean (SD/CI)		*Total*	
	s.l. misoprostol	4.5 (3.3)	50	
	i.v. oxytocin	4.3 (2.97)	50	
Parsons, 2007[139]	Response to e-mail queries			
	Trial arm	**Duration (minutes) of third stage of labour**		**Total**
		> 30 minutes (number of women)	**Mean number of women, SD (95% CI)**	
	Intervention	3	6.95, 6.11 (6.13 to 7.76)	218
	Control	2	6.18, 4.62 (5.57 to 6.79)	222

First author and publication year	Additional data		
Rosseland, 2013[148]	Response to e-mail queries		
	The data on estimated blood loss were the visually estimated blood loss in the OR		
	The authors believed that these data were of limited value and have based their analyses of blood loss on change in Hb level instead		
	A strict perioperative i.v. fluid protocol was followed		
	Trial arm	**Number of events**	**Total**
	PPH blood loss of > 500 ml		
	Oxytocin	4	26
	Carbetocin	6	25
	Placebo	8	25
	PPH blood loss of > 1000 ml		
	Oxytocin	0	26
	Carbetocin	0	25
	Placebo	0	25
	Change in Hb levels (g/dl), mean (SD/CI)		
	Oxytocin	–0.82 (0.67)	26
	Carbetocin	–0.50 (0.82)	25
	Placebo	–0.84 (0.53)	25
	Change in Hb levels (%), mean (SD/CI)		
	Oxytocin	27.9 (14.1)	26
	Carbetocin	25.6 (13.6)	25
	Placebo	15.7 (16.5)	25

First author and publication year	Additional data
Sadiq, 2011[150]	Response to e-mail queries
	For fever, there were no patients lost to follow-up because each round of the study lasted only 24 hours, and throughout this period the patients were hospitalised (admitted)
	For fever, the authors have a full data set, but a number of the data were published elsewhere
	There were no deaths in the study (despite the global reports on maternal mortality in Nigeria)
	There were differences in baseline characteristics like age, parity, etc.
	However, the authors thought to minimise the effects of these differences through randomisation of treatment, even though what was carried out was not the literary meaning of the term 'randomisation' as the authors did not initially consider a specific patient population
	However, the authors suggested further studies (in my reports) in which baseline characteristics are made uniform between the two trial groups
	In the case of baseline treatment with oxytocin, there is clear demarcation in that the misoprostol group had no pretreatment with oxytocin
Samimi, 2013[151]	Response to e-mail queries
	Because the aim of this study was prevention of PPH not treatment of PPH, the authors had no mortality or morbidity in the study population
	The authors also used Hb level as an indicator of blood loss instead of a measurement of blood loss volume
Shrestha, 2011[152]	Response to e-mail queries
	The authors did not find hyperpyrexia (i.e. a temperature > 40 °C), vital organ failure, ICU admission, surgery or death in either the intervention or the control group of this study

First author and publication year	Additional data	
Tewatia, 2014[160]	Response to e-mail queries	
	Trial arm	**Number of events**
	PPH blood loss of > 500 ml	
	Misoprostol	0
	Oxytocin	0
	PPH blood loss of > 1000 ml	
	Misoprostol	0
	Oxytocin	0
	Death	
	Misoprostol	0
	Oxytocin	0
	Morbidity	
	Misoprostol	13 fever, 10 shivering, 1 nausea, 1 vomiting
	Oxytocin	1 nausea, 1 vomiting

First author and publication year	Additional data		
Ugwu, 2014[162]	Response to e-mail queries		
	Trial arm	**Events**	**Total**
	PPH blood loss of > 500 ml		
	Misoprostol	15	60
	Oxytocin	33	60
	PPH blood loss of > 1000 ml		
	Misoprostol	1	60
	Oxytocin	2	60
	Death		
	Misoprostol	0	60
	Oxytocin	0	60
	Morbidity		
	Misoprostol	0	60
	Oxytocin	0	60
Walley, 2000[170]	Response to e-mail queries		
	Trial arm	**Mean, SD (95% CI)**	
	Duration of third stage of labour > 30 minutes		
	Misoprostol	6.15, 3.76 (5.62 to 6.69)	
	Oxytocin	7.30, 13.08 (5.40 to 9.19)	
	Trial arm	**Events**	**Total**
	Duration of third stage of labour > 30 minutes		
	Misoprostol	0	194
	Oxytocin	2	185

First author and publication year	Additional data		
Whigham, 2014[168]	Response to e-mail queries		
	Trial arm	**Events**	**Total**
	Carbetocin vs. oxytocin in non-elective caesarean section		
	PPH blood loss of > 500 ml		
	Carbetocin	42	59
	Oxytocin	37	53
	PPH blood loss of > 1000 ml		
	Carbetocin	6	59
	Oxytocin	6	53
	Active labour at time of caesarean section		
	PPH blood loss of > 500 ml		
	Carbetocin	22	30
	Oxytocin	19	28
	PPH blood loss of > 1000 ml		
	Carbetocin	4	30
	Oxytocin	3	28
Zachariah, 2006[173]	Response to e-mail queries		
	The authors did not have any maternal deaths in any of the study groups		

i.m., intramuscular(ly); i.v., intravenous(ly); ICU, intensive care unit; OR, operating room; Q–Q, quantile–quantile; SD, standard deviation; s.l., sublingual.

Appendix 8 Network diagrams

Secondary outcomes

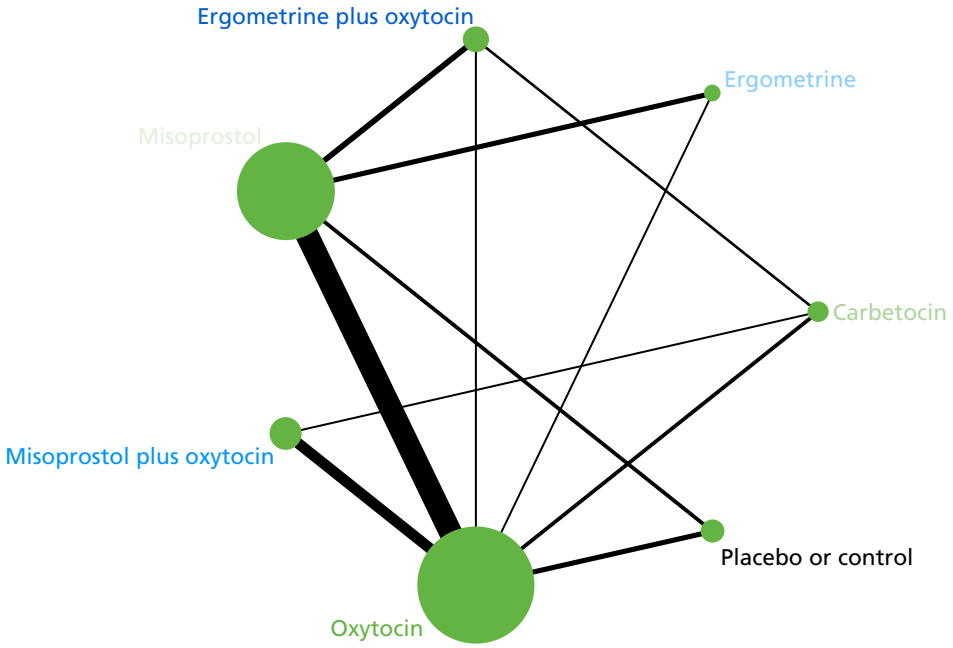

FIGURE 113 Network diagram for maternal deaths.

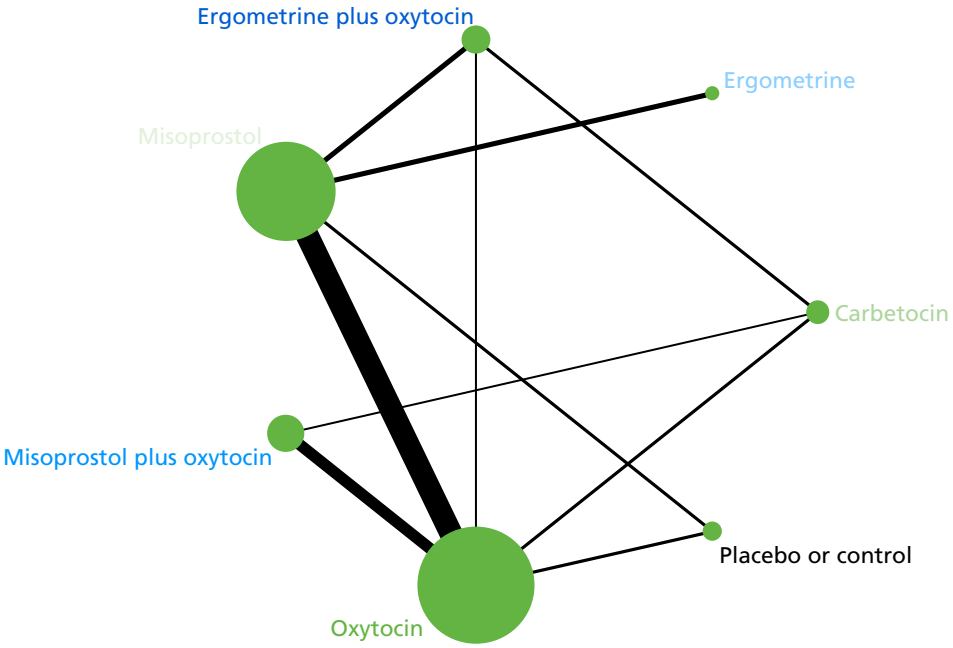

FIGURE 114 Network diagram for maternal deaths or severe morbidity events adapted from WHO 'near-miss' criteria.[25]

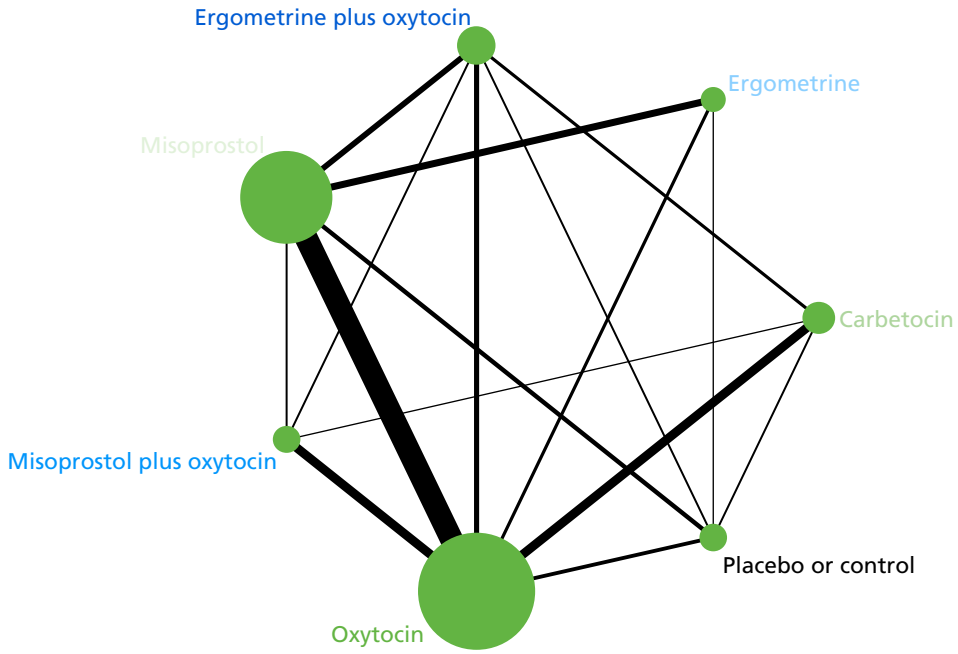

FIGURE 115 Network diagram for additional uterotonics requirements.

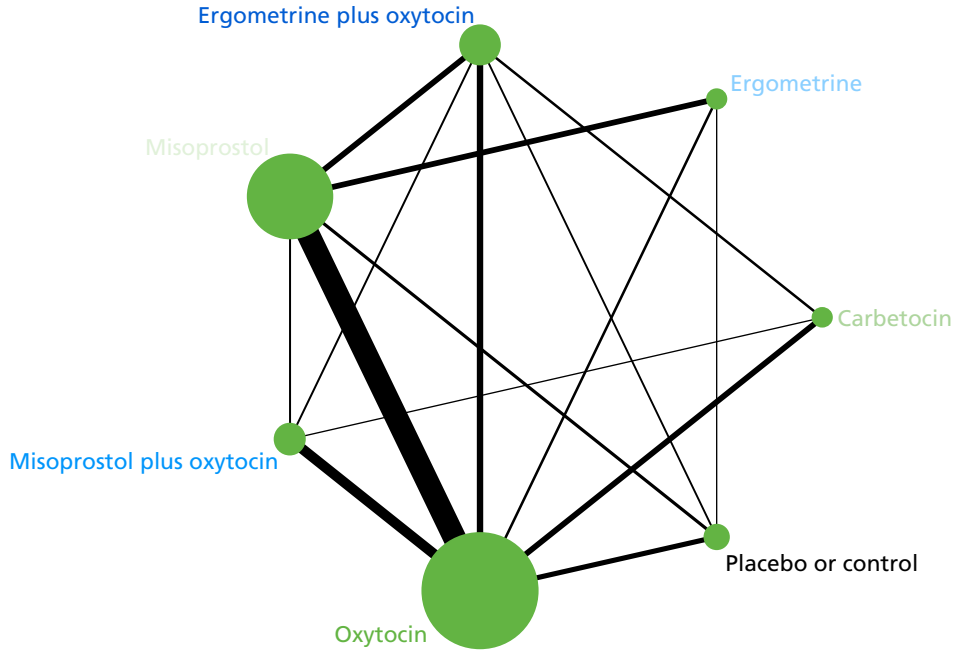

FIGURE 116 Network diagram for transfusion requirements.

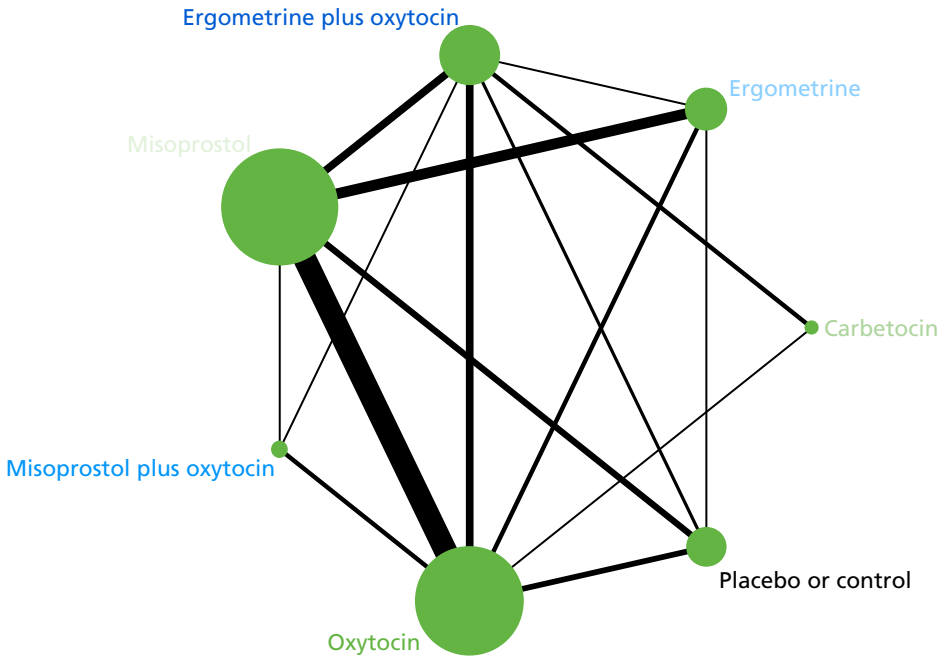

FIGURE 117 Network diagram for manual removal of the placenta.

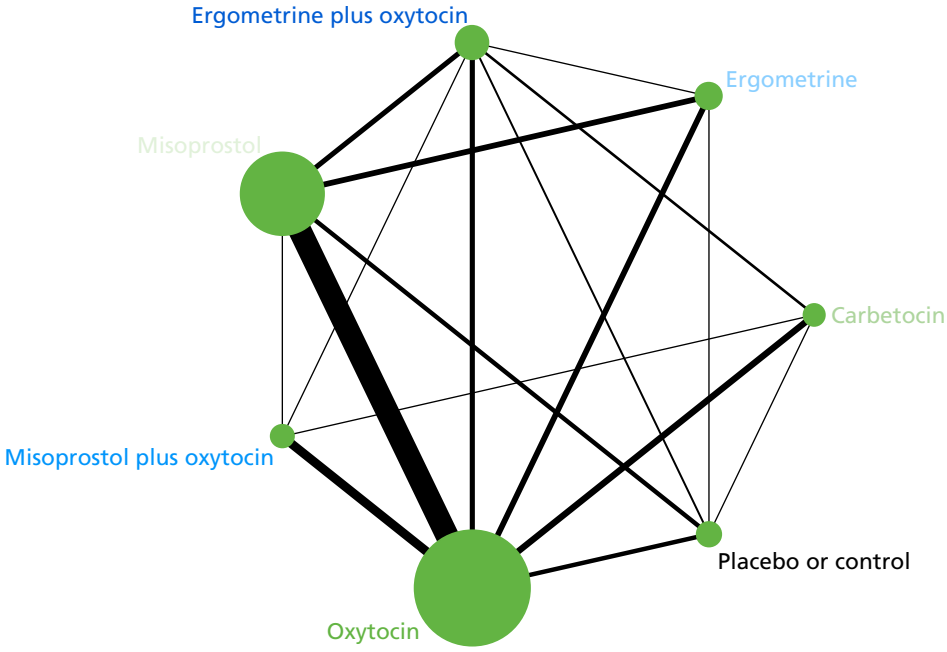

FIGURE 118 Network diagram for mean volumes of blood loss (ml).

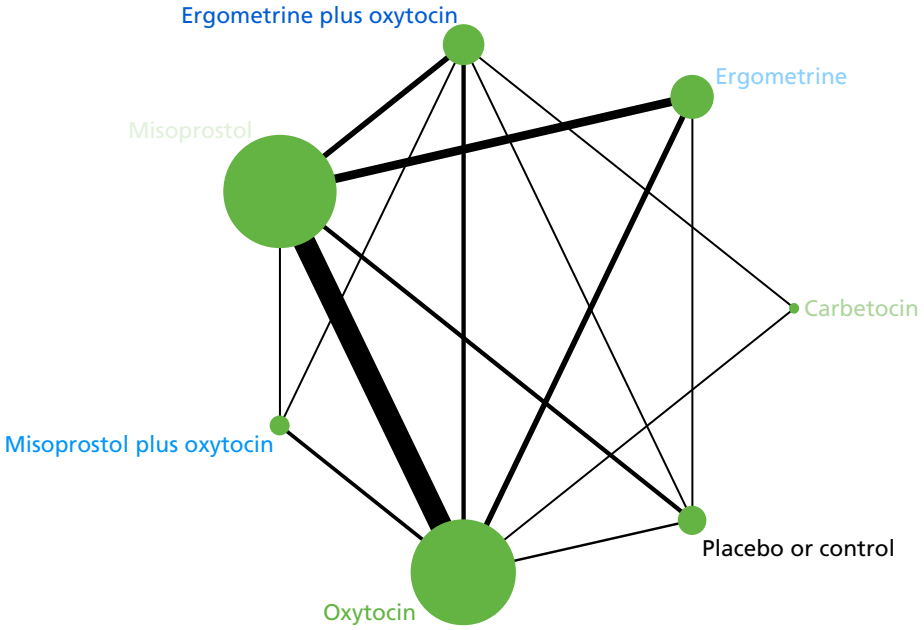

FIGURE 119 Network diagram for mean durations (minutes) of the third stage in labour.

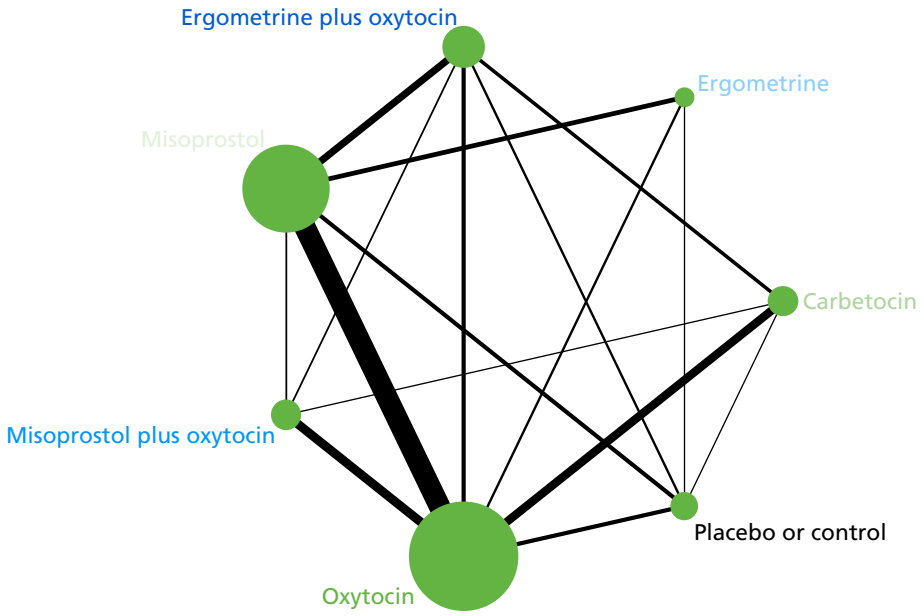

FIGURE 120 Network diagram for change in Hb (g/l) measurements before and after birth.

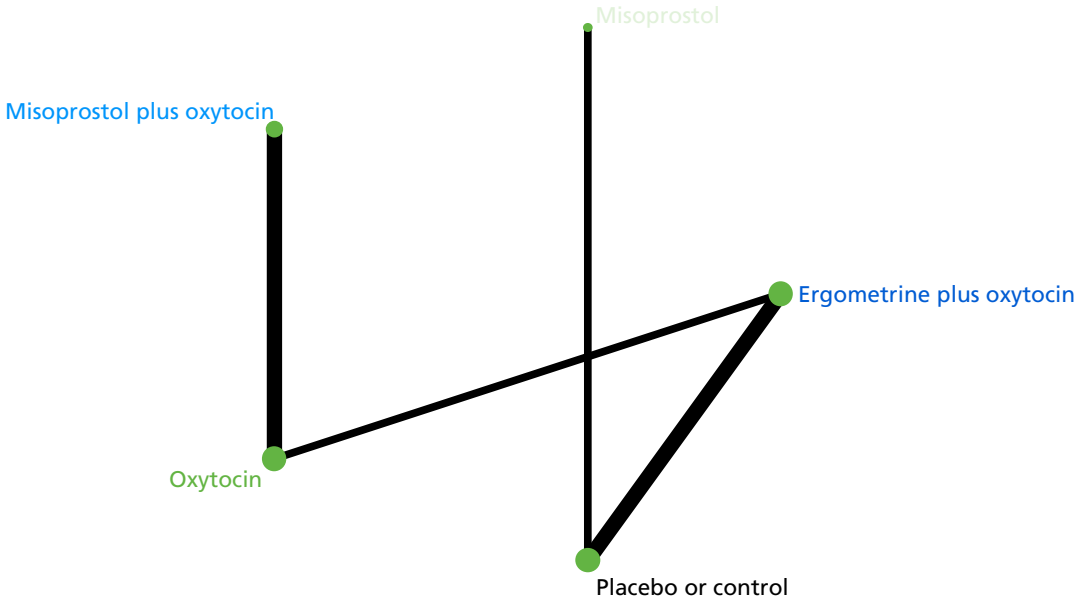

FIGURE 121 Network diagram for neonatal unit admission requirements.

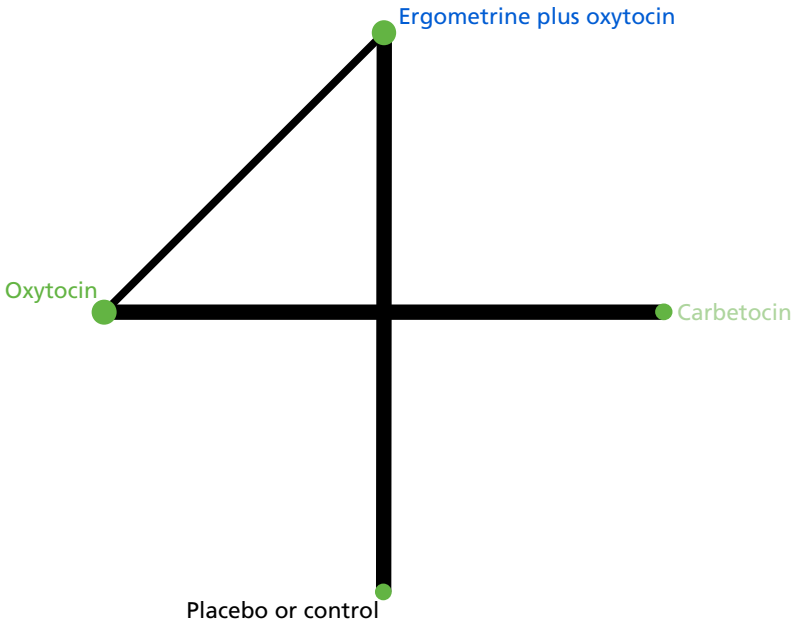

FIGURE 122 Network diagram for breastfeeding at discharge.

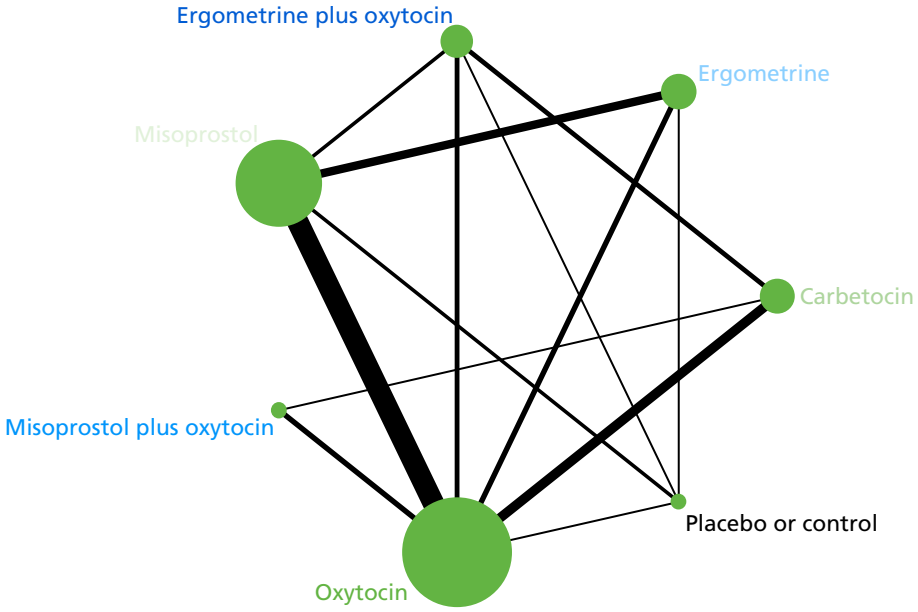

FIGURE 123 Network diagram for nausea in the first 24 hours post partum.

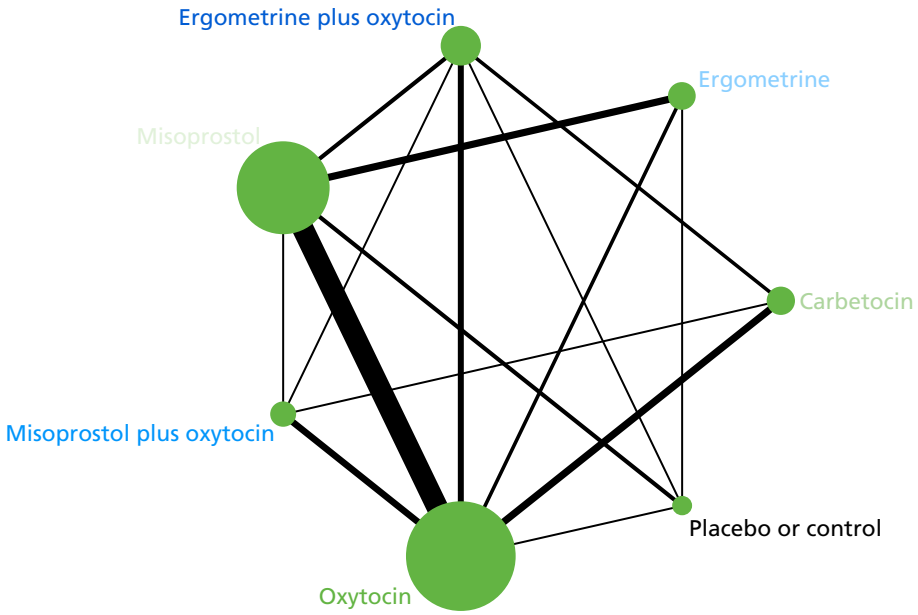

FIGURE 124 Network diagram for vomiting in the first 24 hours post partum.

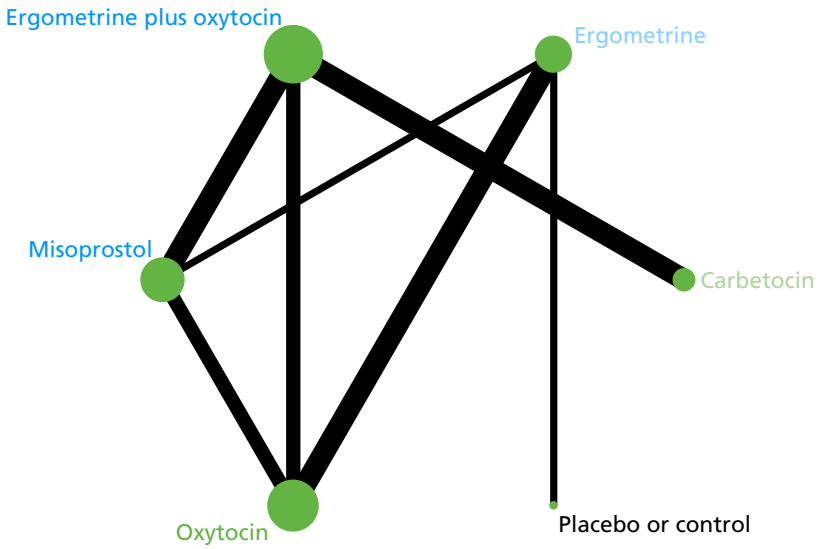

FIGURE 125 Network diagram for hypertension in the first 24 hours post partum.

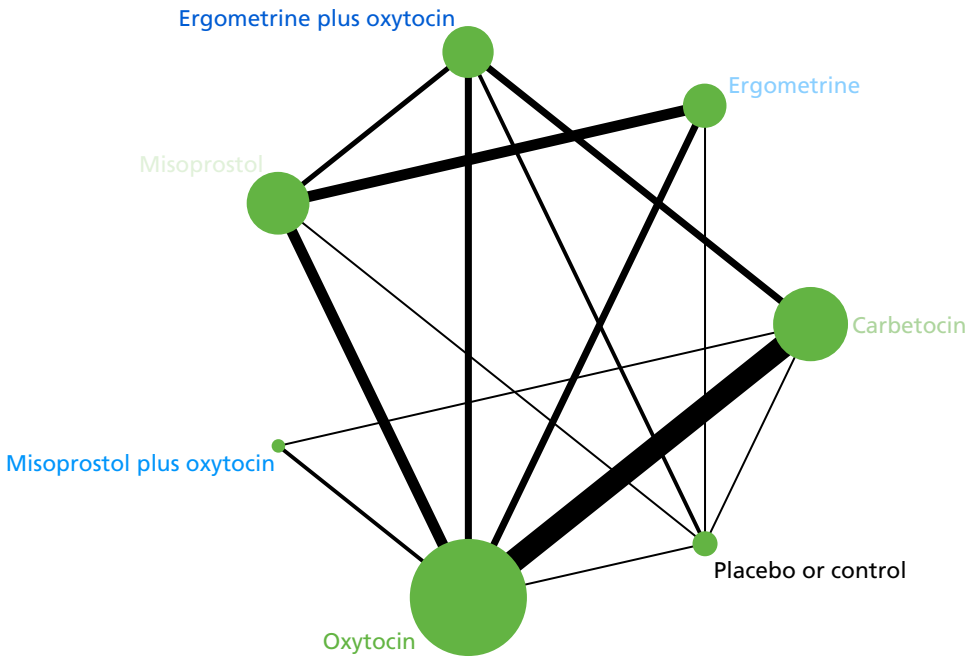

FIGURE 126 Network diagram for headache in the first 24 hours post partum.

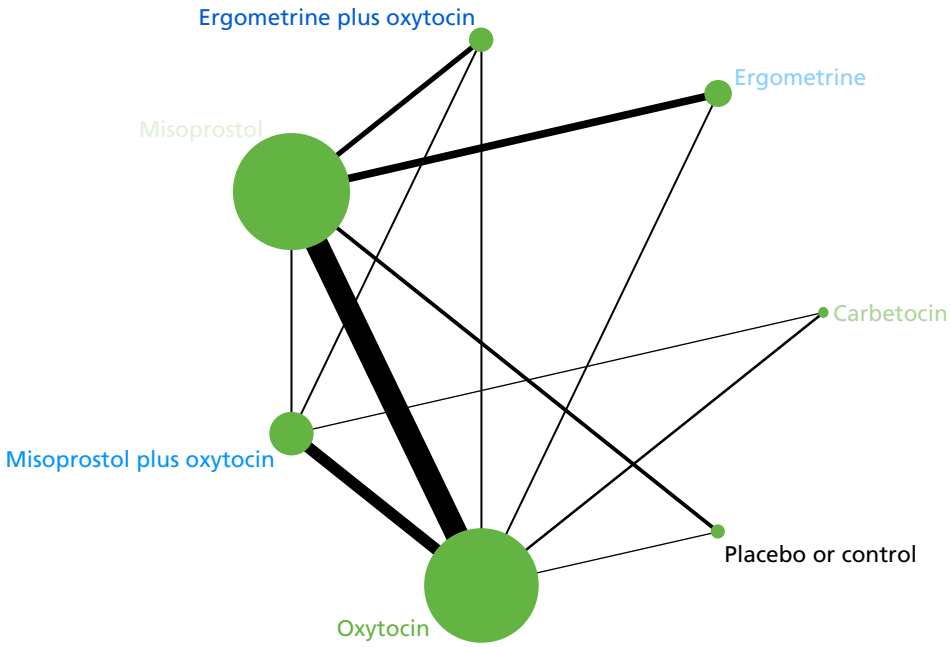

FIGURE 127 Network diagram for fever in the first 24 hours post partum.

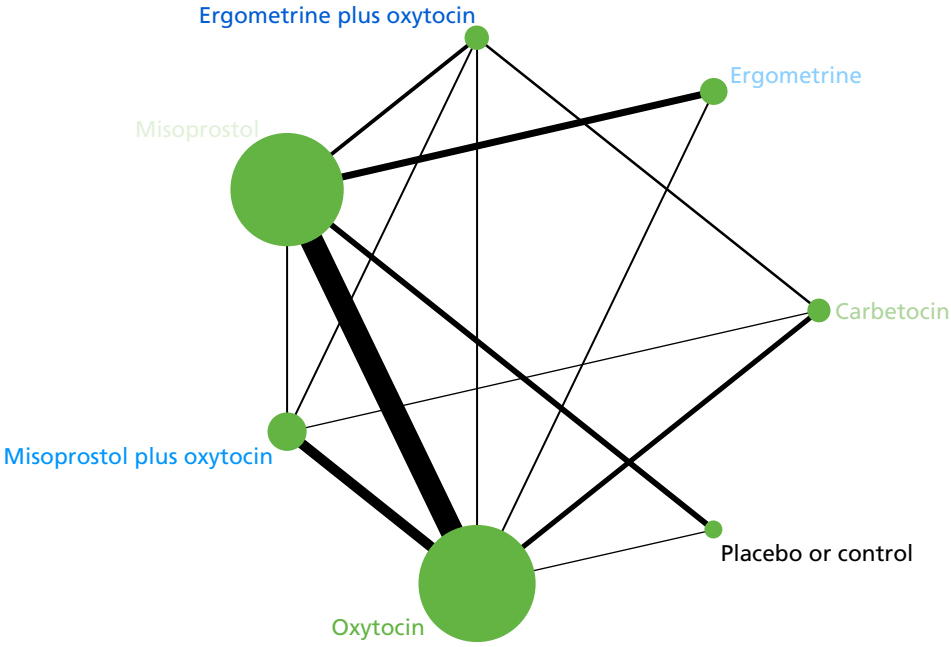

FIGURE 128 Network diagram for shivering in the first 24 hours post partum.

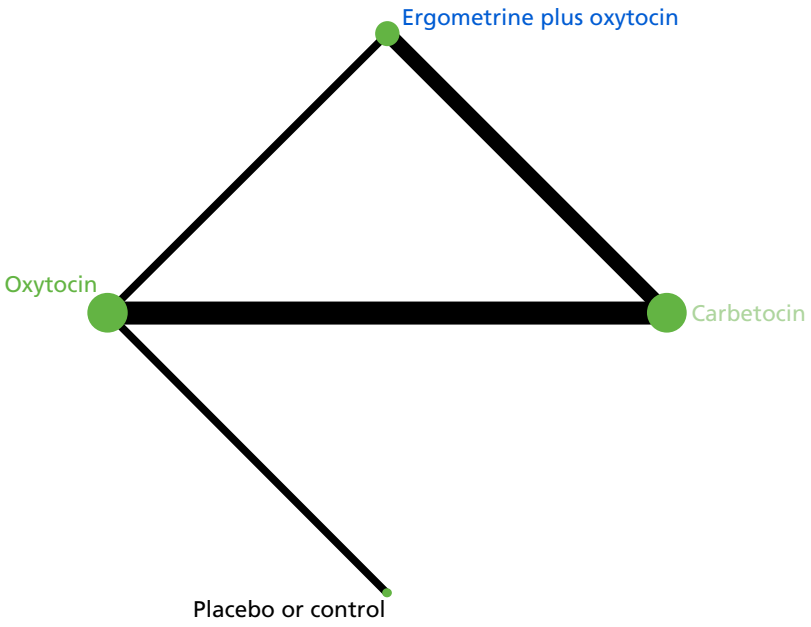

FIGURE 129 Network diagram for tachycardia in the first 24 hours post partum.

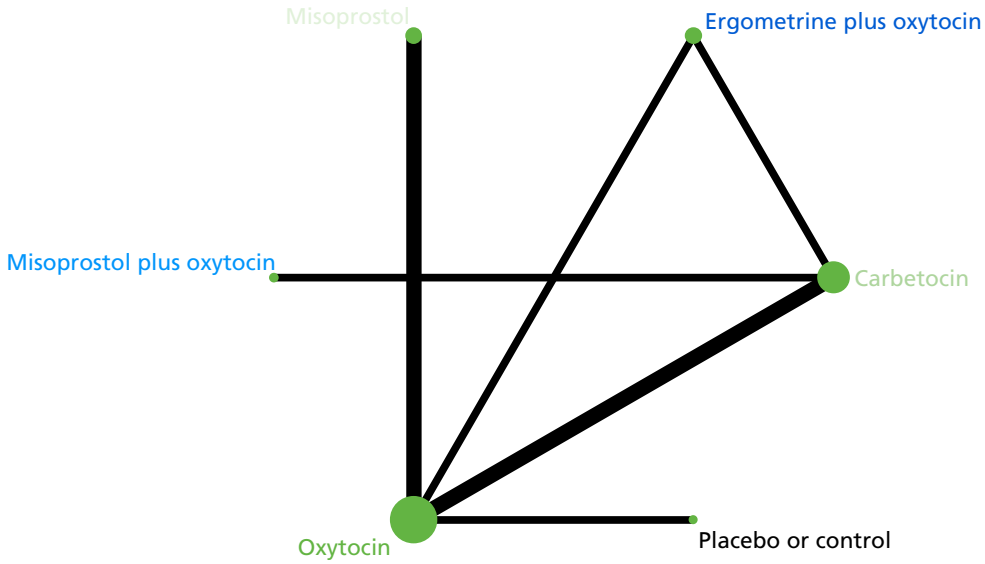

FIGURE 130 Network diagram for hypotension in the first 24 hours post partum.

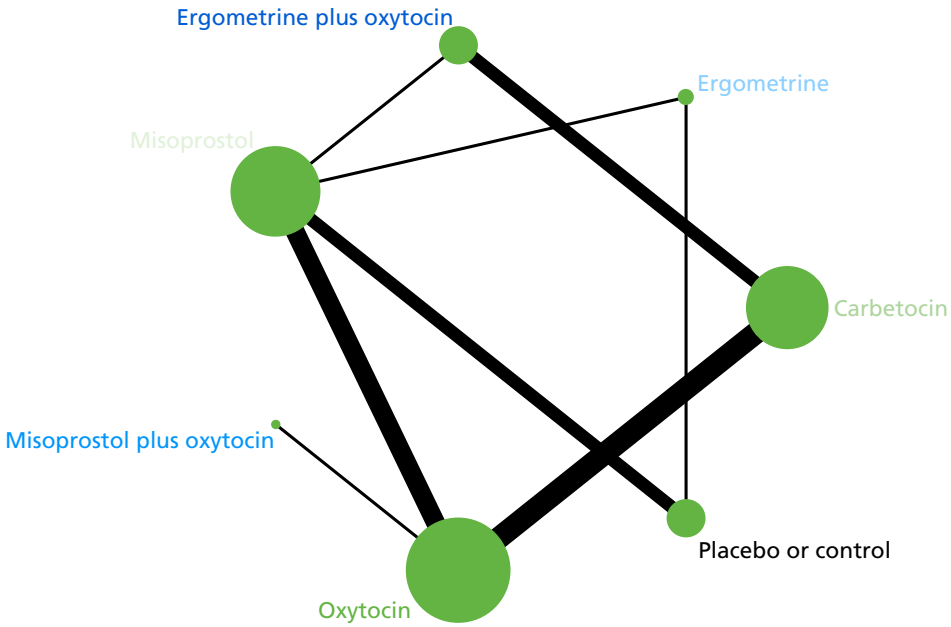

FIGURE 131 Network diagram for abdominal pain in the first 24 hours post partum.

Subgroup analyses

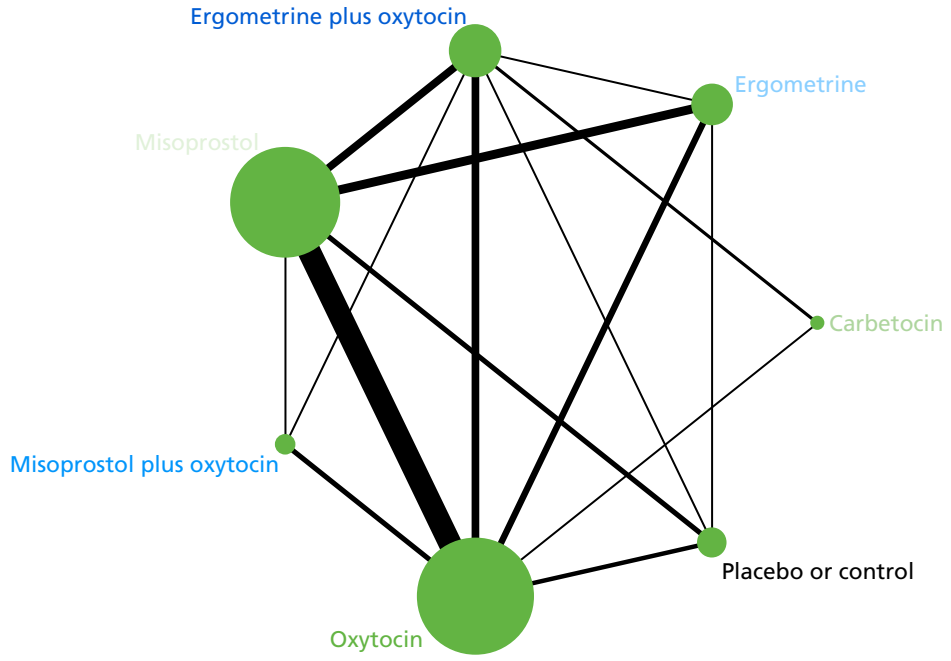

FIGURE 132 Network diagram for the prevention of PPH blood loss of ≥ 500 ml by mode of birth (vaginal birth).

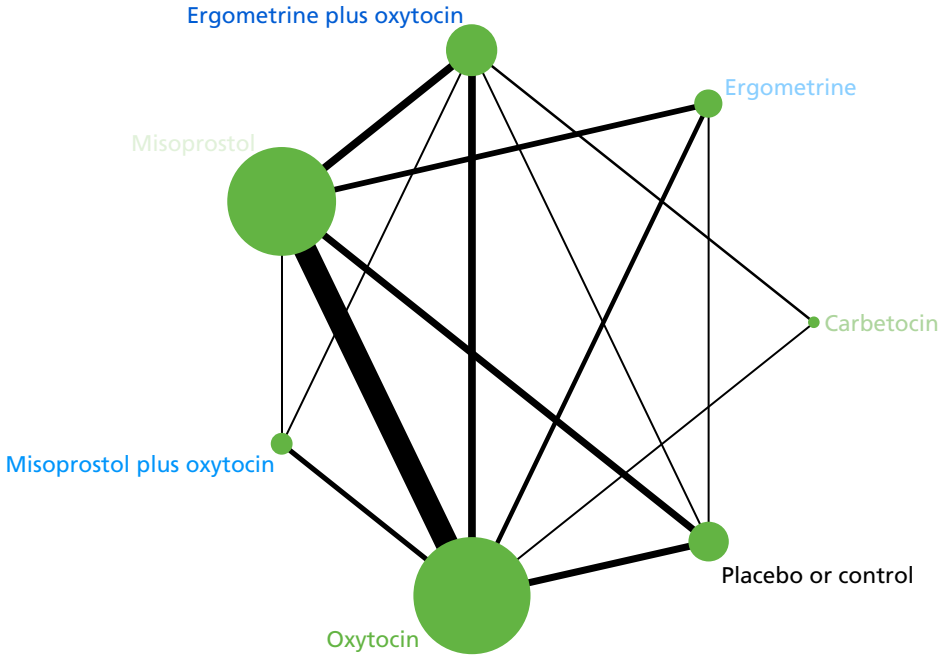

FIGURE 133 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml by mode of birth (vaginal birth).

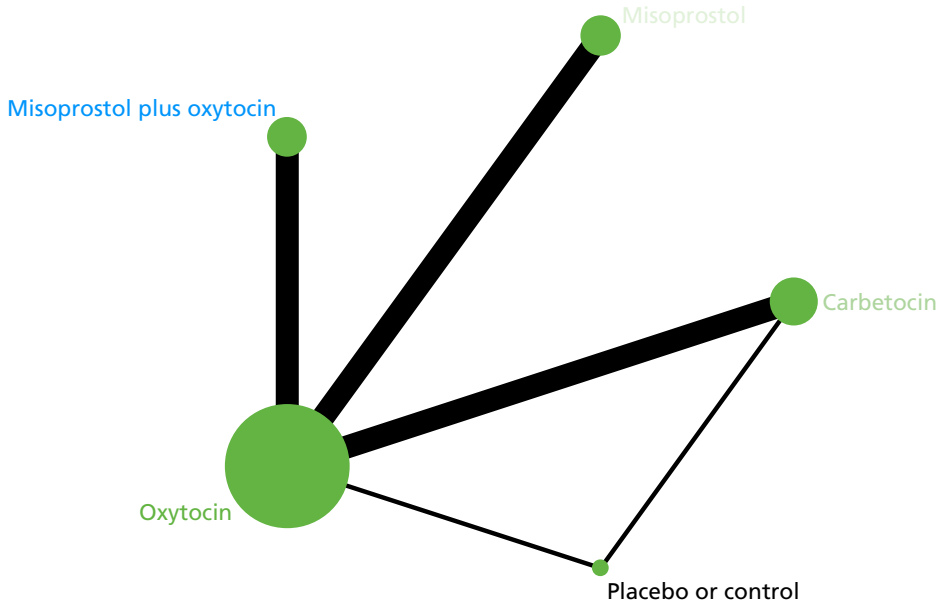

FIGURE 134 Network diagram for the prevention of PPH blood loss of ≥ 500 ml by mode of birth (caesarean).

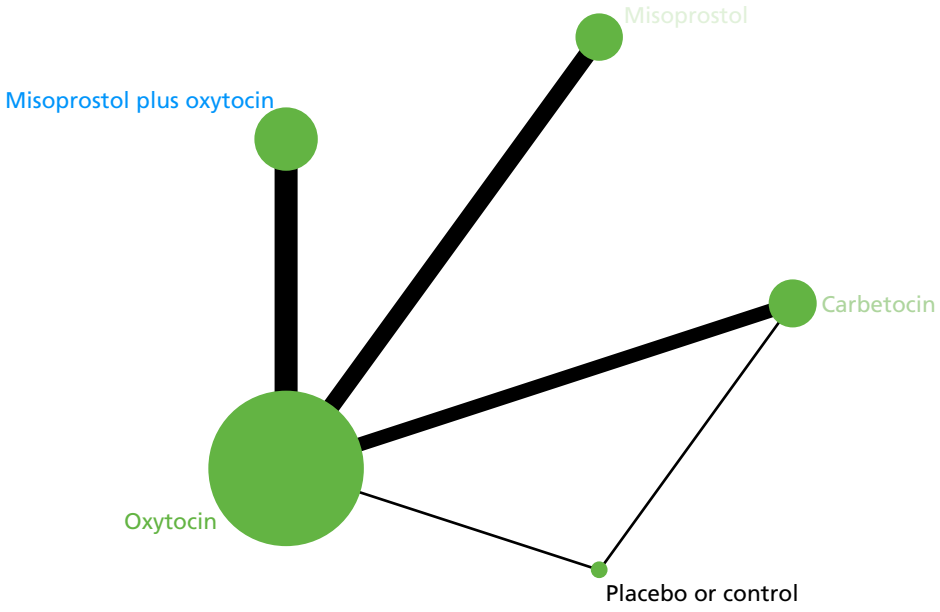

FIGURE 135 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml by mode of birth (caesarean).

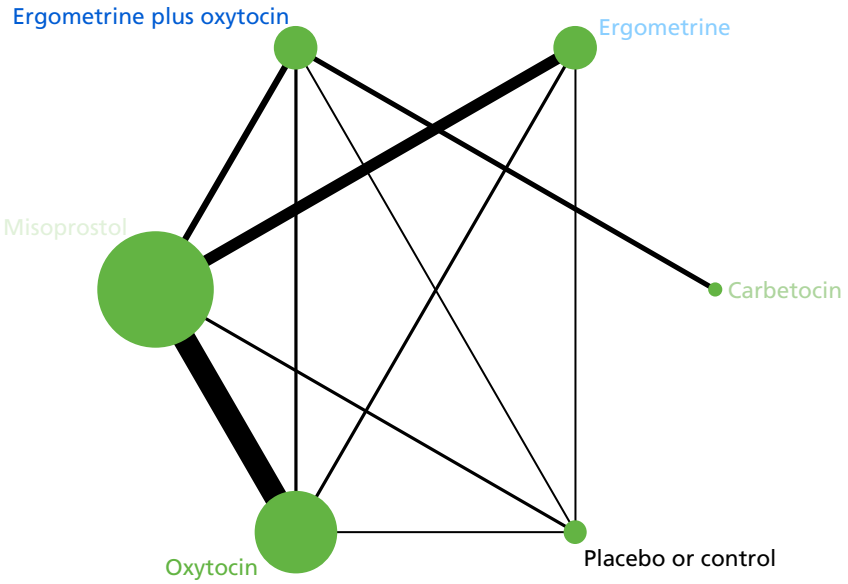

FIGURE 136 Network diagram for the prevention of PPH blood loss of ≥ 500 ml by prior risk for PPH (low risk).

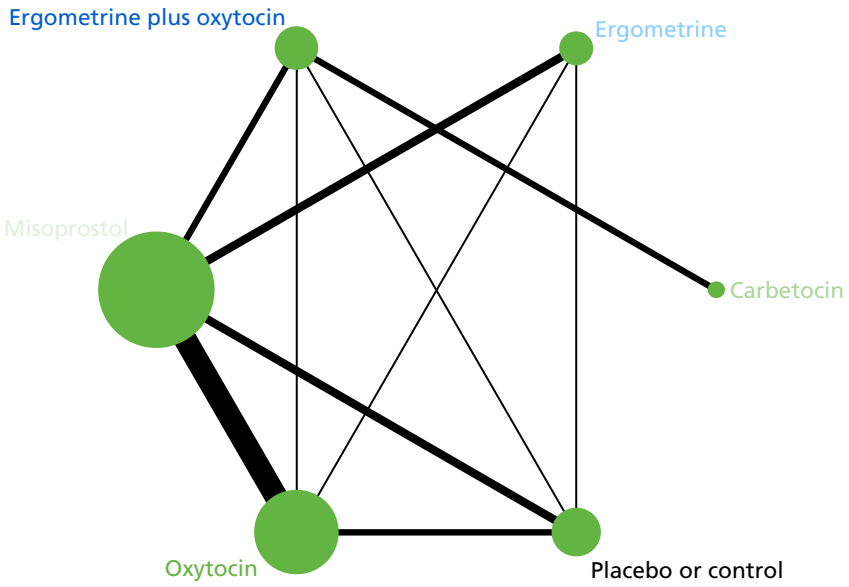

FIGURE 137 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml by prior risk for PPH (low risk).

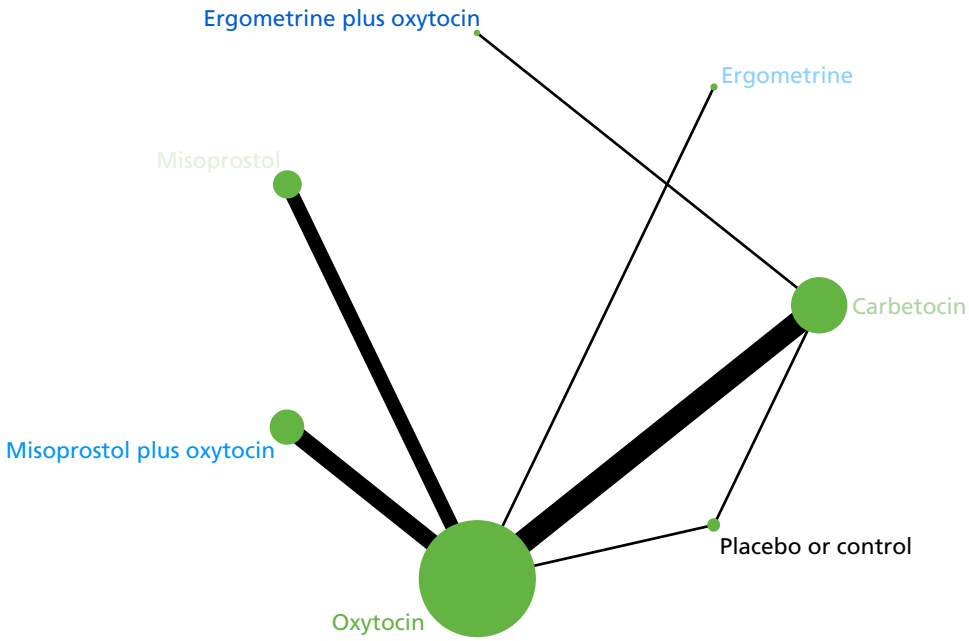

FIGURE 138 Network diagram for the prevention of PPH blood loss of ≥ 500 ml by prior risk for PPH (high risk).

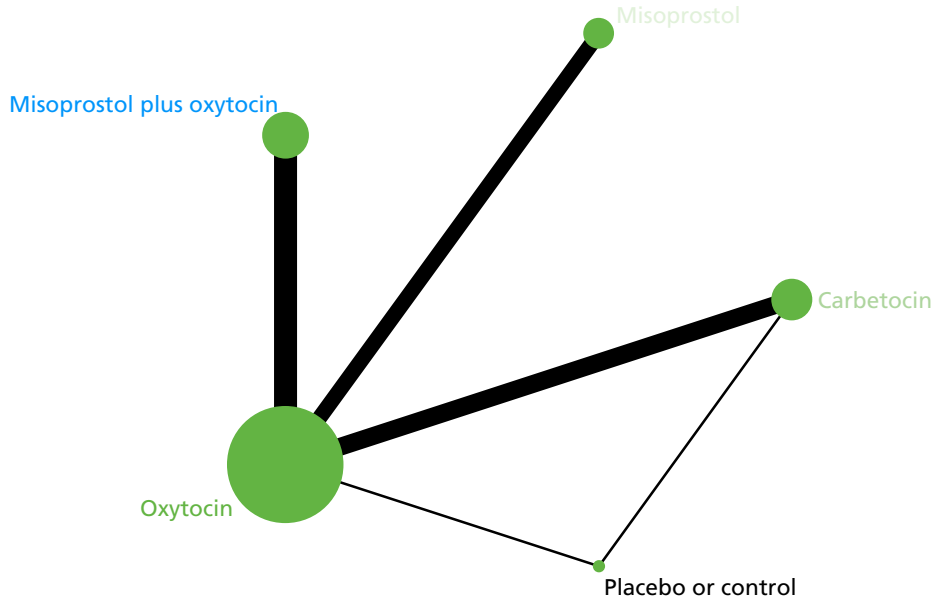

FIGURE 139 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml by prior risk for PPH (high risk).

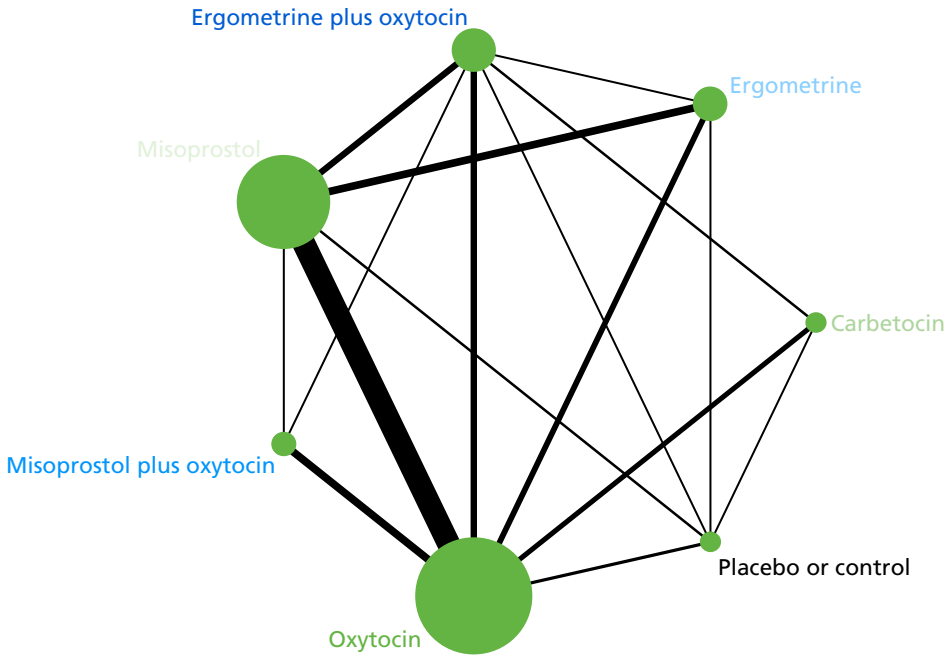

FIGURE 140 Network diagram for the prevention of PPH blood loss of ≥ 500 ml by health-care setting (hospital setting).

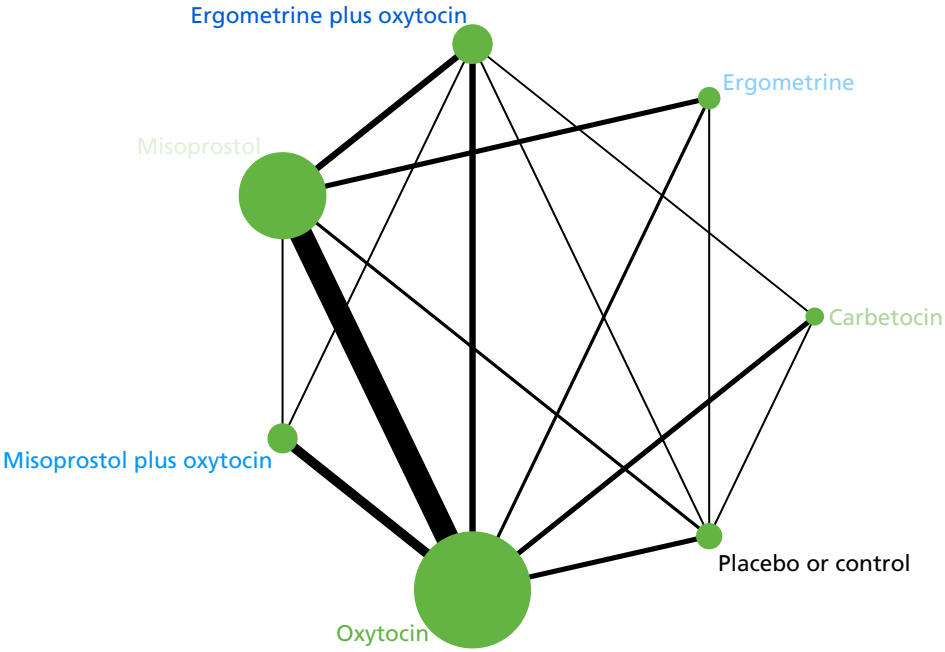

FIGURE 141 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml by health-care setting (hospital setting).

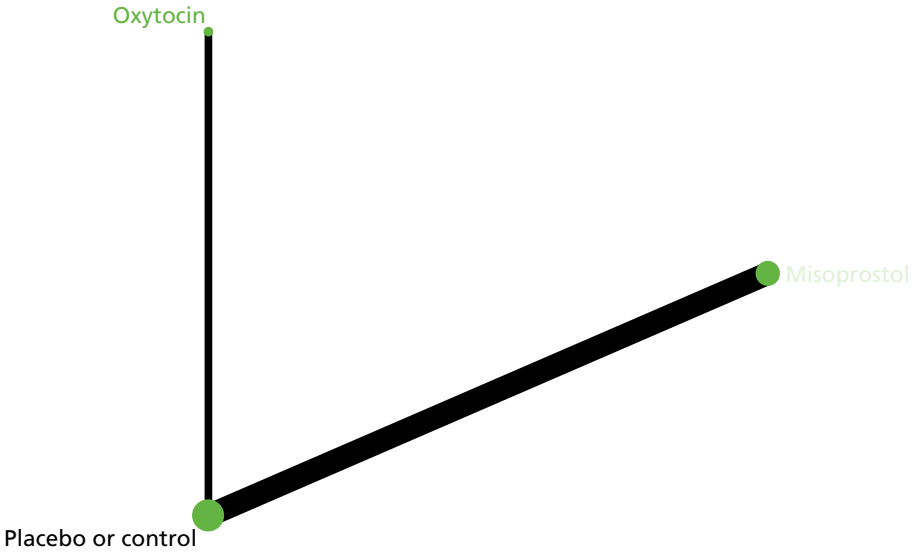

FIGURE 142 Network diagram for the prevention of PPH blood loss of ≥ 500 ml by health-care setting (community setting).

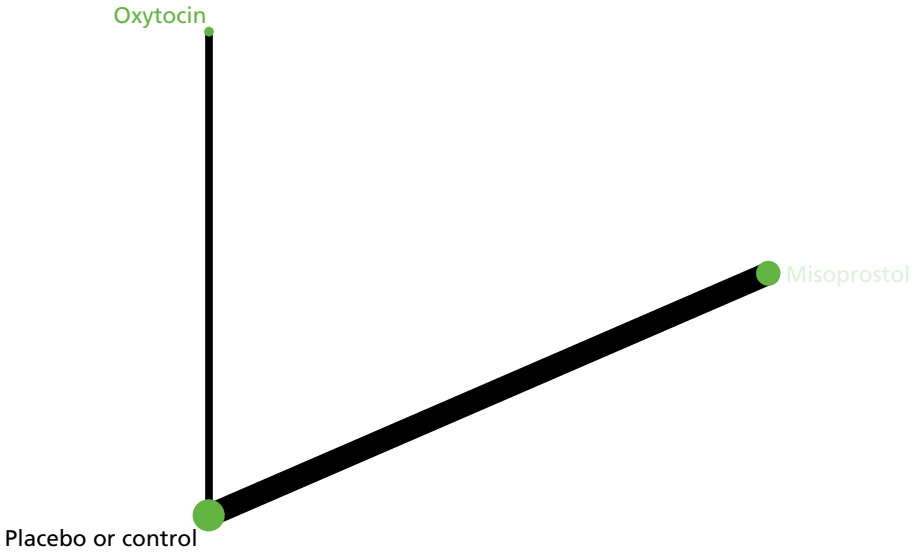

FIGURE 143 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml by health-care setting (community setting).

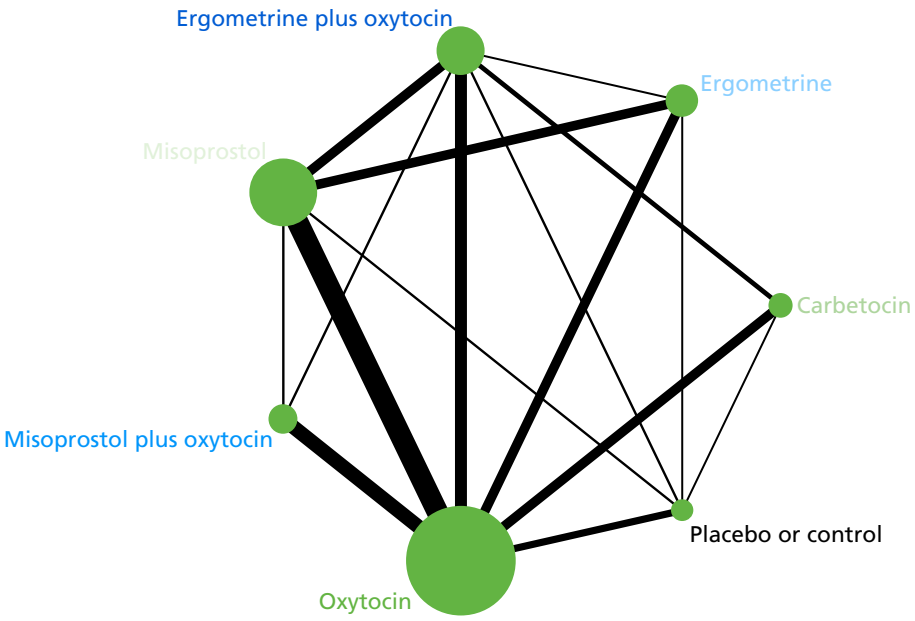

FIGURE 144 Network diagram for the prevention of PPH blood loss of ≥ 500 ml restricted to misoprostol studies that used a low dose (i.e. ≤ 500 µg).

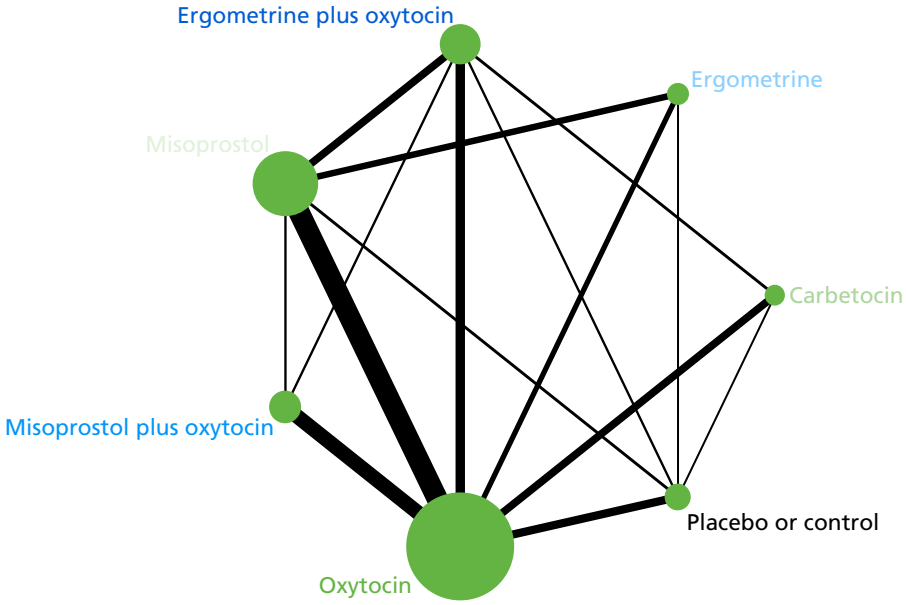

FIGURE 145 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml restricted to misoprostol studies that used a low dose (i.e. ≤ 500 µg).

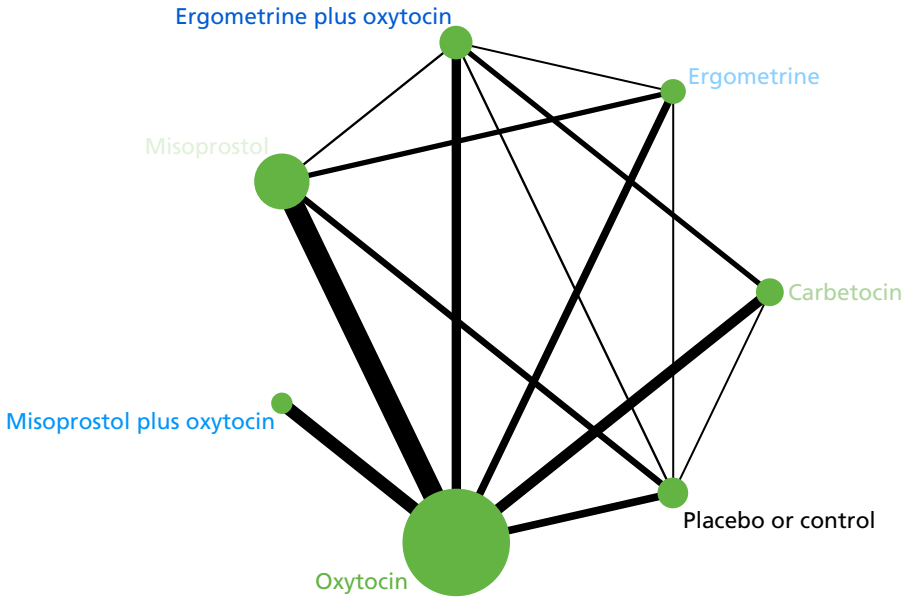

FIGURE 146 Network diagram for the prevention of PPH blood loss of ≥ 500 ml restricted to misoprostol studies that used a high dose (i.e. > 600 µg).

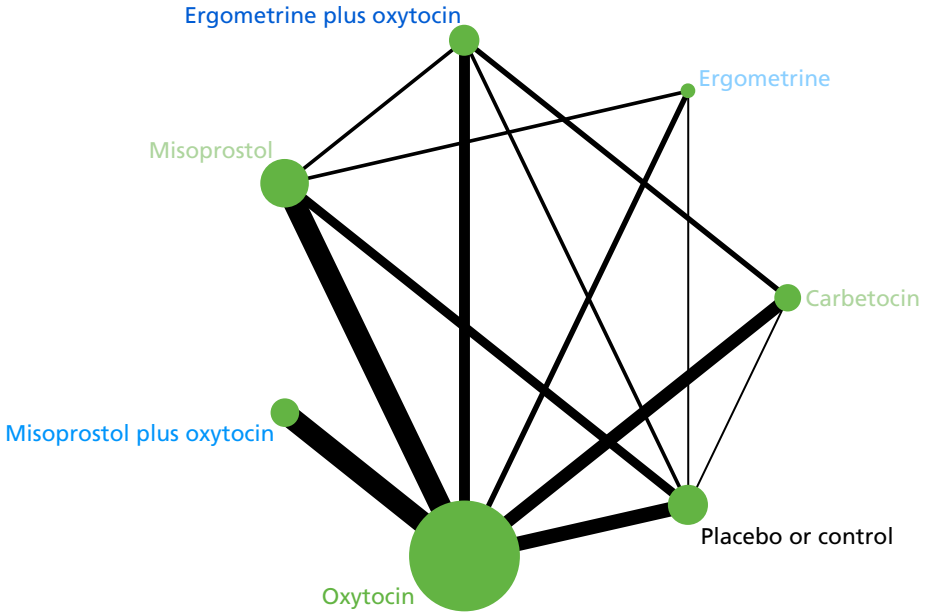

FIGURE 147 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml restricted to misoprostol studies that used a high dose (i.e. > 600 µg).

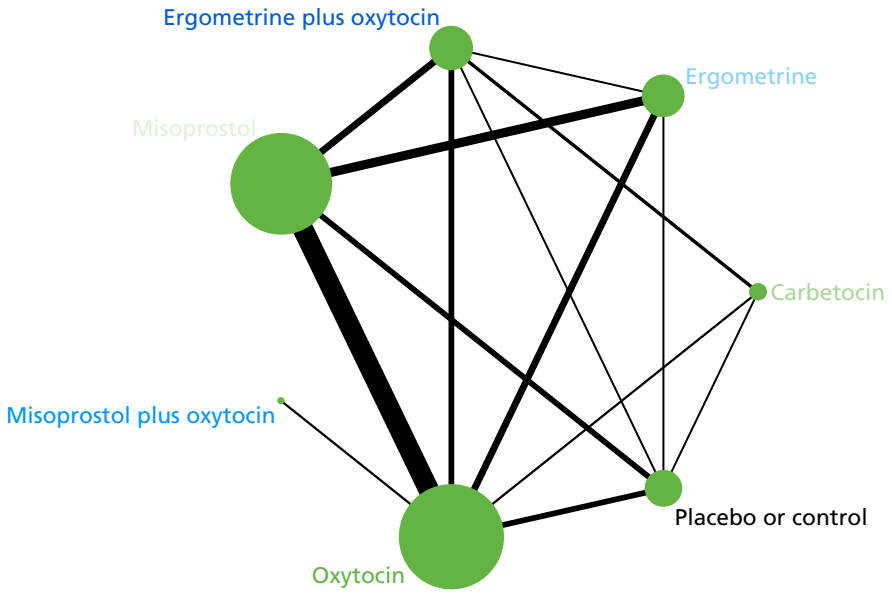

FIGURE 148 Network diagram for the prevention of PPH blood loss of ≥ 500 ml restricted to oxytocin studies that used an intramuscular or intravenous bolus of any dose.

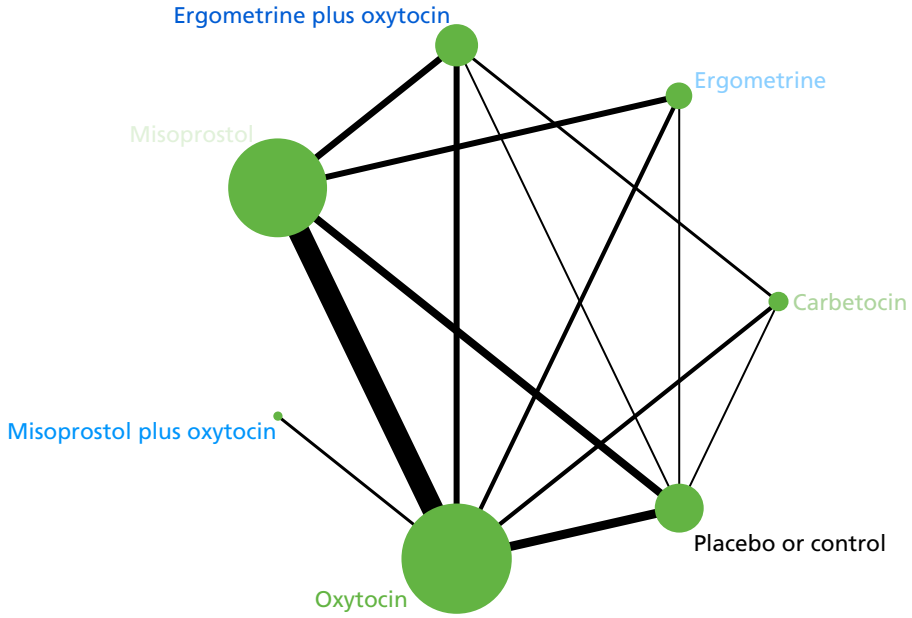

FIGURE 149 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml restricted to oxytocin studies that used an intramuscular or intravenous bolus of any dose.

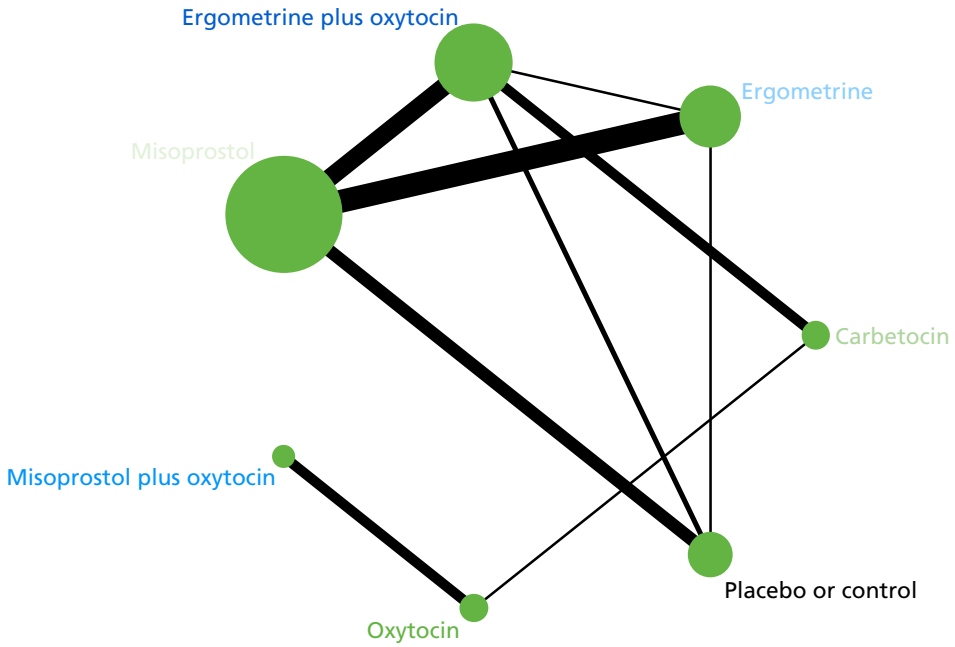

FIGURE 150 Network diagram for the prevention of PPH blood loss of ≥ 500 ml restricted to oxytocin studies that used an intravenous bolus plus an infusion of any dose.

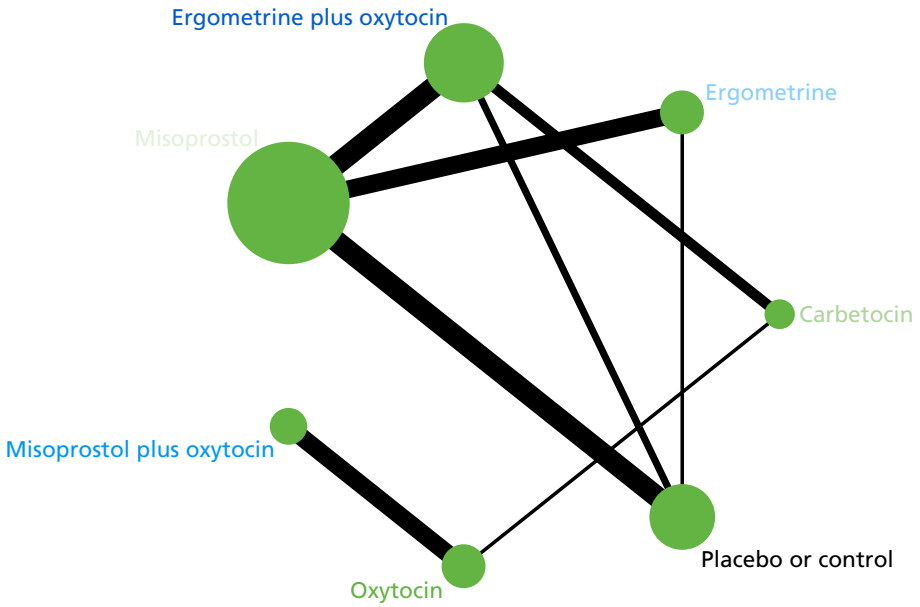

FIGURE 151 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml restricted to oxytocin studies that used an intravenous bolus plus an infusion of any dose.

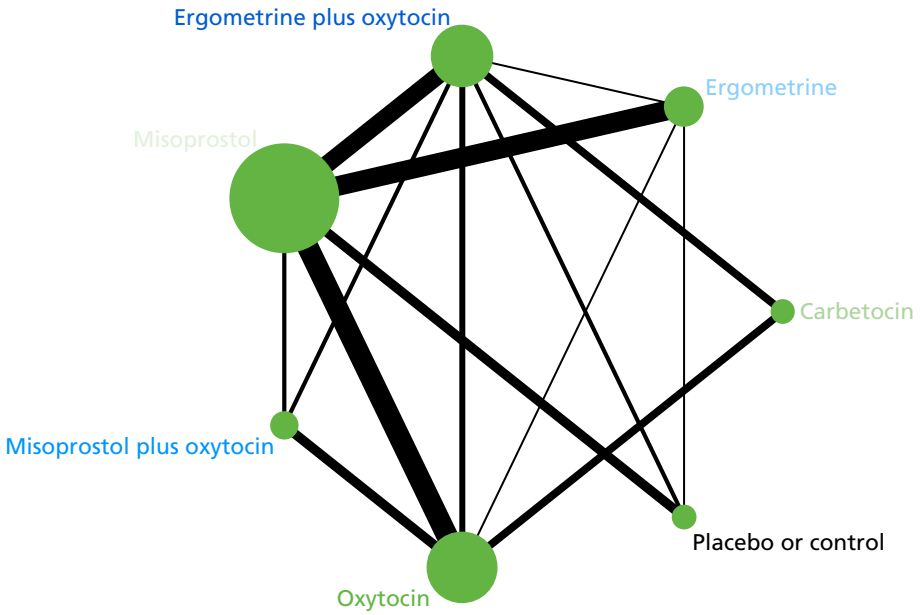

FIGURE 152 Network diagram for the prevention of PPH blood loss of ≥ 500 ml restricted to oxytocin studies that used an intravenous infusion only of any dose.

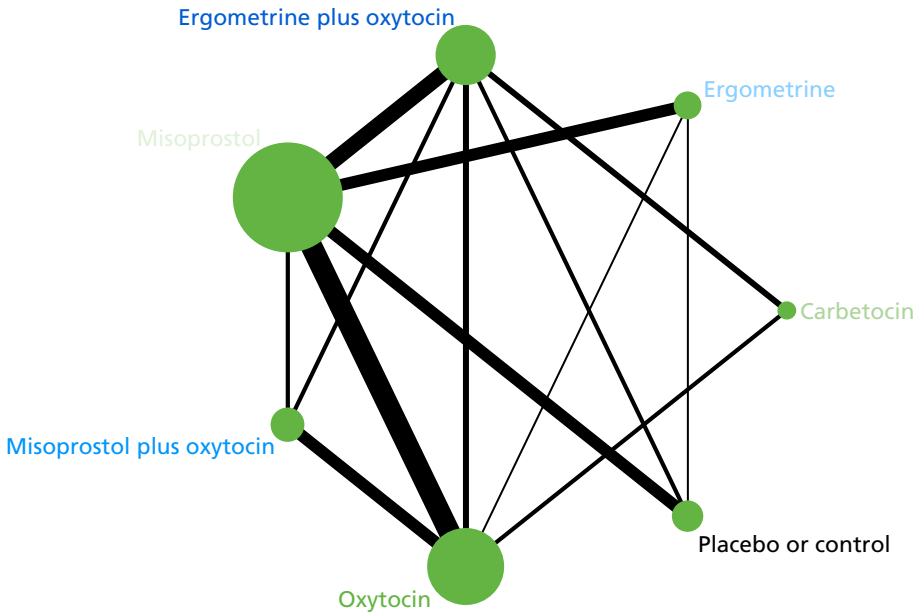

FIGURE 153 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml restricted to oxytocin studies that used an intravenous infusion only of any dose.

Sensitivity analyses

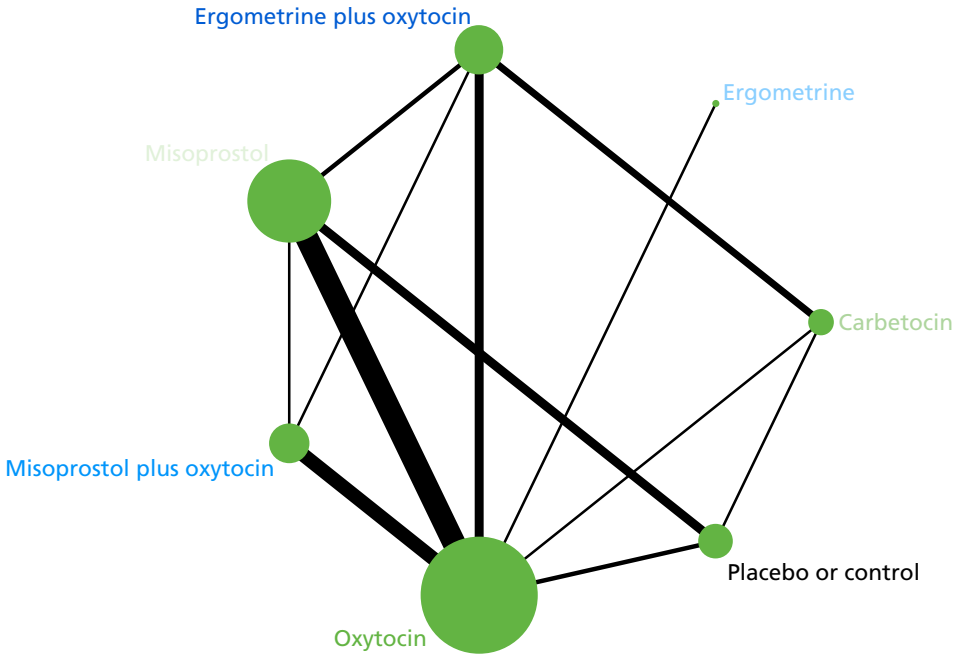

FIGURE 154 Network diagram for the prevention of PPH blood loss of ≥ 500 ml restricted to high-quality studies only.

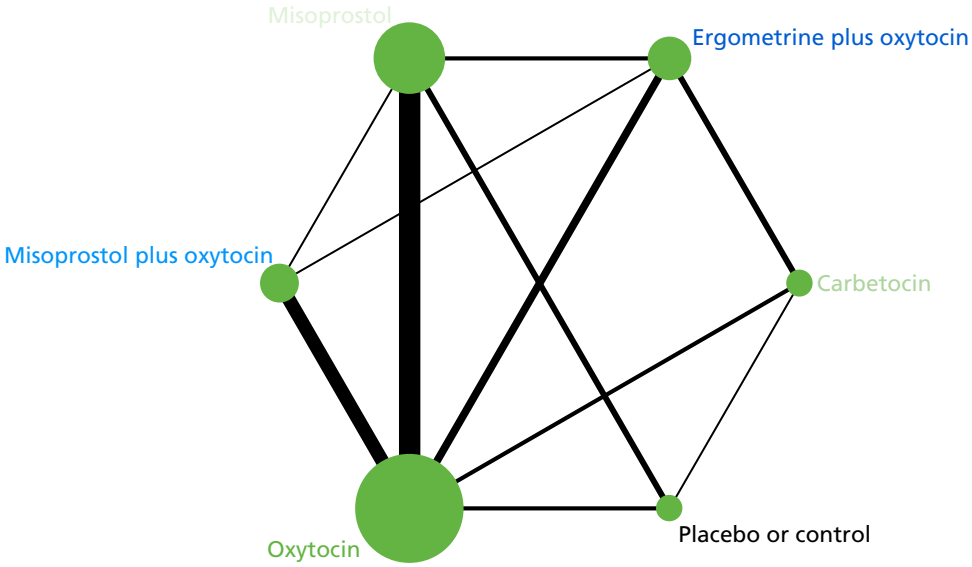

FIGURE 155 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml restricted to high-quality studies only.

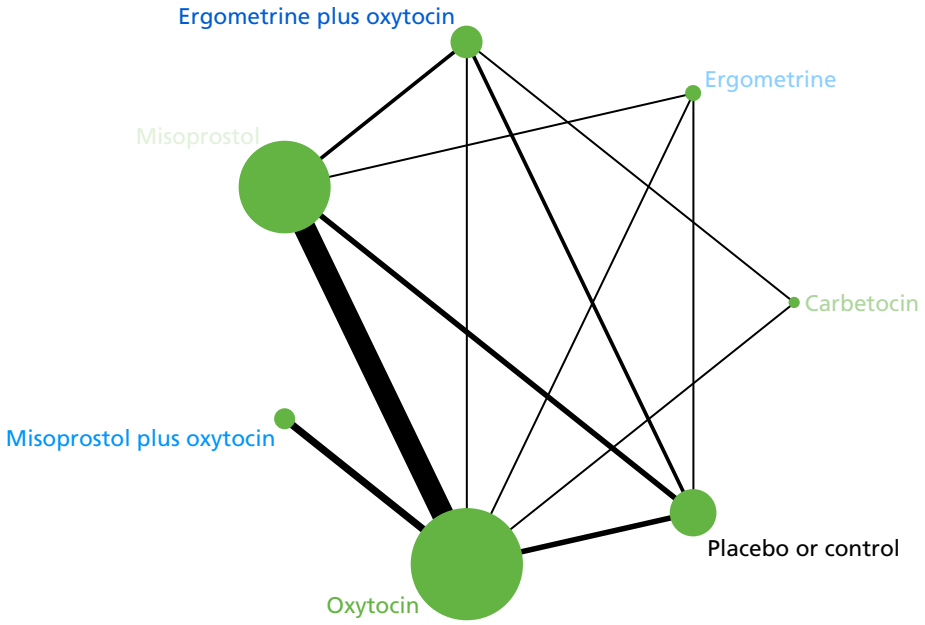

FIGURE 156 Network diagram for the prevention of PPH blood loss of ≥ 500 ml restricted to studies with funding source rated as being at a low risk of bias (public or no funding).

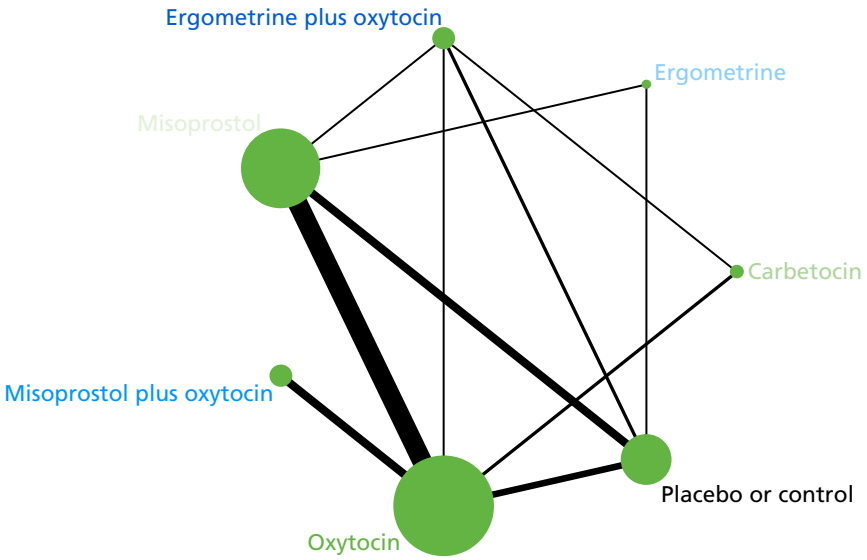

FIGURE 157 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml restricted to studies with funding source rated as being at a low risk of bias (public or no funding).

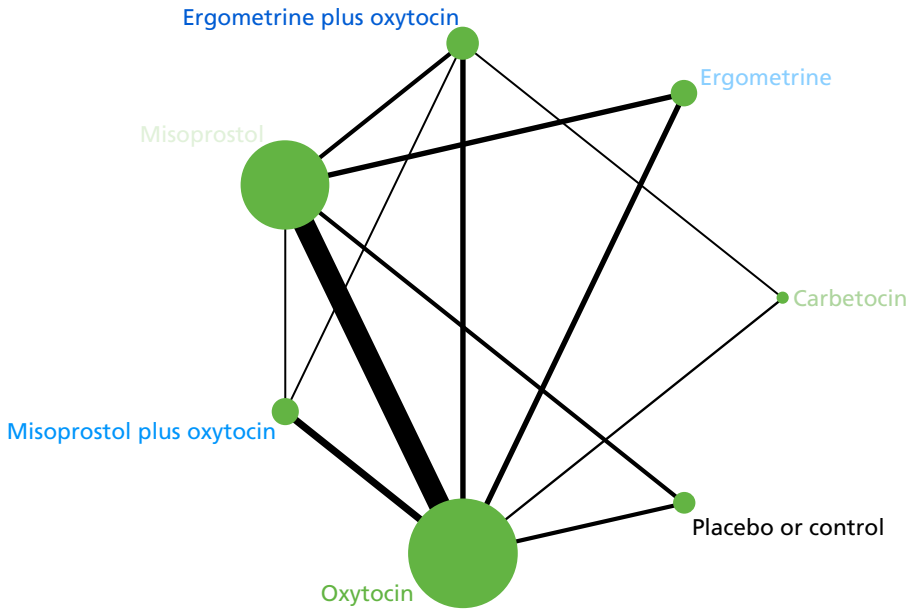

FIGURE 158 Network diagram for the prevention of PPH blood loss of ≥ 500 ml restricted to studies with an objective method of measuring blood loss.

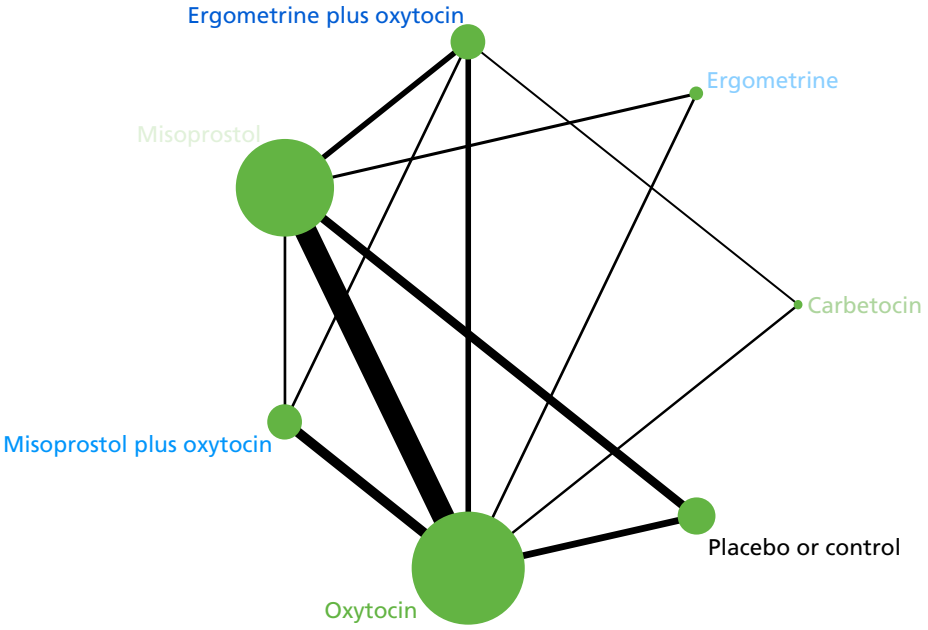

FIGURE 159 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml restricted to studies with an objective method of measuring blood loss.

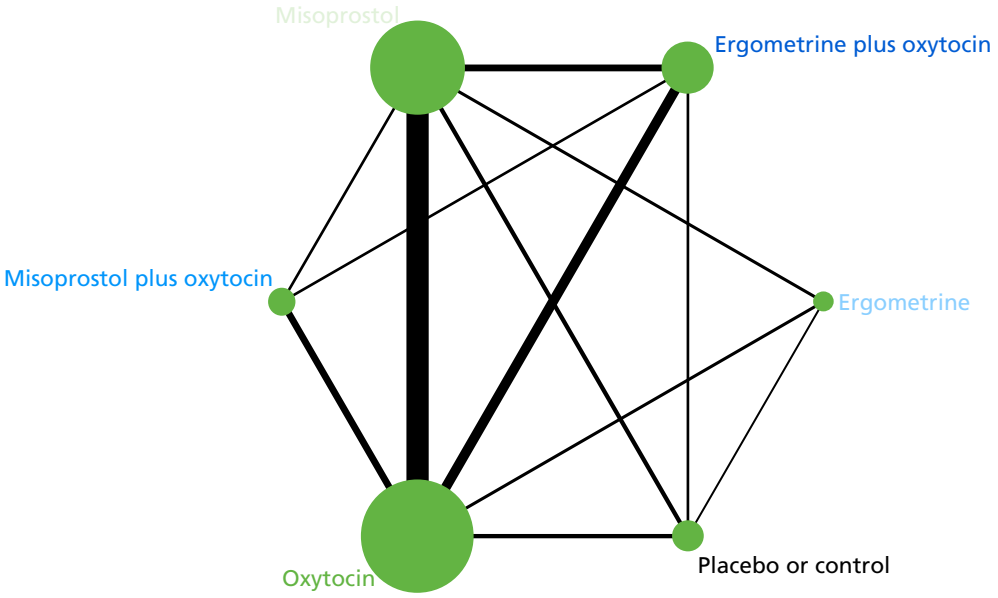

FIGURE 160 Network diagram for the prevention of PPH blood loss of ≥ 500 ml restricted to large studies (i.e. > 400 participants).

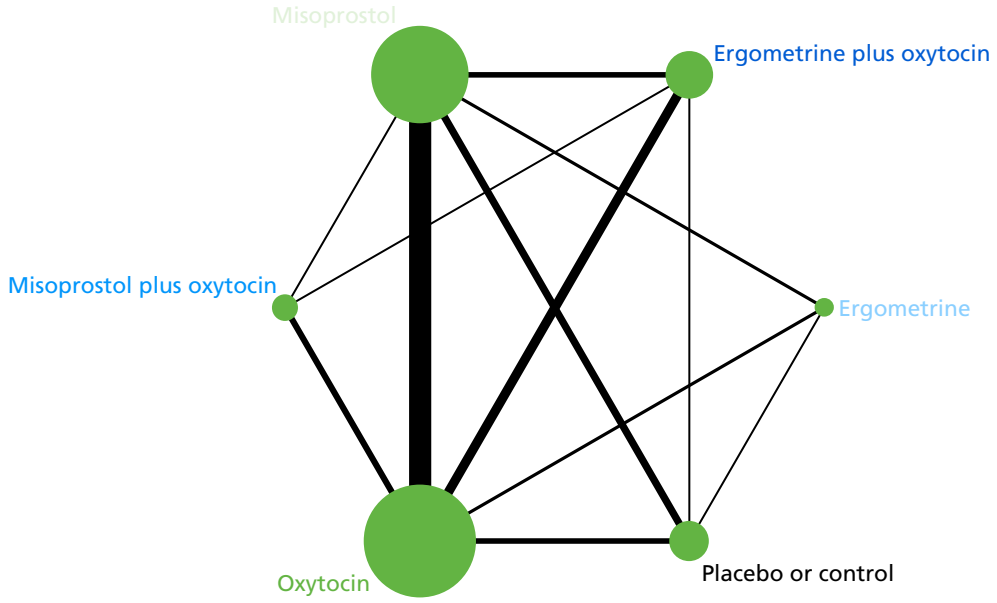

FIGURE 161 Network diagram for the prevention of PPH blood loss of ≥ 1000 ml restricted to large studies (i.e. > 400 participants).

Appendix 9 Probability of adverse events for each prevention strategy

Prevention strategy	Probability of adverse events (standard error in parenthesis)								
	Nausea	Vomiting	Hypertension	Headache	Tachycardia	Hypotension	Fever	Shivering	Abdominal pain
Vaginal delivery									
Oxytocin	0.039 (0.005)	0.010 (0.002)	0.021 (0.005)	0.044 (0.009)	0.025 (0.014)	0.005 (0.005)	0.020 (0.003)	0.071 (0.007)	0.134 (0.043)
Misoprostol plus oxytocin	0.270 (0.891)	0.039 (0.255)	–	–	–	–	0.090 (0.229)	0.261 (0.246)	–
Misoprostol	0.058 (0.161)	0.029 (0.097)	0.033 (0.655)	0.068 (0.323)	–	0.002 (1.630)	0.105 (0.162)	0.271 (0.140)	0.127 (0.158)
Ergometrine plus oxytocin	0.081 (0.202)	0.043 (0.099)	0.059 (0.633)	0.072 (0.294)	0.040 (0.551)	–	0.020 (0.336)	0.087 (0.282)	0.149 (0.245)
Ergometrine	0.106 (0.226)	0.042 (0.148)	0.172 (0.814)	0.129 (0.412)	–	–	0.020 (0.303)	0.097 (0.265)	0.172 (0.464)
Carbetocin	0.028 (0.341)	0.010 (0.305)	0.030 (0.808)	0.054 (0.382)	0.074 (0.498)	–	–	–	0.099 (0.307)
Caesarean section									
Oxytocin	0.091 (0.019)	0.056 (0.011)	0.167 (0.076)	0.094 (0.021)	0.024 (0.016)	0.169 (0.065)	0.033 (0.005)	0.050 (0.010)	0.172 (0.071)
Misoprostol plus oxytocin	0.164 (0.393)	0.085 (0.299)	–	0.141 (0.576)	–	0.220 (0.672)	0.073 (0.274)	0.160 (0.262)	0.333 (0.328)
Misoprostol	0.043 (0.687)	0.048 (0.407)	–	0.059 (0.451)	–	0.034 (1.077)	0.049 (0.639)	0.244 (0.400)	–
Ergometrine plus oxytocin	0.453 (1.012)	0.337 (1.127)	0.042 (1.080)	–	0.018 (0.707)	0.141 (0.532)	–	–	–
Ergometrine	–	–	–	–	–	–	–	–	–
Carbetocin	0.092 (0.327)	0.049 (0.282)	–	0.083 (0.151)	0.120 (1.546)	0.157 (0.346)	0.026 (0.785)	0.035 (0.392)	0.178 (0.089)

–, data are missing.

Appendix 10 Breakdown of delivery costs: vaginal delivery (normal and assisted)

Setting	Activity[a]	National average unit cost (£)	Source
Elective inpatient[b]	1362	2038.40	*NHS Reference Costs 2014–15*[187]
Non-elective long stay[b]	139,514	2634.20	*NHS Reference Costs 2014–15*[187]
Non-elective short stay[b]	223,663	1322.60	*NHS Reference Costs 2014–15*[187]
Day case[b]	77	418.51	*NHS Reference Costs 2014–15*[187]
Total[b]	364,616	1826.95	*NHS Reference Costs 2014–15*[187]
Minus average UK standard practice for preventing and treating PPH (10 IU i.m. injection of oxytocin)		0.91	*British National Formulary*[189]
Total cost of delivery		1826.04	

CC, complications and comorbidities; i.m., intramuscular.

a Activity is measured by the number of attendances, bed-days, clients, episodes, tests or other units of activity appropriate to the service.

b National average unit costs are weighted averages of the NHS reference costs for vaginal delivery (normal and assisted) without a postpartum surgical intervention in all inpatient settings.

The types of delivery include:

- normal delivery with a CC score of ≥ 2
- normal delivery with a CC score of 1
- normal delivery with a CC score of 0
- normal delivery, with epidural or induction, with a CC score of ≥ 2
- normal delivery, with epidural or induction, with a CC score of ≥ 1
- normal delivery, with epidural or induction, with a CC score of 0
- assisted delivery with a CC score of ≥ 2
- assisted delivery with a CC score of 1
- assisted delivery with a CC score of 0
- assisted delivery, with epidural or induction, with a CC score of ≥ 2
- assisted delivery, with epidural or induction, with a CC score of 1
- assisted delivery, with epidural or induction, with a CC score of 0.

Appendix 11 Breakdown of delivery costs: caesarean section (planned and emergency)

Setting	Activity[a]	National average unit cost (£)	Source
Elective inpatient[b]	5745	3035.09	*NHS Reference Costs 2014–15*[187]
Non-elective long stay[b]	138,750	4059.79	*NHS Reference Costs 2014–15*[187]
Non-elective short stay[b]	20,987	2312.54	*NHS Reference Costs 2014–15*[187]
Day case[b]	1	1598.44	*NHS Reference Costs 2014–15*[187]
Total[b]	165,483	3802.61	*NHS Reference Costs 2014–15*[187]
Minus average UK standard practice for preventing and treating PPH (10 IU i.m. injection of oxytocin)		0.91	*British National Formulary*[189]
Total cost of delivery		3801.70	

CC, complications and comorbidities; i.m., intramuscular.

a Activity is measured by the number of attendances, bed-days, clients, episodes, tests or other units of activity appropriate to the service.

b National average unit costs are weighted averages of the NHS reference costs for caesarean section delivery (planned and emergency).

The types of delivery include:

- planned caesarean section with a CC score of ≥ 4
- planned caesarean section with a CC score of 2–3
- planned caesarean section with a CC score of 0–1
- emergency caesarean section with a CC score of ≥ 4
- emergency caesarean section with a CC score of 2–3
- emergency caesarean section with a CC score of 0–1.

Appendix 12 Breakdown of delivery costs: vaginal delivery (normal and assisted) – community health-care setting

Setting	Activity[a]	National average unit cost (£)	Source
Community health-care setting[b]	8270	1283.84	*NHS Reference Costs 2013–14*[188]
Minus average UK standard practice for preventing and treating PPH (10 IU i.m. injection of oxytocin)		0.91	*British National Formulary*[189]
Total cost of delivery		1282.93	

CC, complications and comorbidities; i.m., intramuscular.

a Activity is measured by the number of attendances, bed-days, clients, episodes, tests or other units of activity appropriate to the service.

b National average unit costs are weighted averages of the NHS reference costs for vaginal delivery (normal and assisted) without a postpartum surgical intervention in a community healthcare setting.

The types of delivery include:

- normal delivery with a CC score of ≥ 2
- normal delivery with a CC score of 1
- normal delivery with a CC score of 0
- normal delivery with epidural or induction, with a CC score of ≥ 2
- normal delivery with epidural or induction, with a CC score of 1
- normal delivery with epidural or induction, with a CC score of 0
- assisted delivery with a CC score of ≥ 2
- assisted delivery with a CC score of 1
- assisted delivery with a CC score of 0
- assisted delivery with epidural or induction, with a CC score of 2
- assisted delivery with epidural or induction, with a CC score of 1
- assisted delivery with epidural or induction, with a CC score of 0.

Appendix 13 Mean length of hospital stay

Blood loss (ml)	Stage of model	Mean length of hospital stay (days) *vaginal delivery*	Mean length of hospital stay (days) *caesarean section*	Source
< 500	No PPH after prevention stage	1.57	2.8	Birmingham Women's Hospital real data
≥ 500	Bleeding stops after treatment stage 1	2.2	3.3	Birmingham Women's Hospital real data
≥ 1000	Bleeding stops after treatment stage 2	2.6	3.6	Birmingham Women's Hospital real data
≥ 1500	Bleeding stops after treatment stage 3	3	4.5	Birmingham Women's Hospital real data
	Bleeding stops after treatment stage 4	6	6	Glaze *et al.*[193]

Table shows mean length of hospital stay for each stage of the decision tree model.

Appendix 14 Breakdown of excess bed-day costs: vaginal delivery

Setting	Activity[a]	National average unit cost (£)	Source
Elective inpatient excess bed-days[b]	173	432.56	*NHS Reference Costs 2014–15*[187]
Non-elective excess bed-days[b]	58,278	440.51	*NHS Reference Costs 2014–15*[187]
Total[a]	58,451	440.49	

a Activity is measured by the number of attendances, bed-days, clients, episodes, tests or other units of activity appropriate to the service.
b National average unit costs are weighted averages of the NHS reference costs for excess bed-days associated with vaginal delivery (normal and assisted).

The types of delivery include:

- normal delivery with a CC score of ≥ 2
- normal delivery with a CC score of 1
- normal delivery with a CC score of 0
- normal delivery, with epidural or induction, with a CC score of 2
- normal delivery, with epidural or induction, with a CC score of 1
- normal delivery, with epidural or induction, with a CC score of 0
- normal delivery, with epidural and induction, or with post-partum surgical intervention, with a CC score of ≥ 2
- normal delivery, with epidural and induction, or with post-partum surgical intervention, with a CC score of 1
- normal delivery, with epidural and induction, or with post-partum surgical intervention, with a CC score of 0
- normal delivery, with epidural or induction, and with post-partum surgical intervention, with a CC score of ≥ 2
- normal delivery, with epidural or induction, and with post-partum surgical intervention, with a CC score of 1
- normal delivery, with epidural or induction, and with post-partum surgical intervention, with a CC score of 0
- normal delivery, with epidural, induction and post-partum surgical intervention, with a CC score of ≥ 2
- normal delivery, with epidural, induction and post-partum surgical intervention, with a CC score of 1
- normal delivery, with epidural, induction and post-partum surgical intervention, with a CC score of 0
- assisted delivery with a CC score of ≥ 2
- assisted delivery with a CC score of 1
- assisted delivery with a CC score of 0
- assisted delivery, with epidural or induction, with a CC score of ≥ 2
- assisted delivery, with epidural or induction, with a CC score of 1
- assisted delivery, with epidural or induction, with a CC score of 0
- assisted delivery, with epidural and induction, or with post-partum surgical intervention, with a CC score of ≥ 2
- assisted delivery, with epidural and induction, or with post-partum surgical intervention, with a CC score of 1
- assisted delivery, with epidural and induction, or with post-partum surgical intervention, with a CC score of 0
- assisted delivery, with epidural or induction, and with post-partum surgical intervention, with a CC score of ≥ 2
- assisted delivery, with epidural or induction, and with post-partum surgical intervention, with a CC score of 1
- assisted delivery, with epidural or induction, and with post-partum surgical intervention, with a CC score of 0
- assisted delivery, with epidural, induction and post-partum surgical intervention, with a CC score of ≥ 2
- assisted delivery, with epidural, induction and post-partum surgical intervention, with a CC score of 1
- assisted delivery, with epidural, induction and post-partum surgical intervention, with a CC score of 0

for which CC stands for complications and comorbidities.

Appendix 15 Breakdown of excess bed-day costs: caesarean section

Setting	Activity[a]	National average unit cost (£)	Source
Elective inpatient excess bed-days[b]	361	452.35	*NHS Reference Costs 2014–15*[187]
Non-elective excess bed-days[b]	34,042	444.31	*NHS Reference Costs 2014–15*[187]
Total	34,403	444.39	

a Activity is measured by the number of attendances, bed-days, clients, episodes, tests or other units of activity appropriate to the service.
b National average unit costs are weighted averages of the NHS reference costs for excess bed-days associated with caesarean delivery (planned and emergency).
The types of delivery include:
- planned caesarean section with a CC score of ≥ 4
- planned caesarean section with a CC score of 2–3
- planned caesarean section with a CC score of 0–1
- emergency caesarean section with a CC score of ≥ 4
- emergency caesarean section with a CC score of 2–3
- emergency caesarean section with a CC score of 0–1

for which CC stands for complications and comorbidities.

Appendix 16 Treatment of adverse events with associated costs

Adverse event	Treatment	Cost (£)	Breakdown of costs	Source
Nausea[a]	Cyclizine (50 mg, twice, intravenous injection) and ondansatron (4 mg twice, intramuscular)	28.50	Cyclizine (£5.42) and ondansetron (£23.08)	*NHS Reference Costs 2014–15*[187]
Vomiting	Prochlorperazine (12.5 mg 3 times daily, intramuscular) with i.v. fluids – 24 hours	442.05–445.95	Prochlorperazine (£1.56) and excess bed-day (£440.49, vaginal delivery; £444.39, caesarean section)	*NHS Reference Costs 2014–15*;[187] *British National Formulary*[189]
Hypertension[a]	Labetalol (200 mg over 24 hours,) and nifedipine (20 mg over 24 hours, orally)	630.55–634.45	Labetalol (£189.61) and nifedipine (£0.45) and excess bed-day (£440.49, vaginal delivery; £444.39, caesarean section)	*NHS Reference Costs 2014–15*;[187] *British National Formulary*[189]
Headache[a]	Paracetamol and codeine for 24 hours	0.66	Paracetamol (£0.19) and codeine (£0.47)	*NHS Reference Costs 2014–15*[187]
Tachycardia	Observation over 24 hours	440.49–444.39	Excess bed-day (£440.49, vaginal delivery; £444.39 caesarean section)	*British National Formulary*[189]
Hypotension	i.v. fluids and observation over 24 hours	440.49–444.39	Excess bed-day (£440.49, vaginal delivery; £444.39, caesarean section)	*British National Formulary*[189]
Fever[a]	Paracetamol and i.v. antibiotics with fluids Observation over 24 hours, including a blood culture, high vaginal swab, full blood count and C-Reactive Protein (CRP) test	443.04–446.94	Paracetamol (£0.19) and amoxicillin (£2.36) and excess bed-day for tests and observation (£440.49, vaginal delivery; £444.39 caesarean section)	*NHS Reference Costs 2014–15*;[187] *British National Formulary*[189]
Shivering	Observation over 24 hours	440.49–444.39	Excess bed-day (£440.49, vaginal delivery; £444.39 caesarean section)	*British National Formulary*[189]
Abdominal pain[a]	Paracetamol and oral morphine for 24 hours	0.25	Paracetamol (£0.06) and ibuprofen (£0.19)	*NHS Reference Costs 2014–15*[187]

i.v., intravenous.
a Weighted average excess bed-day cost for vaginal delivery.
Table shows the treatment of possible adverse events from uterotonic drugs.
Treatment choices sourced from expert opinion.
i.v. fluids are included in excess bed-day costs.

Appendix 17 Summary of results: scenario analysis (vaginal delivery in a community health-care setting)

Prevention Strategy	Average cost per woman (£)	Effectiveness	ICER[a] (£)
PPH blood loss of ≥ 500 ml avoided			
Oxytocin	2098.01	0.908	–
Carbetocin	2122.46	0.944	686.92
Ergometrine and oxytocin	2137.11	0.936	Dominated
Misoprostol and oxytocin	2238.23	0.931	Dominated
Ergometrine	2240.31	0.891	Dominated
Misoprostol	2258.22	0.899	Dominated
PPH blood loss of ≥ 1000 ml avoided			
Oxytocin	2098.01	0.995718	–
Carbetocin	2122.46	0.997204	16,459.15
Ergometrine and oxytocin	2137.11	0.995370	Dominated
Misoprostol and oxytocin	2238.23	0.994674	Dominated
Ergometrine	2240.31	0.988329	Dominated
Misoprostol	2258.22	0.987929	Dominated
Major outcome averted			
Oxytocin	2098.01	0.999890	–
Carbetocin	2122.46	0.999928	642,935.50
Ergometrine and oxytocin	2137.11	0.999881	Dominated
Misoprostol and oxytocin	2238.23	0.999864	Dominated
Ergometrine	2240.31	0.999701	Dominated
Misoprostol	2258.22	0.999691	Dominated

a ICER: incremental cost-effectiveness ratio expressed as the additional cost per additional case of PPH (500 ml) avoided.

Appendix 18 Summary of results: one-way sensitivity analyses

Prevention strategies not dominated			
PPH blood loss ≥ 500 ml avoided, ICER[a] (£)		PPH blood loss ≥ 1000 ml avoided, ICER[a] (£)	Major outcome averted, ICER[a] (£)
Sensitivity analysis 2 (increasing the cost of treatment stage 4)			
Vaginal delivery			
Oxytocin	–	–	–
Carbetocin	926.99	22,883.10	893,874.25
Sensitivity analysis 3 (decreasing the cost of treatment stage 4)			
Vaginal delivery			
Oxytocin	–	–	–
Carbetocin	928.32	22,915.96	895,154.67
Sensitivity analysis 4 (increasing the cost of treatment stage 4)			
Vaginal delivery			
Oxytocin	–	–	–
Carbetocin	925.69	22,851.69	892,624.26
Sensitivity analysis 5 (changing the effectiveness of treatment stage 3) 1 Treatment stage 3 is 0% effective			
Vaginal delivery			
Oxytocin	–	–	–
Carbetocin	840.69	20,752.77	129,704.79
2 Treatment stage 3 is 100% effective			
Vaginal delivery			
Oxytocin	–	–	–
Carbetocin	944.22	23,308.49	Dominated

a ICER: incremental cost-effectiveness ratio expressed as the additional cost per additional case of PPH (500 ml) avoided. ICERs for delivery by caesarean section are not shown for any one-way sensitivity analyses as ergometrine plus oxytocin was the only dominant strategy across all one-way sensitivity analyses.
There were, therefore, no ICERs for delivery by caesarean section.

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