National Institute for Health and Care Excellence

Final

Intrapartum care

[M] Evidence reviews for uterotonics for the prevention of postpartum haemorrhage

NICE guideline NG235

Evidence reviews underpinning recommendations 1.10.9 to 1.10.11 and 1.10.13 in the NICE guideline

September 2023

Final

These evidence reviews were developed by NICE

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ISBN: 978-1-4731-5398-1

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Uterotonics for the prevention of postpartum haemorrhage

Review question

What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Introduction

Women who choose to have active management of the third stage of labour are routinely offered a uterotonic during the third stage of labour. This medicine leads to contraction of the uterus, separation of the placenta and reduces blood loss from the placental site, reducing the risk of postpartum haemorrhage (PPH). A number of different uterotonics are available including oxytocin, the oxytocin analogue carbetocin, prostaglandins and the ergot alkaloid ergometrine.

The aim of this review was to determine which uterotonic agent is the most effective and cost-effective for the prevention of postpartum haemorrhage.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• Women in the third stage of labour following a vaginal or caesarean birth
Intervention	• The following uterotonic agents: ○ Carbetocin ○ Ergometrine (includes also ergonovine, methylergonovine) ○ Injectable prostaglandins (carboprost, tromethamine, sulprostone) ○ Misoprostol - Dose ≤600 mcg - Dose >600 mcg to ≤800 mcg - Dose >800 mcg to ≤1000 mcg - Dose >1000 mcg ○ Oxytocin - Dose ≤1 iu - Dose >1 iu to ≤ 5 iu - Dose >5 iu to ≤ 10 iu - Dose > 10 iu • The following combination agents: ○ Syntometrine ® as a fixed-combination agent containing 5 international units (IU) of oxytocin and 500 mcg of ergometrine; any oxytocin dose and route when combined with any dose and route of ergometrine, ergonovine, or methylergonovine ○ Misoprostol plus oxytocin (any oxytocin dose and route when combined with any dose and route of misoprostol) The uterotonic or combination agents noted above will be eligible if they are administered systemically by a healthcare professional for preventing PPH at birth. Any dosage, route and regimen will be included

Comparison	• Any uterotonic agent listed as part of the interventions compared to another • Placebo • No treatment
Outcome	**Critical:** • Primary PPH ≥1000 mL **Important:** • Severe maternal morbidity: intensive care admission • Additional uterotonics • Blood transfusions • Mean volume of blood loss (mL)

IU: international units; PPH: postpartum haemorrhage

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

A total of 220 randomised controlled trials (RCTs) were included in this evidence review. Most of these studies were identified from a published network meta-analysis (NMA) (n=196) (Gallos, 2018). A further 24 studies were identified by the updated literature search and included in the review.

53 studies provided evidence that was not included in the NMA and pairwise analysis was conducted for these studies (see supplement 5).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

There was evidence available for all the specified outcomes, but not all studies provided data for every outcome included in this evidence review, therefore a narrative summary is presented below, which describes the overall evidence, and the studies that provided evidence for specific outcomes.

Trials were predominantly in population with high risk of PPH (n=78), or a combination of high and low risk for PPH (n=73). There were 69 trials with a population of low risk for PPH. High risk for PPH was defined as women with comorbidities and pregnancy complications

predisposing them to a high risk of PPH, and low risk for PPH was defined as healthy women with a singleton term pregnancy delivering vaginally.

The majority of the studies reported vaginal births (n=149). The rest reported caesarean births (n=67), both vaginal and caesarean births (n=3) and 1 study did not specify mode of birth.

Most studies included both nulliparous and multiparous women (n=125). A minority of trials included either nulliparous (n=7) or multiparous (n=1) women, and the remainder did not state the parity of participants (n=87).

Trials were predominantly conducted in women with a singleton pregnancy (n=145). Forty trials included a mixed population of women with both a singleton and multi-fetal pregnancies. One trial was conducted exclusively in women with a multi-fetal pregnancy. The remaining studies (n=35) did not explicitly state whether participants had a single or multi-fetal pregnancy.

Most of the trials were in a hospital setting (n=212), with only a minority in a community setting (n=8).

The majority of studies included (n=185) were 2 arm trials, directly comparing 2 different interventions, 24 studies were 3 arm trials, 9 studies were 4 arm trials and 2 were 5 arm trials.

There was evidence available for all listed interventions, apart from 2 specified injectable prostaglandins: tromethamine and sulprostone. There was evidence for all specified doses of misoprostol and oxytocin.

See the full evidence tables in appendix D (which is provided as a separate document, supplement 4) and the forest plots in appendix E.

Quality assessment of included studies

See the clinical evidence profiles in appendix D (which is provided as a separate document, supplement 4).

Clinical evidence profile for outcomes included in the network meta-analysis

NMA was used to synthesise evidence for the following outcomes (both for the whole population of women and for the subgroups of either vaginal or caesarean birth):

- PPH ≥ 1000 mL
- Additional uterotonics
- Blood transfusion
- ICU admission (severe maternal morbidity)
- Mean blood loss (mL).

Where possible, placebo was used as the reference treatment in the NMAs. In two of the outcomes for the caesarean birth subgroup, placebo was not included in the evidence network and therefore another treatment (carbetocin) was used as the reference for those two analyses.

PPH ≥ 1000ml

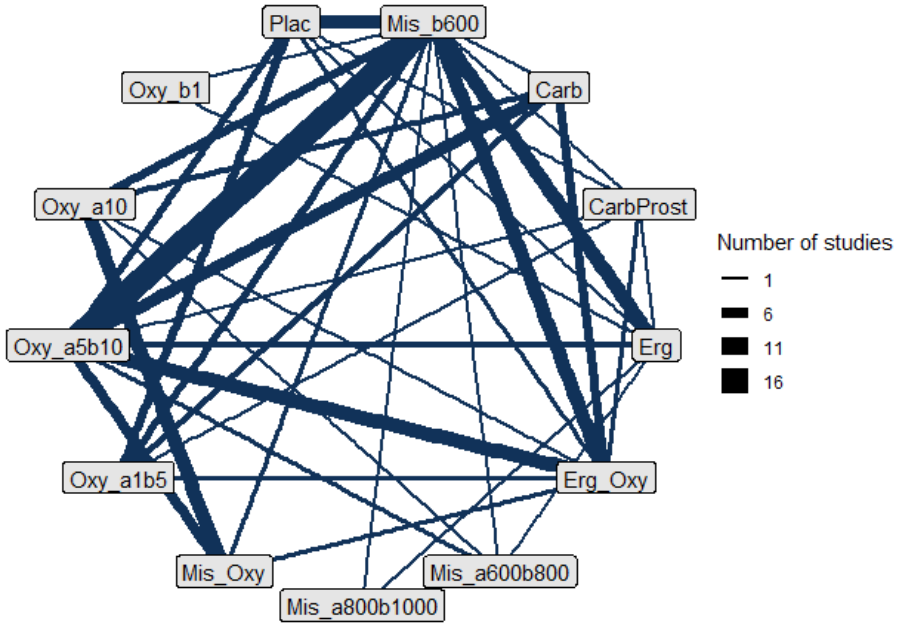
98 studies, comparing 13 interventions in 113,135 women were included in this analysis. Of these studies, 1 included women who had either vaginal or caesarean births, 71 were

conducted in women who had vaginal births only, and 26 in women who had caesarean births only.

Of the 122 studies that reported this outcome, 24 studies were excluded as they reported no events in any arm for this outcome.

The network plot for this outcome is shown below at Figure 1, the odds ratios and log odds ratios compared to placebo in Table 2, the Forest plot at Figure 2 and the median treatment ranks in Table 3.

Figure 1: Network of evidence for PPH ≥ 1000 mL, full dataset



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; CarbProst, carboprost; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Mis_a800b1000, misoprostol >800mcg and ≤1000mcg; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU; Oxy_b1, oxytocin ≤1IU.

Table 2: Odds ratio, log odds ratio and 95% CrIs for PPH ≥ 1000 mL for all interventions compared with placebo

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Misoprostol >800 mcg and ≤ 1000 mcg	0.000 (0.000, 0.065)	-44.31 (-81.14, -2.735)	-
Misoprostol >600 mcg and ≤ 800 mcg	0.199 (0.045, 0.713)	-1.613 (-3.112, -0.339)	-
Carbetocin	0.425 (0.293, 0.577)	-0.857 (-1.228, -0.551)	-
Ergometrine	0.434 (0.214, 0.837)	-0.8344 (-1.54, -0.179)	1
Ergometrine plus oxytocin	0.449 (0.332, 0.600)	-0.800 (-1.104, -0.511)	2
Carboprost	0.467 (0.198, 1.116)	-0.762 (-1.621, 0.1096)	1
Oxytocin >1 IU and ≤ 5 IU	0.548 (0.391, 0.766)	-0.601 (-0.938, -0.266)	5
Oxytocin >5 IU and ≤	0.555 (0.435, 0.711)	-0.589 (-0.832, -0.341)	4

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
10 IU			
Misoprostol plus oxytocin	0.569 (0.383, 0.838)	-0.565 (-0.961, -0.177)	-
Misoprostol ≤ 600 mcg	0.647 (0.502, 0.817)	-0.436 (-0.690, -0.203)	8
Oxytocin > 10 IU	0.803 (0.545, 1.170)	-0.2196 (-0.607, 0.157)	-
Oxytocin ≤1 IU	0.824 (0.134, 5.018)	-0.1938 (-2.008, 1.613)	-

Results from the random effects NMA. OR<1 favours the intervention (lower risk of PPH≥1000ml in the intervention arm) with lower numbers indicating greater benefit, OR>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

In this analysis only one study included the high-dose misoprostol arm and reported no PPH ≥ 1000 mL events in that arm which led to high uncertainty in the comparison with this treatment. Therefore high-dose misoprostol has been excluded from the ranking in Table 3 as the probability of being best can be biased for highly uncertain estimates.

Figure 2: Forest plot, PPH ≥ 1000 mL full population (OR<1 favours the intervention)

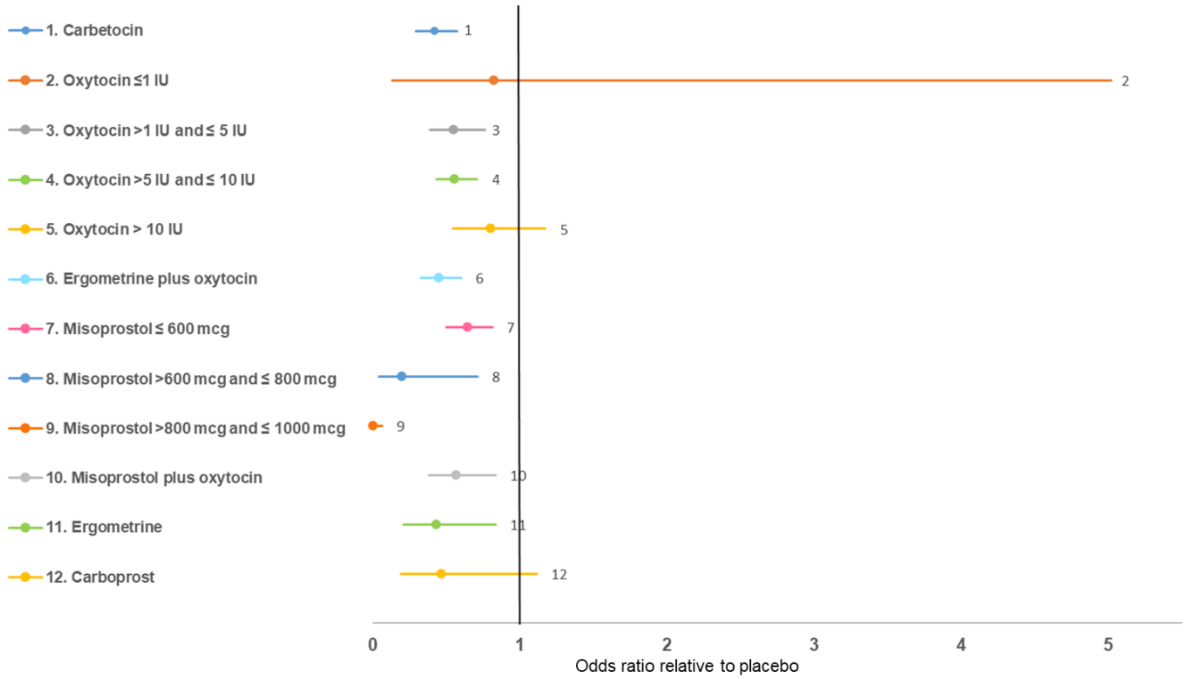


Table 3: Median treatment ranks and probability of being the best treatment for all interventions for PPH ≥ 1000 mL

Intervention	Median (95% CrI) treatment rank	Probability of being best
Misoprostol >600 mcg and ≤ 800 mcg	1 (1, 9)	74.23%
Carbetocin	3 (1, 6)	1.83%
Ergometrine plus oxytocin	4 (2, 7)	0.34%
Ergometrine	4 (1, 10)	1.26%
Carboprost	4 (1, 12)	12.71%
Oxytocin >1 IU and ≤ 5 IU	7 (3, 10)	0.00%
Oxytocin >5 IU and ≤ 10 IU	7 (4, 9)	0.00%
Misoprostol plus oxytocin	7 (3, 10)	0.00%

Intervention	Median (95% CrI) treatment rank	Probability of being best
Oxytocin ≤1 IU	11 (1, 12)	9.62%
Misoprostol ≤ 600 mcg	9 (6, 10)	0.00%
Oxytocin > 10 IU	10 (8, 12)	0.00%
Placebo	11 (10, 12)	0.00%

Misoprostol >800 mcg and ≤ 1000 mcg is excluded from the ranking due to highly uncertain estimates.

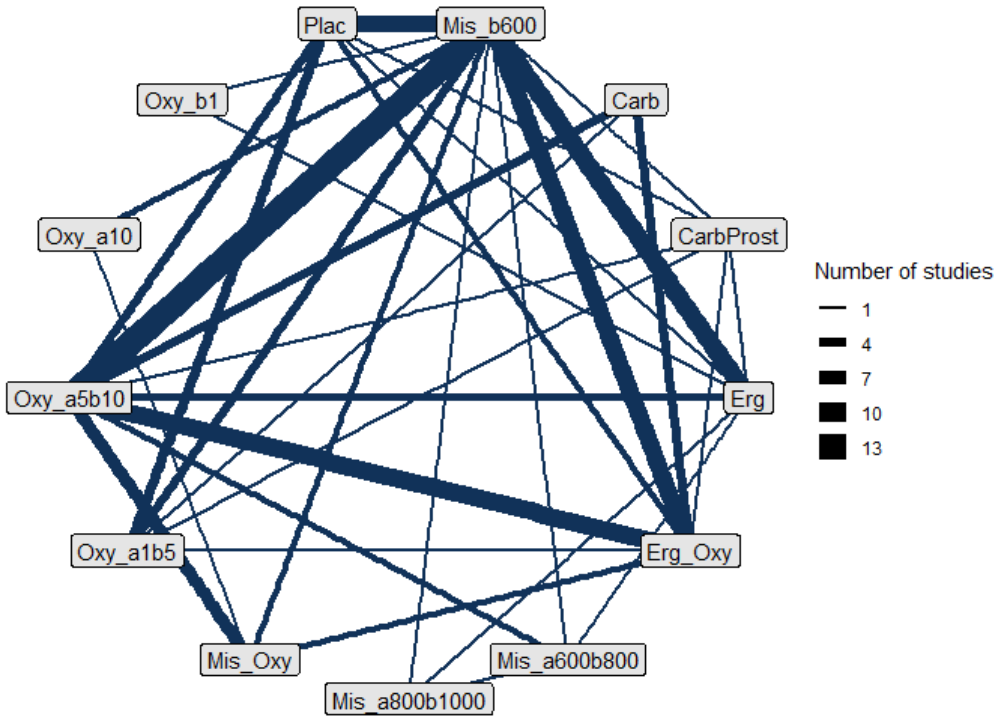
Vaginal birth subgroup analysis

71 studies comparing 13 treatments in 107,322 women were included in this subgroup analysis.

Of the 91 studies that reported this outcome, 20 studies were excluded as they reported no events in any arm for this outcome.

The network plot for this outcome is shown below at Figure 3, the odds ratios compared to placebo in Table 4, the Forest plot at Figure 4 and the median treatment ranks in Table 5.

Figure 3: Network of evidence for PPH ≥ 1000 mL, vaginal birth subgroup



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; CarbProst, carboprost; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Mis_a800b1000, misoprostol >800mcg and ≤1000mcg; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU; Oxy_b1, oxytocin ≤1IU.

Table 4: Odds ratio, log odds ratio and 95% CrIs for PPH ≥ 1000mL for all interventions compared with placebo, vaginal birth subgroup

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Misoprostol >800 mcg and ≤ 1000 mcg	0.000 (0.000, 0.413)	-21.83 (-66.24, -0.885)	-
Misoprostol >600 mcg and ≤ 800 mcg	0.300 (0.035, 1.759)	-1.205 (-3.347, 0.5648)	-
Carboprost	0.312 (0.094, 1.023)	-1.166 (-2.365, 0.0231)	1
Ergometrine	0.451 (0.213, 0.913)	-0.796 (-1.546, -0.091)	1
Ergometrine plus oxytocin	0.453 (0.328, 0.602)	-0.792 (-1.115, -0.507)	2
Misoprostol plus oxytocin	0.468 (0.295, 0.733)	-0.759 (-1.222, -0.311)	-
Carbetocin	0.470 (0.302, 0.680)	-0.755 (-1.197, -0.386)	-
Oxytocin >1 IU and ≤ 5 IU	0.547 (0.375, 0.788)	-0.603 (-0.981, -0.239)	5
Oxytocin >5 IU and ≤ 10 IU	0.556 (0.429, 0.721)	-0.586 (-0.847, -0.327)	4
Misoprostol ≤ 600 mcg	0.650 (0.497, 0.814)	-0.431 (-0.699, -0.206)	8
Oxytocin > 10 IU	0.779 (0.359, 1.780)	-0.2493 (-1.024, 0.577)	-
Oxytocin ≤1 IU	0.819 (0.131, 5.254)	-0.1993 (-2.03, 1.659)	-

Results from the random effects NMA. OR<1 favours the intervention (lower risk of PPH≥1000ml in the intervention arm) with lower numbers indicating greater benefit, OR>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

In this analysis only one study included the high-dose misoprostol arm, and reported no PPH ≥ 1000 mL events in that arm which led to high uncertainty in the comparison with this treatment. Therefore high-dose misoprostol has been excluded from the ranking in Table 5 as the probability of being best can be biased for highly uncertain estimates.

Figure 4: Forest plot, PPH ≥ 1000mL vaginal birth (OR< 1 favours intervention)

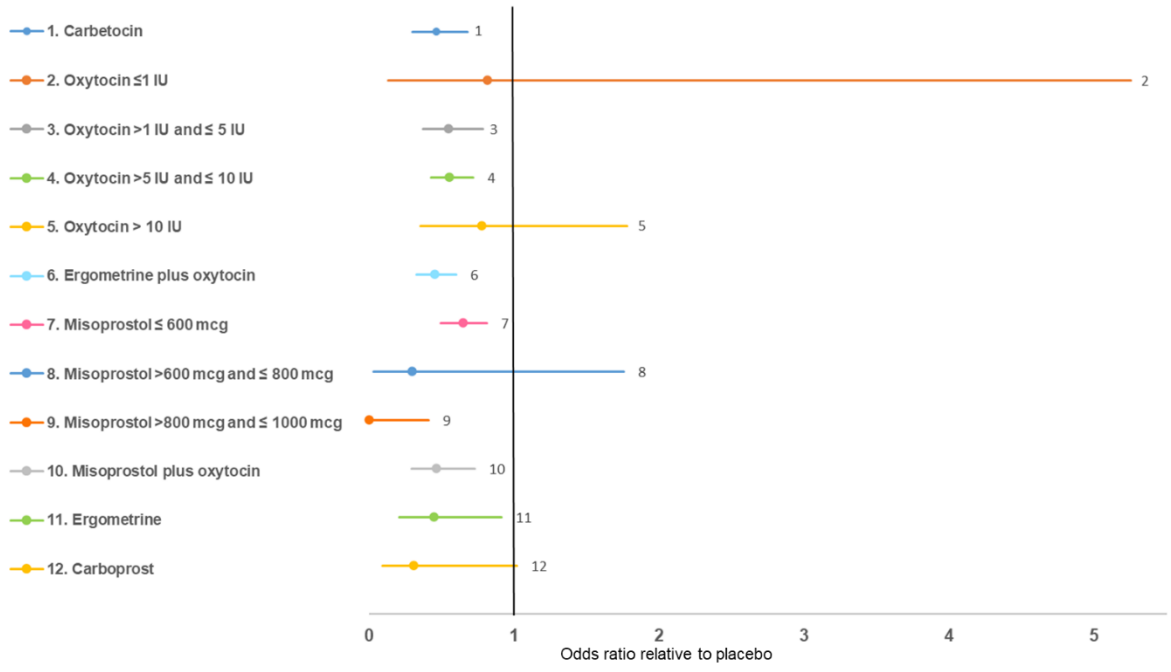


Table 5: Median treatment ranks and probability of being the best treatment for all interventions for PPH ≥ 1000mL, vaginal birth subgroup

Intervention	Median (95% CrI) treatment rank	Probability of being best
Carboprost	2 (1, 11)	23.14%
Misoprostol >600 mcg and ≤ 800 mcg	2 (0, 12)	57.63%
Ergometrine plus oxytocin	4 (2, 7)	1.10%
Carbetocin	5 (2, 9)	1.17%
Misoprostol plus oxytocin	5 (1, 10)	1.39%
Ergometrine	4 (1, 11)	4.66%
Oxytocin >1 IU and ≤ 5 IU	7 (2, 10)	0.39%
Oxytocin >5 IU and ≤ 10 IU	7 (4, 10)	0.00%
Oxytocin ≤1 IU	10 (1, 12)	9.95%
Misoprostol ≤ 600 mcg	9 (6, 11)	0.00%
Oxytocin > 10 IU	10 (3, 12)	0.57%
Placebo	11 (10, 12)	0.00%

Misoprostol >800 mcg and ≤ 1000 mcg is excluded from the ranking due to highly uncertain estimates.

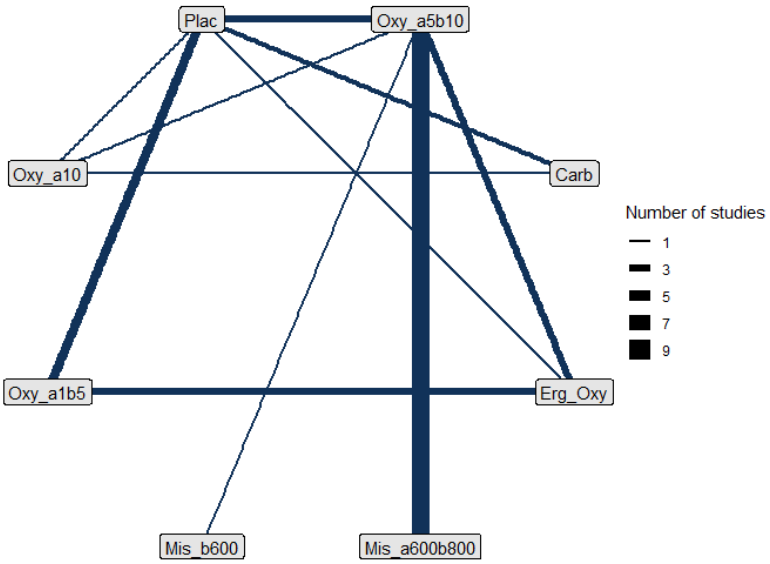
Caesarean birth subgroup analysis

26 studies comparing 8 treatments in 5,284 women were included in this subgroup analysis.

Of the 30 studies that reported this outcome, 4 studies were excluded as they reported no events in any arm for this outcome.

The network plot for this outcome is shown below at Figure 5, the odds ratios compared to carbetocin in Table 6, the Forest plot at Figure 6 and the median treatment ranks in Table 7.

Figure 5: Network of evidence for PPH ≥ 1000mL, caesarean birth subgroup



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU.

Table 6: Odds ratio, log odds ratio and 95% CrIs for PPH ≥ 1000mL for all interventions compared with carbetocin, caesarean birth subgroup

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Misoprostol >600 mcg and ≤ 800 mcg	0.267 (0.010, 2.861)	-1.322 (-4.655, 1.051)	-
Ergometrine plus oxytocin	1.400 (0.674, 3.187)	0.3363 (-0.3947, 1.159)	1
Oxytocin >1 IU and ≤ 5 IU	1.445 (0.663, 3.168)	0.3684 (-0.4111, 1.153)	2
Oxytocin >5 IU and ≤ 10 IU	1.480 (0.853, 3.114)	0.3918 (-0.1594, 1.136)	4
Misoprostol ≤ 600 mcg	1.759 (0.832, 4.039)	0.5649 (-0.1839, 1.396)	1
Misoprostol plus oxytocin	2.399 (1.101, 5.458)	0.8752 (0.0964, 1.697)	-
Oxytocin > 10 IU	2.694 (1.500, 5.207)	0.9909 (0.4055, 1.65)	3

Results from the random effects NMA. OR<1 favours the intervention (lower risk of PPH≥1000ml in the intervention arm), OR>1 favours carbetocin, with higher numbers indicating greater benefit of carbetocin in that comparison. Abbreviations: OR, odds ratio; CrI, credible interval.

Figure 6: Forest plot, PPH ≥ 1000mL caesarean birth (OR< 1 favours intervention, compared to carbetocin)

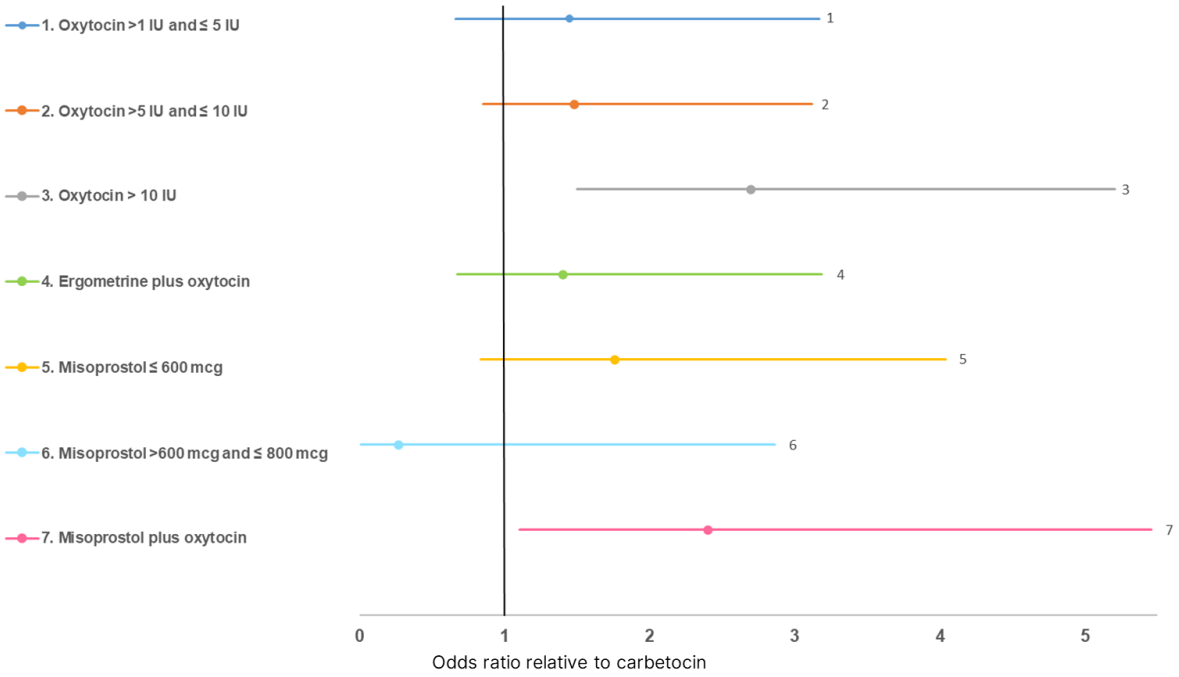


Table 7: Median treatment ranks and probability of being the best treatment for all interventions for PPH ≥ 1000mL, caesarean birth subgroup

Intervention	Median (95% CrI) treatment rank	Probability of being best

Intervention	Median (95% CrI) treatment rank	Probability of being best
Misoprostol >600 mcg and ≤ 800 mcg	1 (1, 7)	82.44%
Carbetocin	2 (1, 4)	10.46%
Ergometrine plus oxytocin	4 (2, 8)	2.21%
Oxytocin >1 IU and ≤ 5 IU	4 (1, 8)	2.85%
Oxytocin >5 IU and ≤ 10 IU	4 (2, 8)	1.14%
Misoprostol ≤ 600 mcg	5 (2, 8)	0.79%
Misoprostol plus oxytocin	7 (3, 8)	0.11%
Oxytocin > 10 IU	8 (5, 8)	0.00%

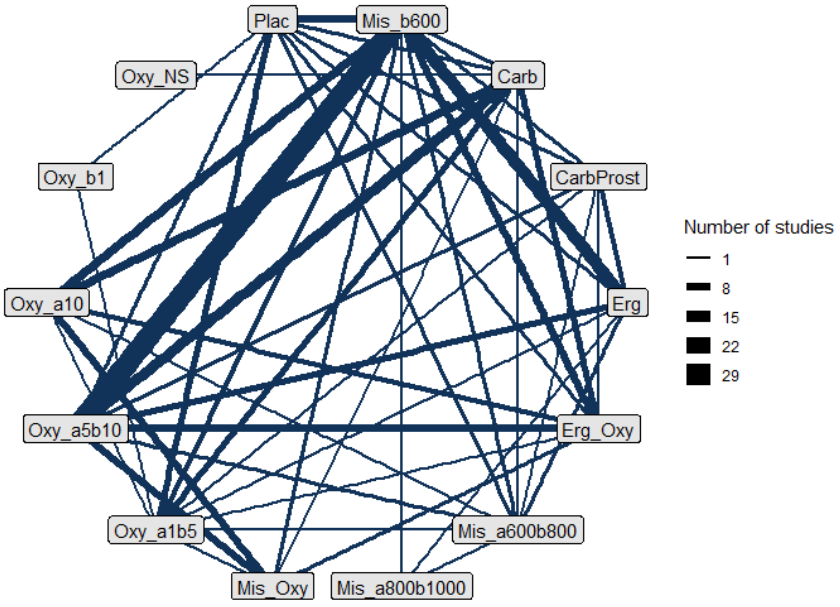
Additional uterotonics

161 studies, comparing 14 interventions in 123,183 women were included in this analysis. Of these studies, 1 included women who had either vaginal or caesarean births, 109 were conducted in women who had vaginal births only, and 51 in women who had caesarean births only.

Of the 163 studies that reported this outcome, 2 studies were excluded as they reported no events in any arm for this outcome.

The network plot for this outcome is shown below at Figure 7, the odds ratios compared to placebo in Table 8, the Forest plot at Figure 8 and the median treatment ranks in Table 9.

Figure 7: Network of evidence for additional uterotonics, full dataset



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; CarbProst, carboprost; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Mis_a800b1000, misoprostol >800mcg and ≤1000mcg; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU; Oxy_b1, oxytocin ≤1IU; Oxy_NS, oxytocin unspecified dose.

Table 8: Odds ratio, log odds ratio and 95% CrIs for additional uterotonics for all interventions compared with placebo

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Carbetocin	0.087 (0.051, 0.146)	-2.442 (-2.968, -1.927)	2
Carboprost	0.161 (0.068, 0.378)	-1.826 (-2.687, -0.972)	2
Misoprostol plus oxytocin	0.184 (0.102, 0.333)	-1.694 (-2.284, -1.1)	-
Ergometrine plus oxytocin	0.189 (0.112, 0.313)	-1.668 (-2.185, -1.16)	3
Oxytocin >1 IU and ≤ 5 IU	0.211 (0.121, 0.366)	-1.558 (-2.116, -1.005)	6
Misoprostol >800 mcg and ≤ 1000 mcg	0.259 (0.046, 1.410)	-1.352 (-3.072, 0.3433)	-
Misoprostol >600 mcg and ≤ 800 mcg	0.331 (0.150, 0.724)	-1.105 (-1.896, -0.323)	2
Ergometrine	0.347 (0.195, 0.615)	-1.058 (-1.635, -0.486)	2
Oxytocin >5 IU and ≤ 10 IU	0.350 (0.220, 0.557)	-1.05 (-1.516, -0.5854)	2
Misoprostol ≤ 600 mcg	0.390 (0.252, 0.605)	-0.942 (-1.379, -0.503)	9
Oxytocin ≤1 IU	0.447 (0.065, 3.010)	-0.8055 (-2.731, 1.102)	-
Oxytocin > 10 IU	0.464 (0.267, 0.809)	-0.769 (-1.321, -0.212)	-
Oxytocin unspecified dose	1.658 (0.099, 59.323)	0.5054 (-2.313, 4.083)	-

Results from the random effects NMA. OR<1 favours the intervention (lower risk of additional uterotonics in the intervention arm) with lower numbers indicating greater benefit, OR>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

Figure 8: Forest plot, Additional uterotonics full population (OR < 1 favours intervention)

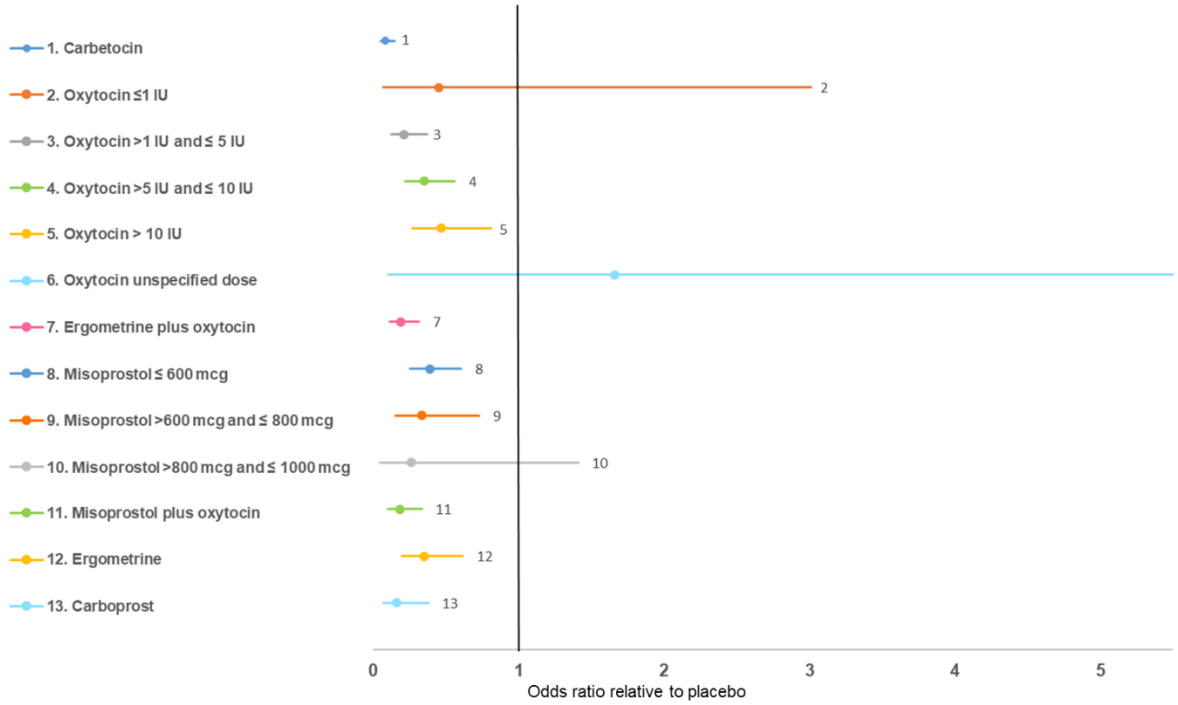


Table 9: Median treatment ranks and probability of being the best treatment for all interventions for additional uterotonics

Intervention	Median (95% CrI) treatment rank	Probability of being best
Carbetocin	1 (1, 2)	77.54%
Carboprost	3 (1, 8)	6.53%
Misoprostol plus oxytocin	4 (2, 7)	0.09%
Ergometrine plus oxytocin	4 (2, 7)	0.00%
Oxytocin >1 IU and ≤ 5 IU	5 (2, 8)	0.03%
Misoprostol >800 mcg and ≤ 1000 mcg	6 (1, 14)	9.78%
Misoprostol >600 mcg and ≤ 800 mcg	8 (3, 12)	0.02%
Oxytocin >5 IU and ≤ 10 IU	8 (6, 11)	0.00%
Ergometrine	8 (5, 12)	0.00%
Oxytocin ≤1 IU	11 (1, 14)	4.44%
Misoprostol ≤ 600 mcg	10 (7, 12)	0.00%
Oxytocin > 10 IU	11 (7, 13)	0.00%
Oxytocin unspecified dose	14 (2, 14)	1.57%
Placebo	13 (12, 14)	0.00%

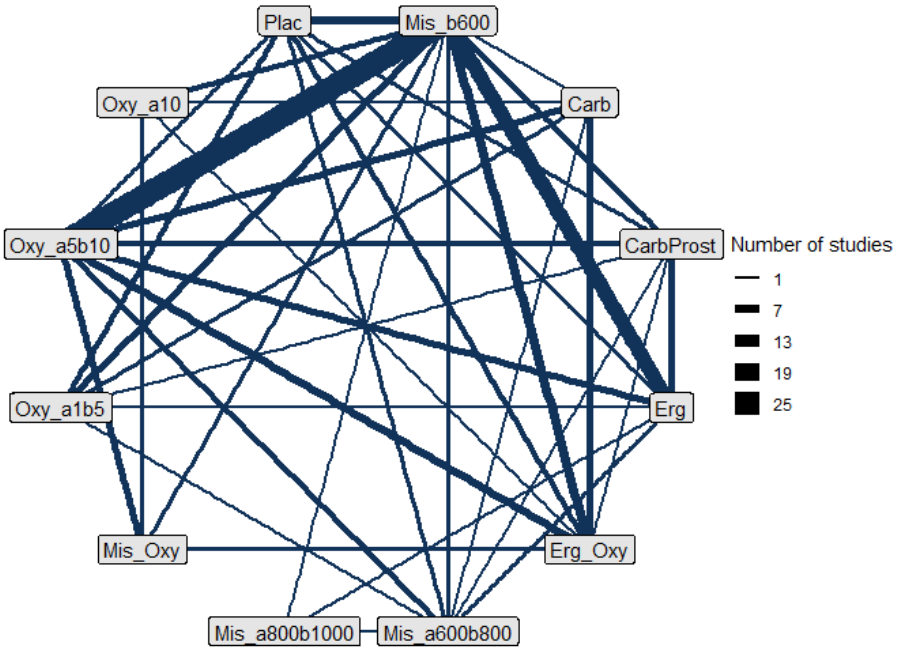
Vaginal birth subgroup analysis

109 studies comparing 12 treatments in 112,805 women were included in this subgroup analysis.

Of the 109 studies that reported this outcome, 0 studies were excluded as they reported no events in any arm for this outcome.

The network plot for this outcome is shown below at Figure 9, the odds ratios compared to placebo in Table 10, the Forest plot at Figure 10 and the median treatment ranks in Table 11.

Figure 9: Network of evidence for additional uterotonics, vaginal birth subgroup



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; CarbProst, carboprost; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Mis_a800b1000, misoprostol >800mcg and ≤1000mcg; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU.

Table 10: Odds ratio, log odds ratio and 95% CrIs for additional uterotonics for all interventions compared with placebo, vaginal birth subgroup

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Carbetocin	0.141 (0.075, 0.256)	-1.96 (-2.59, -1.363)	-
Carboprost	0.177 (0.078, 0.398)	-1.734 (-2.545, -0.922)	2
Ergometrine plus oxytocin	0.219 (0.131, 0.363)	-1.52 (-2.034, -1.012)	3
Misoprostol plus oxytocin	0.249 (0.123, 0.505)	-1.39 (-2.094, -0.6832)	-
Misoprostol >800 mcg and ≤ 1000 mcg	0.302 (0.060, 1.457)	-1.196 (-2.807, 0.3764)	-
Oxytocin >1 IU and ≤ 5 IU	0.332 (0.180, 0.603)	-1.104 (-1.716, -0.505)	4
Oxytocin >5 IU and ≤ 10 IU	0.372 (0.235, 0.591)	-0.989 (-1.448, -0.527)	2
Misoprostol >600 mcg and ≤ 800 mcg	0.384 (0.178, 0.838)	-0.958 (-1.727, -0.177)	2

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Ergometrine	0.414 (0.240, 0.719)	-0.881 (-1.426, -0.33)	2
Misoprostol ≤ 600 mcg	0.451 (0.292, 0.699)	-0.797 (-1.23, -0.358)	9
Oxytocin > 10 IU	0.541 (0.231, 1.284)	-0.615 (-1.466, 0.2503)	-

Results from the random effects NMA. OR<1 favours the intervention (lower risk of additional uterotonics in the intervention arm) with lower numbers indicating greater benefit, OR>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

Figure 10: Forest plot, Additional uterotonics vaginal birth (OR <1 favours intervention)

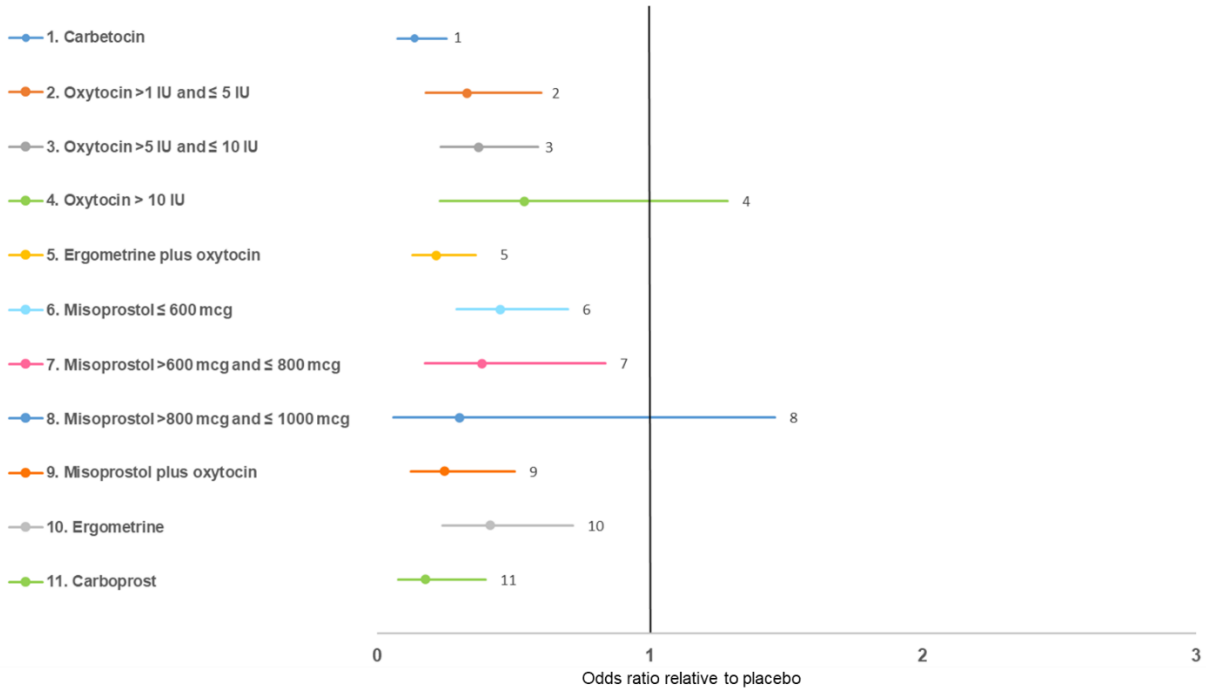


Table 11: Median treatment ranks and probability of being the best treatment for all interventions for additional uterotonics, vaginal birth subgroup

Intervention	Median (95% CrI) treatment rank	Probability of being best
Carbetocin	1 (1, 3)	56.12%
Carboprost	2 (1, 7)	24.96%
Ergometrine plus oxytocin	3 (2, 6)	1.11%
Misoprostol plus oxytocin	4 (1, 9)	2.74%
Misoprostol >800 mcg and ≤ 1000 mcg	5 (1, 12)	14.69%
Oxytocin >1 IU and ≤ 5 IU	6 (3, 11)	0.13%
Oxytocin >5 IU and ≤ 10 IU	7 (5, 10)	0.00%
Misoprostol >600 mcg and ≤ 800 mcg	7 (3, 11)	0.20%
Ergometrine	8 (5, 11)	0.00%
Misoprostol ≤ 600 mcg	9 (7, 11)	0.00%
Oxytocin > 10 IU	10 (5, 12)	0.04%

Intervention	Median (95% CrI) treatment rank	Probability of being best
Placebo	12 (11, 12)	0.00%

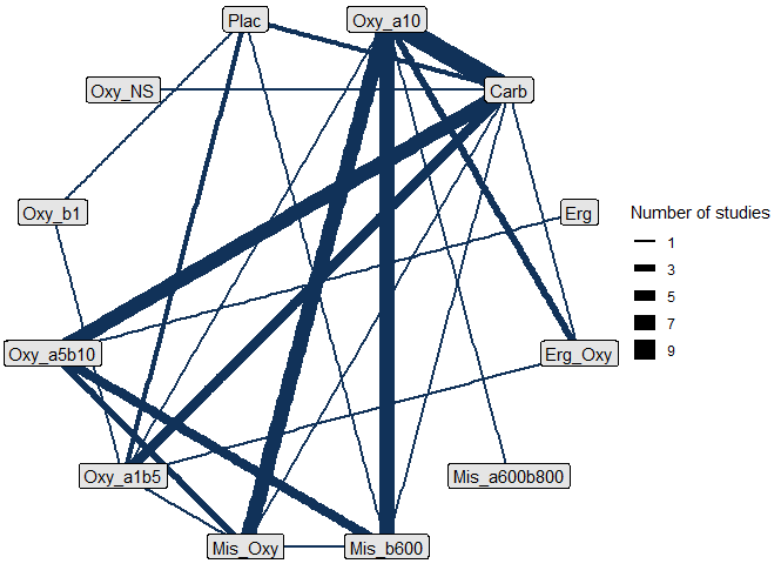
Caesarean birth subgroup analysis

51 studies comparing 12 treatments in 10,323 women were included in this subgroup analysis.

Of the 53 studies that reported this outcome, 2 studies were excluded as they reported no events in any arm for this outcome.

The network plot for this outcome is shown below at Figure 11, the odds ratios compared to placebo in Table 12, the Forest plot at Figure 12 and the median treatment ranks in Table 13.

Figure 11: Network of evidence for additional uterotonics, caesarean birth subgroup



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU; Oxy_b1, oxytocin ≤1IU; Oxy_NS, oxytocin unspecified dose.

Table 12: Odds ratio, log odds ratio and 95% CrIs for additional uterotonics for all interventions compared with placebo, caesarean birth subgroup

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Ergometrine	0.000 (0.000, 0.001)	-95.56 (-198.1, -7.428)	-
Carbetocin	0.033 (0.009, 0.115)	-3.412 (-4.71, -2.166)	2
Oxytocin >1 IU and ≤ 5 IU	0.066 (0.016, 0.251)	-2.724 (-4.106, -1.383)	2
Misoprostol plus oxytocin	0.072 (0.017, 0.292)	-2.636 (-4.054, -1.231)	-

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Ergometrine plus oxytocin	0.090 (0.018, 0.442)	-2.404 (-4.023, -0.817)	-
Misoprostol >600 mcg and ≤ 800 mcg	0.145 (0.011, 1.923)	-1.929 (-4.518, 0.6539)	-
Misoprostol ≤ 600 mcg	0.181 (0.047, 0.693)	-1.712 (-3.068, -0.367)	1
Oxytocin > 10 IU	0.199 (0.052, 0.746)	-1.616 (-2.951, -0.293)	-
Oxytocin >5 IU and ≤ 10 IU	0.227 (0.055, 0.910)	-1.482 (-2.902, -0.094)	-
Oxytocin ≤1 IU	0.276 (0.028, 2.660)	-1.286 (-3.567, 0.9785)	1
Oxytocin unspecified dose	0.614 (0.022, 30.417)	-0.4883 (-3.813, 3.415)	-

Results from the random effects NMA. OR<1 favours the intervention (lower risk of additional uterotonics in the intervention arm) with lower numbers indicating greater benefit, OR>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

In this analysis only one study included the ergometrine arm, and reported no additional uterotonic events in that arm which led to high uncertainty in the comparison with this treatment. Therefore, ergometrine has been excluded from the ranking in Table 13 as the probability of being best can be biased for highly uncertain estimates.

Figure 12: Forest plot, Additional uterotonics caesarean birth (OR <1 favours intervention)

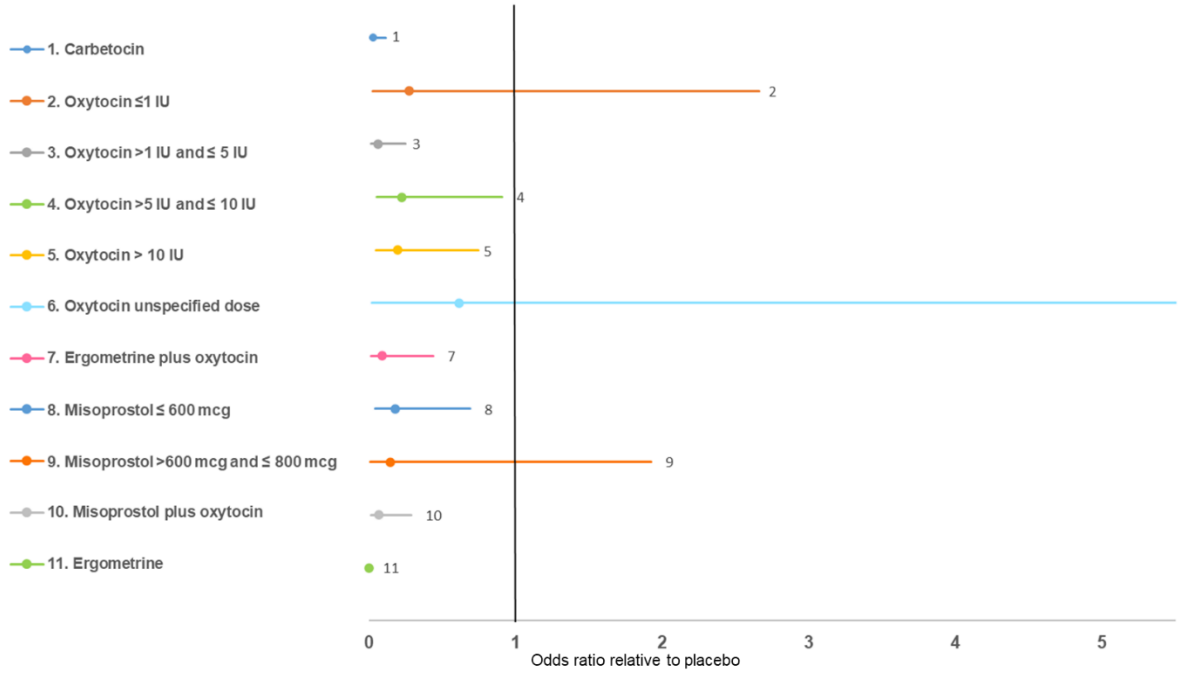


Table 13: Median treatment ranks and probability of being the best treatment for all interventions for additional uterotonics, caesarean birth subgroup

Intervention	Median (95% CrI) treatment rank	Probability of being best
Carbetocin	1 (1, 3)	67.09%
Oxytocin >1 IU and ≤ 5 IU	3 (1, 6)	5.06%
Misoprostol plus oxytocin	3 (2, 6)	0.84%

Intervention	Median (95% CrI) treatment rank	Probability of being best
Ergometrine plus oxytocin	4 (1, 8)	3.37%
Misoprostol >600 mcg and ≤ 800 mcg	6 (1, 11)	11.82%
Misoprostol ≤ 600 mcg	7 (4, 9)	0.00%
Oxytocin > 10 IU	7 (5, 10)	0.00%
Oxytocin ≤1 IU	8 (1, 11)	5.49%
Oxytocin >5 IU and ≤ 10 IU	8 (5, 10)	0.00%
Oxytocin unspecified dose	10 (1, 11)	6.33%
Placebo	11 (9, 11)	0.00%

Ergometrine is excluded from the ranking due to highly uncertain estimates.

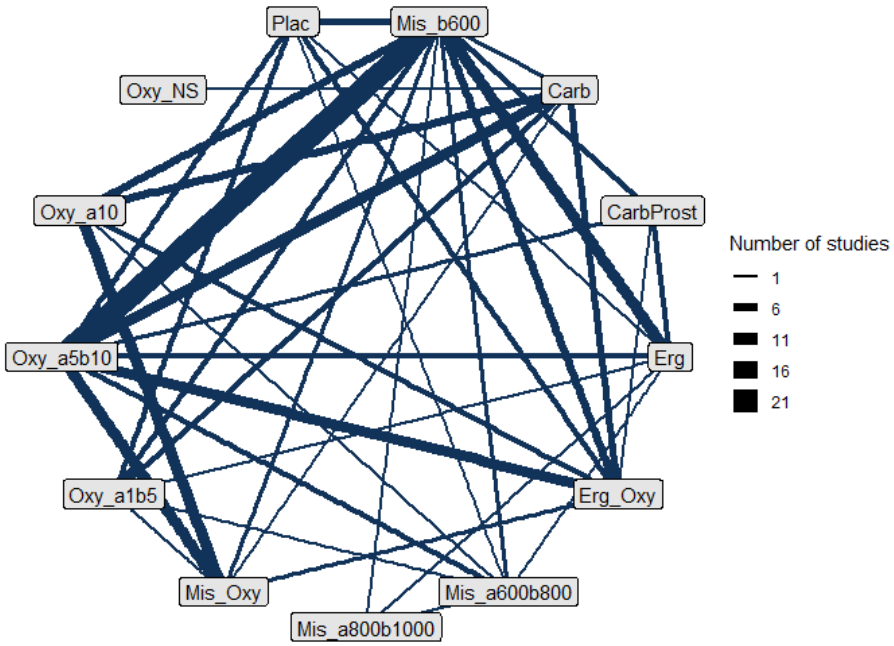
Blood transfusion

113 studies, comparing 13 interventions in 115,872 women were included in this analysis. Of these studies, 1 included women who had either vaginal or caesarean births, 80 were conducted in women who had vaginal births only, and 32 in women who had caesarean births only.

Of the 140 studies that reported this outcome, 27 studies were excluded as they reported no events in any arm for this outcome.

The network plot for this outcome is shown below at Figure 13, the odds ratios compared to placebo in Table 14, the Forest plot at Figure 14 and the median treatment ranks in Table 15.

Figure 13: Network of evidence for blood transfusion, full dataset



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; CarbProst, carboprost; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Mis_a800b1000, misoprostol >800mcg and ≤1000mcg; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU; Oxy_NS, oxytocin unspecified dose.

Table 14: Odds ratio, log odds ratio and 95% CrIs for blood transfusion for all interventions compared with placebo

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Misoprostol >800 mcg and ≤ 1000 mcg	0.000 (0.000, 0.344)	-30.07 (-78.39, -1.067)	-
Carbetocin	0.234 (0.104, 0.504)	-1.452 (-2.259, -0.685)	-
Carboprost	0.260 (0.054, 1.190)	-1.347 (-2.917, 0.1736)	-
Misoprostol plus oxytocin	0.277 (0.128, 0.600)	-1.282 (-2.053, -0.511)	-
Ergometrine plus oxytocin	0.428 (0.219, 0.841)	-0.85 (-1.518, -0.173)	3
Misoprostol >600 mcg and ≤ 800 mcg	0.434 (0.132, 1.390)	-0.8358 (-2.024, 0.33)	1
Oxytocin >1 IU and ≤ 5 IU	0.481 (0.201, 1.124)	-0.7322 (-1.604, 0.117)	3
Oxytocin >5 IU and ≤ 10 IU	0.576 (0.306, 1.083)	-0.551 (-1.183, 0.0801)	3
Misoprostol ≤ 600 mcg	0.615 (0.320, 1.198)	-0.486 (-1.139, 0.1803)	5
Oxytocin unspecified dose	0.700 (0.028, 28.474)	-0.356 (-3.58, 3.349)	-
Ergometrine	0.739 (0.278, 1.985)	-0.3029 (-1.279, 0.686)	1
Oxytocin > 10 IU	0.898 (0.402, 1.994)	-0.108 (-0.9118, 0.69)	-

Results from the random effects NMA. OR<1 favours the intervention (lower risk of transfusion in the intervention arm) with lower numbers indicating greater benefit, OR>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

In this analysis only one study included the high-dose misoprostol arm, and reported no transfusion events in that arm which led to high uncertainty in the comparison with this treatment. Therefore, high-dose misoprostol has been excluded from the ranking in Table 15 as the probability of being best can be biased for highly uncertain estimates.

Figure 14: Forest plot, blood transfusion full population (OR< 1 favours intervention)

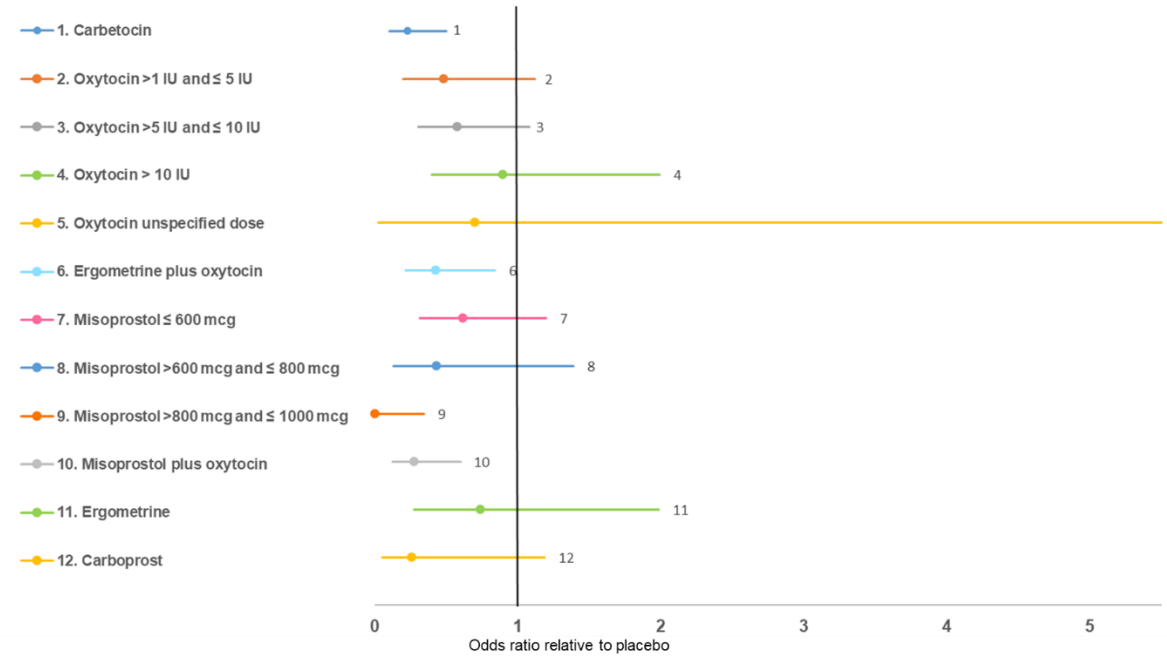


Table 15: Median treatment ranks and probability of being the best treatment for all interventions for blood transfusion

Intervention	Median (95% CrI) treatment rank	Probability of being best
Carbetocin	2 (1, 5)	22.32%
Misoprostol plus oxytocin	3 (1, 6)	8.32%
Carboprost	3 (1, 11)	37.68%
Ergometrine plus oxytocin	5 (3, 8)	0.04%
Misoprostol >600 mcg and ≤ 800 mcg	5 (1, 11)	5.35%
Oxytocin >1 IU and ≤ 5 IU	6 (2, 11)	0.66%
Oxytocin unspecified dose	8 (1, 12)	25.62%
Oxytocin >5 IU and ≤ 10 IU	7 (5, 10)	0.00%
Misoprostol ≤ 600 mcg	8 (5, 11)	0.00%
Ergometrine	9 (4, 12)	0.00%
Oxytocin > 10 IU	10 (7, 12)	0.00%
Placebo	11 (7, 12)	0.00%

Misoprostol >800 mcg and ≤ 1000 mcg is excluded from the ranking due to highly uncertain estimates.

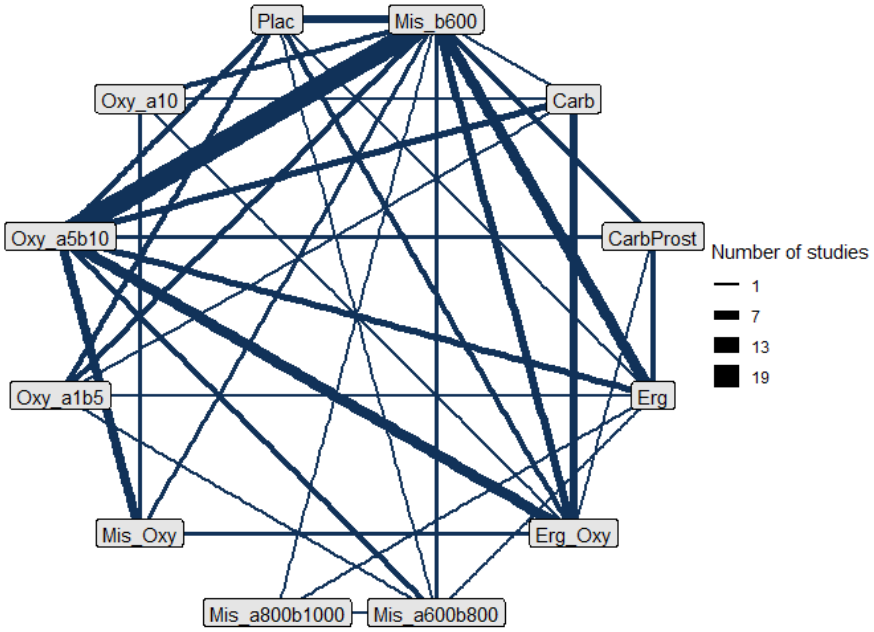
Vaginal birth subgroup analysis

80 studies comparing 12 treatments in 107,850 women were included in this subgroup analysis.

Of the 99 studies that reported this outcome, 19 studies were excluded as they reported no events in any arm for this outcome.

The network plot for this outcome is shown below at Figure 15, the odds ratios compared to placebo in Table 16, the Forest plot at Figure 16 and the median treatment ranks in Table 17.

Figure 15: Network of evidence for blood transfusion, vaginal birth subgroup



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; CarbProst, carboprost; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Mis_a800b1000, misoprostol >800mcg and ≤1000mcg; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU.

Table 16: Odds ratio, log odds ratio and 95% CrIs for blood transfusion for all interventions compared with placebo, vaginal birth subgroup

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Misoprostol >800 mcg and ≤ 1000 mcg	0.000 (0.000, 0.572)	-31.89 (-96.77, -0.558)	-
Misoprostol plus oxytocin	0.214 (0.100, 0.450)	-1.543 (-2.3, -0.7983)	-
Carboprost	0.252 (0.060, 1.007)	-1.377 (-2.81, 0.0065)	-
Ergometrine plus oxytocin	0.453 (0.259, 0.798)	-0.792 (-1.352, -0.226)	3
Carbetocin	0.471 (0.215, 1.004)	-0.7522 (-1.537, 0.004)	-
Oxytocin >5 IU and ≤ 10 IU	0.509 (0.298, 0.865)	-0.675 (-1.209, -0.144)	3
Misoprostol >600 mcg and ≤ 800 mcg	0.551 (0.184, 1.624)	-0.5962 (-1.694, 0.485)	1
Oxytocin > 10 IU	0.558 (0.193, 1.570)	-0.5832 (-1.646, 0.451)	-
Oxytocin >1 IU and ≤ 5 IU	0.579 (0.246, 1.323)	-0.547 (-1.403, 0.2796)	3
Misoprostol ≤ 600 mcg	0.587 (0.336, 1.032)	-0.5333 (-1.09, 0.032)	5
Ergometrine	0.671 (0.281, 1.612)	-0.3993 (-1.268, 0.478)	1

Results from the random effects NMA. OR<1 favours the intervention (lower risk of transfusion in the intervention arm) with lower numbers indicating greater benefit, OR>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

In this analysis only one study included the high-dose misoprostol arm, and reported no transfusion events in that arm which led to high uncertainty in the comparison with this treatment. Therefore, high-dose misoprostol has been excluded from the ranking in Table 17 as the probability of being best can be biased for highly uncertain estimates.

Figure 16: Forest plot, blood transfusion vaginal birth (OR <1 favours intervention)

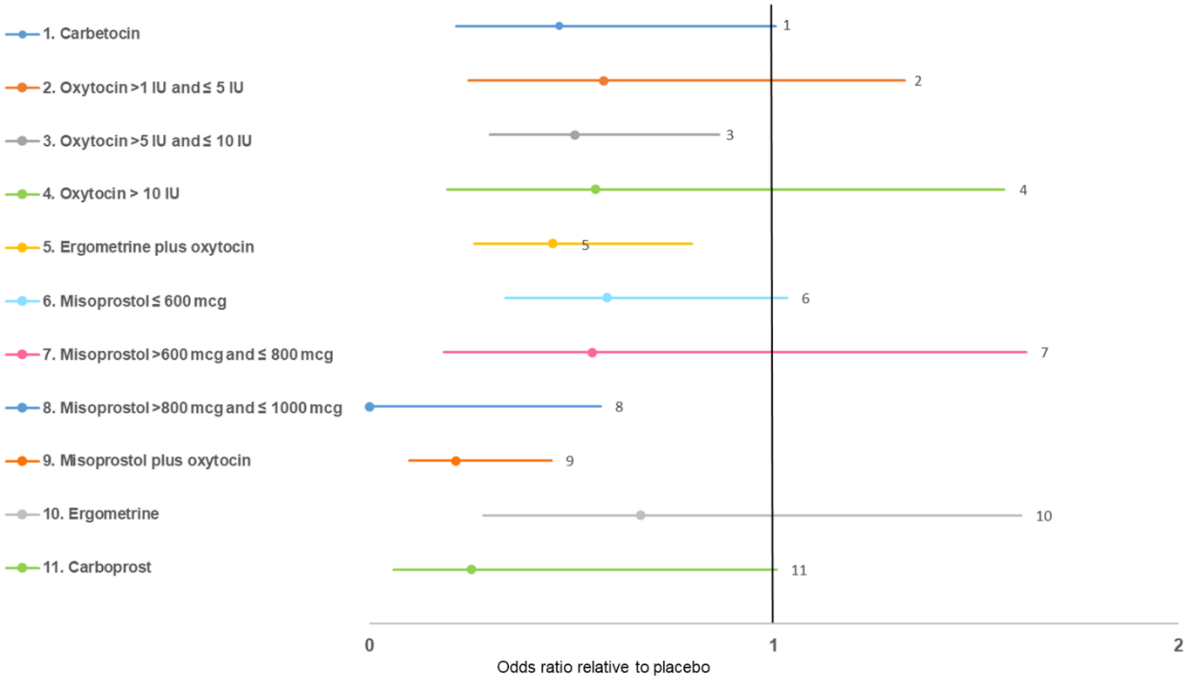


Table 17: Median treatment ranks and probability of being the best treatment for all interventions for blood transfusion, vaginal birth subgroup

Intervention	Median (95% CrI) treatment rank	Probability of being best
Misoprostol plus oxytocin	1 (1, 3)	47.23%
Carboprost	2 (1, 10)	47.72%
Ergometrine plus oxytocin	4 (2, 9)	0.03%
Carbetocin	5 (2, 10)	0.98%
Oxytocin >5 IU and ≤ 10 IU	6 (3, 9)	0.00%
Misoprostol >600 mcg and ≤ 800 mcg	7 (1, 11)	1.99%
Oxytocin > 10 IU	7 (2, 11)	1.52%
Oxytocin >1 IU and ≤ 5 IU	7 (2, 11)	0.27%
Misoprostol ≤ 600 mcg	7 (4, 10)	0.00%
Ergometrine	9 (3, 11)	0.27%
Placebo	11 (8, 11)	0.00%

Misoprostol >800 mcg and ≤ 1000 mcg is excluded from the ranking due to highly uncertain estimates.

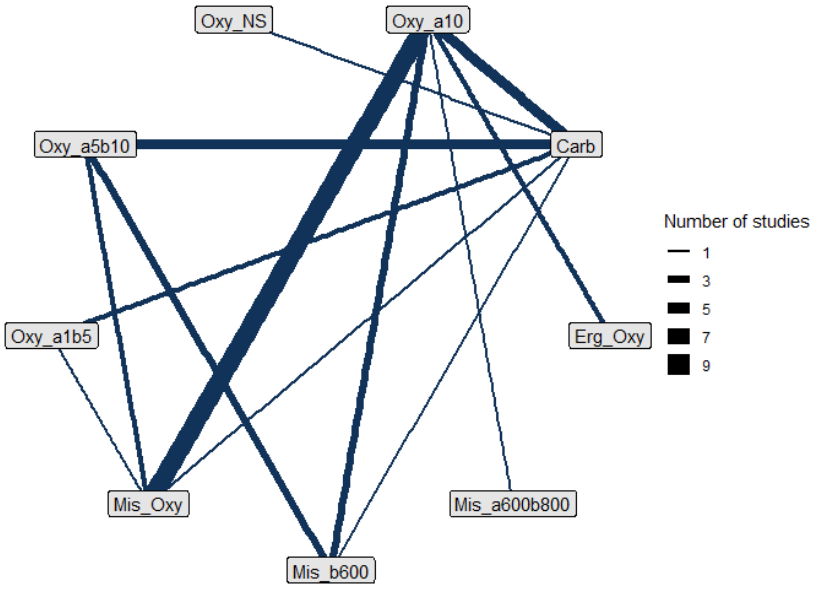
Caesarean birth subgroup analysis

32 studies comparing 9 treatments in 8,114 women were included in this subgroup analysis.

Of the 40 studies that reported this outcome, 8 studies were excluded as they reported no events in any arm for this outcome.

The network plot for this outcome is shown below at Figure 17, the odds ratios compared to carbetocin in Table 18, the Forest plot at Figure 18 and the median treatment ranks in Table 19.

Figure 17: Network of evidence for blood transfusion, caesarean birth subgroup



Abbreviations: Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU; Oxy_NS, oxytocin unspecified dose.

Table 18: Odds ratio, log odds ratio and 95% CrIs for blood transfusion for all interventions compared with carbetocin, caesarean birth subgroup

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Misoprostol >600 mcg and ≤ 800 mcg	0.000 (0.000, 0.178)	-67.24 (-153.2, -1.728)	-
Ergometrine plus oxytocin	1.693 (0.166, 21.802)	0.5265 (-1.797, 3.082)	-
Misoprostol plus oxytocin	2.318 (0.588, 9.796)	0.8407 (-0.531, 2.282)	1
Oxytocin >1 IU and ≤ 5 IU	2.349 (0.329, 15.943)	0.8539 (-1.111, 2.769)	1
Oxytocin unspecified dose	3.083 (0.062, 221.850)	1.126 (-2.777, 5.402)	1
Misoprostol ≤ 600 mcg	6.110 (0.881, 61.992)	1.81 (-0.1266, 4.127)	1
Oxytocin > 10 IU	6.903 (1.978, 30.723)	1.932 (0.6821, 3.425)	5
Oxytocin >5 IU and ≤ 10 IU	11.001 (2.921, 58.440)	2.398 (1.072, 4.068)	4

Results from the random effects NMA. OR<1 favours the intervention (lower risk of transfusion in the intervention arm), OR>1 favours carbetocin, with larger numbers indicating a greater benefit of carbetocin in that comparison. Abbreviations: OR, odds ratio; CrI, credible interval.

In this analysis only one study included the misoprostol >600 mcg and ≤ 800 mcg arm, and reported no transfusion events in that arm which led to high uncertainty in the comparison with this treatment. Therefore, misoprostol >600 mcg and ≤ 800 mcg has been excluded from the ranking in Table 19 as the probability of being best can be biased for highly uncertain estimates.

Figure 18: Forest plot, blood transfusion caesarean birth (OR <1 favours intervention compared to carbetocin)

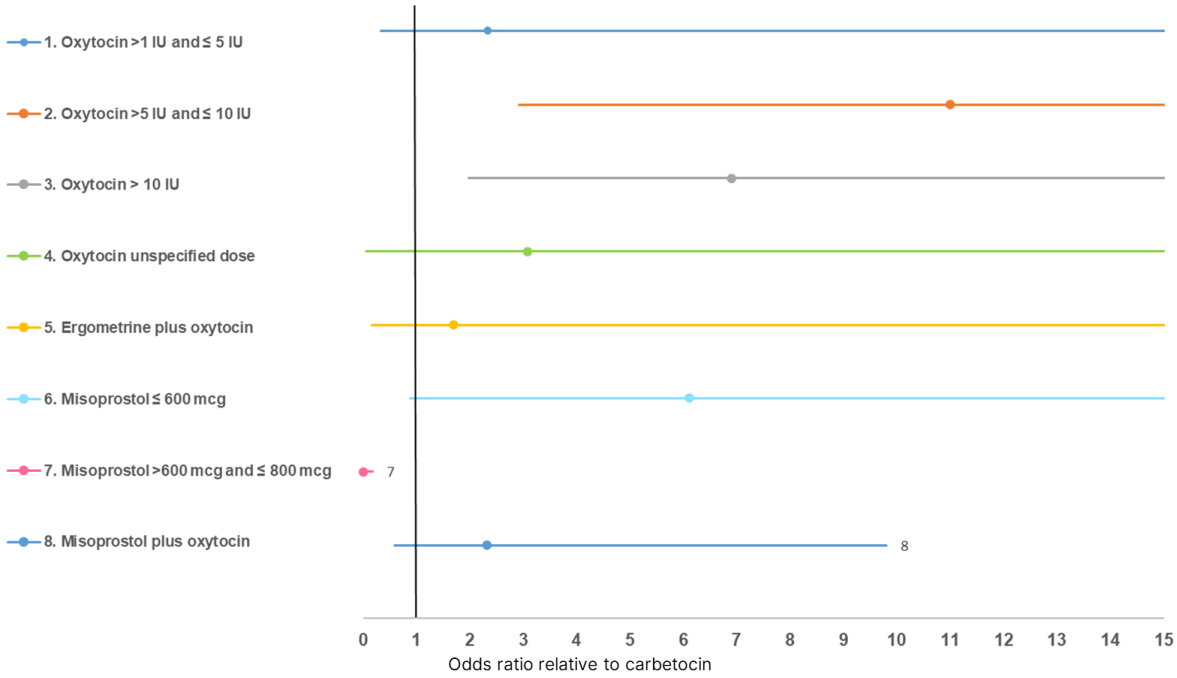


Table 19: Median treatment ranks and probability of being the best treatment for all interventions for blood transfusion, caesarean birth subgroup

Intervention	Median (95% CrI) treatment rank	Probability of being best
Carbetocin	2 (1, 4)	33.30%
Ergometrine plus oxytocin	3 (1, 7)	22.12%
Misoprostol plus oxytocin	4 (1, 6)	1.40%
Oxytocin >1 IU and ≤ 5 IU	4 (1, 8)	11.49%
Oxytocin unspecified dose	4 (1, 8)	31.37%
Misoprostol ≤ 600 mcg	6 (2, 8)	0.32%
Oxytocin > 10 IU	6 (4, 8)	0.00%
Oxytocin >5 IU and ≤ 10 IU	7 (4, 8)	0.00%

Misoprostol >600 mcg and ≤ 800 mcg is excluded from the ranking due to highly uncertain estimates.

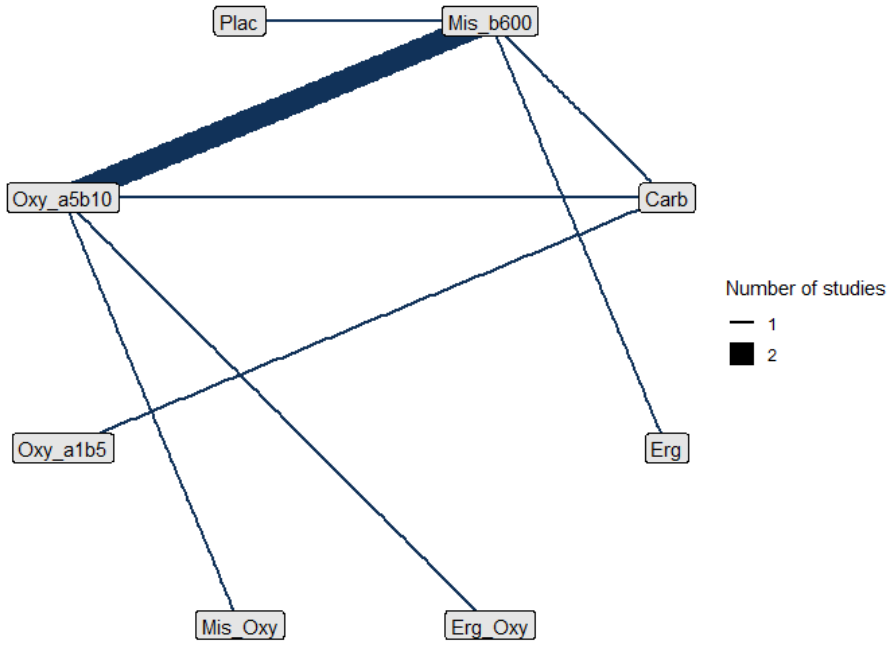
ICU admission (morbidity)

9 studies, comparing 8 interventions in 54,377 women were included in this analysis. Of these studies, 8 were conducted in women who had vaginal births only, and 1 in women who had caesarean births only.

Of the 22 studies that reported this outcome, 13 studies were excluded as they reported no events in any arm for this outcome.

The network plot for this outcome is shown below at Figure 19, the odds ratios compared to placebo in Table 20 and the Forest plot at Figure 20.

Figure 19: Network of evidence for ICU admission, full dataset



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU.

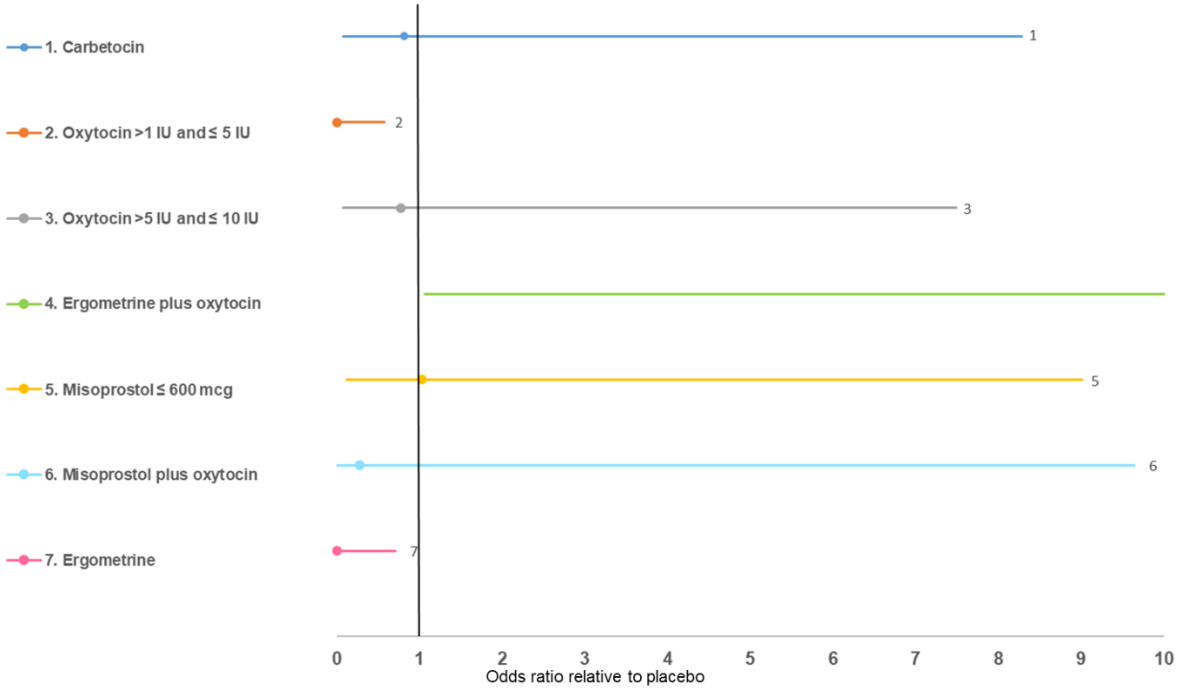
Table 20: Odds ratio, log odds ratio and 95% CrIs for ICU admission for all interventions compared with placebo

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Oxytocin >1 IU and ≤ 5 IU	0.000 (0.000, 0.581)	-25.29 (-70.78, -0.5434)	-
Ergometrine	0.000 (0.000, 0.708)	-25.06 (-70.55, -0.3448)	-
Misoprostol plus oxytocin	0.276 (0.005, 9.641)	-1.287 (-5.267, 2.266)	-
Oxytocin >5 IU and ≤ 10 IU	0.779 (0.082, 7.493)	-0.2502 (-2.507, 2.014)	-
Carbetocin	0.820 (0.081, 8.281)	-0.1984 (-2.511, 2.114)	-
Misoprostol ≤ 600 mcg	1.033 (0.120, 9.016)	0.03242 (-2.117, 2.199)	1
Ergometrine plus oxytocin	7.27E+10 (1.064, 5.22E+30)	25.01 (0.06165, 70.73)	-

Results from the random effects NMA. OR<1 favours the intervention (lower risk of ICU admission in the intervention arm with lower numbers indicating a greater effect), OR>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

In this analysis all of the estimates are highly uncertain given the sparse evidence network, and the treatment ranking has not been presented as the probability of being best is likely to be biased.

Figure 20: Forest plot, ICU admission full population (OR <1 favours intervention)



The forest plot in Figure 20 does not show the point estimate or upper error bar for ergometrine plus oxytocin. This is because these values are very large, so are much further to the right on the graph than all other strategies.

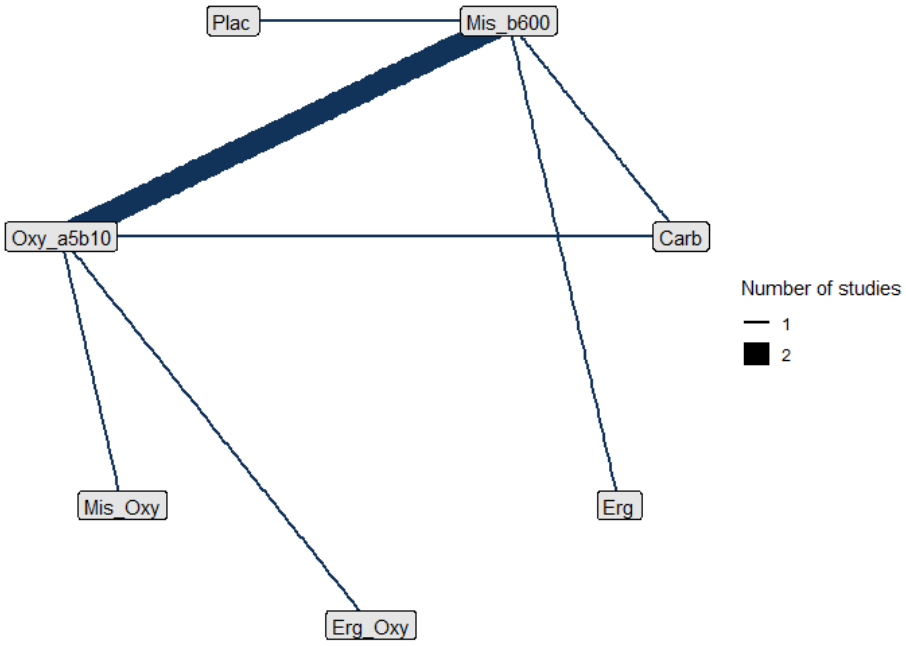
Vaginal birth subgroup analysis

8 studies comparing 7 treatments in 54,000 women were included in this subgroup analysis.

Of the 18 studies that reported this outcome, 10 studies were excluded as they reported no events in any arm for this outcome.

The network plot for this outcome is shown below at Figure 21, the odds ratios compared to placebo in Table 21 and the Forest plot at Figure 22.

Figure 21: Network of evidence for ICU admission, vaginal birth subgroup



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_Oxy, misoprostol plus oxytocin; Oxy_a5b10, oxytocin >5IU and ≤10IU.

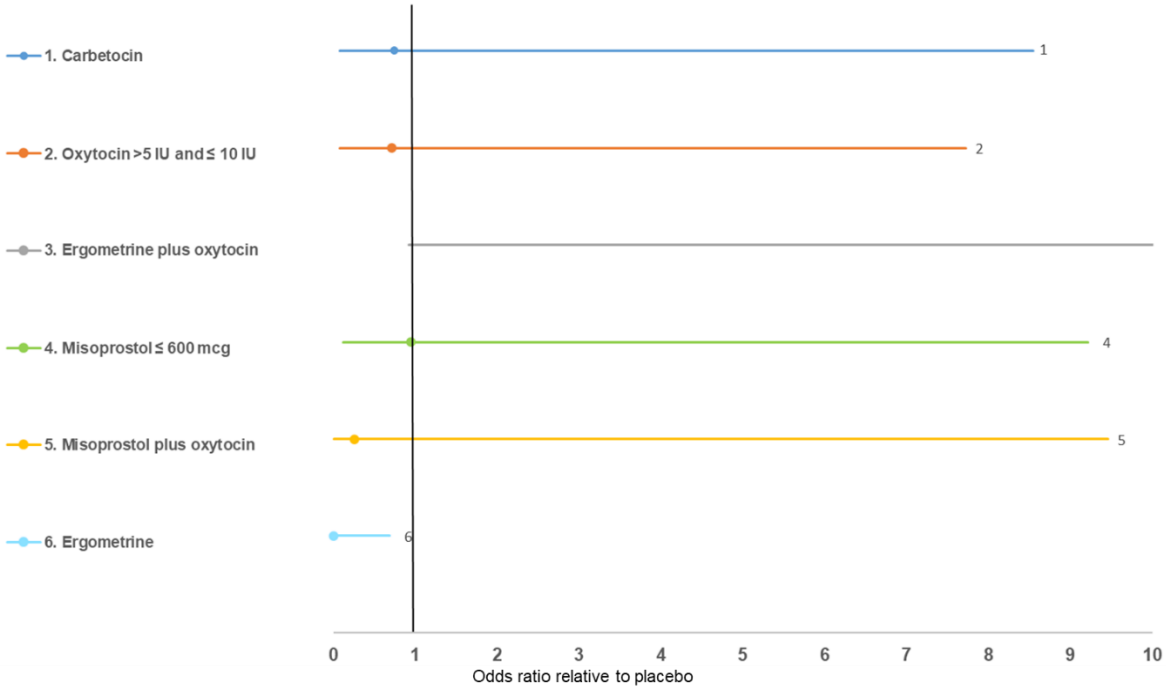
Table 21: Odds ratio, log odds ratio and 95% CrIs for ICU admission for all interventions compared with placebo, vaginal birth subgroup

Intervention	NMA OR (95% CrI)	NMA LogOR (95% CrI)	Number of studies providing direct evidence
Ergometrine	0.000 (0.000, 0.692)	-25.12 (-70.43, -0.3677)	-
Misoprostol plus oxytocin	0.262 (0.005, 9.459)	-1.339 (-5.293, 2.247)	-
Oxytocin >5 IU and ≤ 10 IU	0.711 (0.081, 7.721)	-0.3406 (-2.518, 2.044)	-
Carbetocin	0.746 (0.081, 8.542)	-0.2936 (-2.513, 2.145)	-
Misoprostol ≤ 600 mcg	0.950 (0.118, 9.217)	-0.05112 (-2.141, 2.221)	1
Ergometrine plus oxytocin	7.13E+10 (0.925, 9.80E+30)	24.99 (-0.07789, 71.36)	-

Results from the random effects NMA. OR<1 favours the intervention (lower risk of ICU admission in the intervention arm, with lower numbers indicating a greater effect), OR>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

In this analysis all of the estimates are highly uncertain given the sparse evidence network, and the treatment ranking has not been presented as the probability of being best is likely to be biased.

Figure 22: Forest plot, ICU admission vaginal birth (OR <1 favours intervention)



The forest plot in Figure 22 does not show the point estimate or upper error bar for ergometrine plus oxytocin. This is because these values are very large, so are much further to the right on the graph than all other strategies.

Caesarean birth subgroup analysis

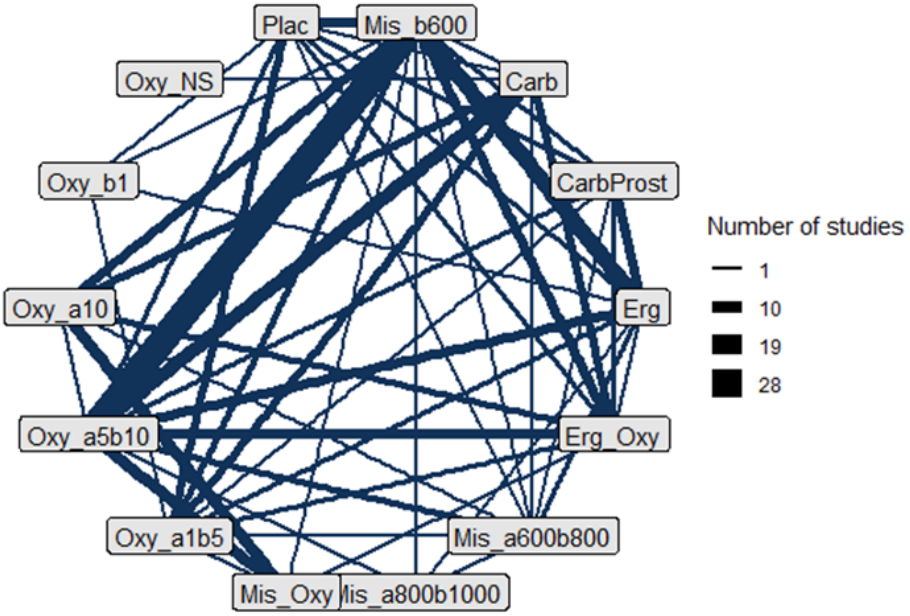
Only 1 study comparing 2 treatments was identified for this outcome in the caesarean birth subgroup, therefore an NMA could not be conducted. These results were analysed using pairwise analysis, which can be found in supplement 5.

Mean blood loss (ml)

156 studies, comparing 14 interventions in 85,514 women were included in this analysis. Of these studies, 1 included women who had either vaginal or caesarean births, 109 were conducted in women who had vaginal births only, and 46 in women who had caesarean births only.

The network plot for this outcome is shown below at Figure 23, the odds ratios compared to placebo in Table 22, the Forest plot at Figure 24 and the median treatment ranks in Table 23.

Figure 23: Network of evidence for mean blood loss, full dataset



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; CarbProst, carboprost; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Mis_a800b1000, misoprostol >800mcg and ≤1000mcg; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU; Oxy_b1, oxytocin ≤1IU; Oxy_NS, oxytocin unspecified dose.

Table 22: blood loss ratio and 95% CrI for mean blood loss for all interventions compared with placebo

Intervention	NMA blood loss ratio (95% CrI)	Number of studies providing direct evidence
Oxytocin unspecified dose	0.6734 (0.3929, 1.077)	-
Carbetocin	0.6819 (0.588, 0.7849)	1
Misoprostol plus oxytocin	0.6931 (0.5858, 0.8168)	-
Carboprost	0.7023 (0.5887, 0.832)	2
Ergometrine plus oxytocin	0.7731 (0.6696, 0.8866)	2
Misoprostol >600 mcg and ≤ 800 mcg	0.7903 (0.6513, 0.9498)	10
Misoprostol ≤ 600 mcg	0.8249 (0.7323, 0.927)	8
Oxytocin >5 IU and ≤ 10 IU	0.825 (0.7271, 0.9341)	2
Oxytocin >1 IU and ≤ 5 IU	0.8266 (0.7146, 0.9509)	6
Misoprostol >800 mcg and ≤ 1000 mcg	0.8317 (0.5921, 1.137)	-
Oxytocin > 10 IU	0.8563 (0.7326, 0.9961)	-
Ergometrine	0.8574 (0.746, 0.979)	2
Oxytocin ≤1 IU	0.9383 (0.6582, 1.297)	1

Results from the random effects NMA. Blood loss ratio <1 favours the intervention (lower amount of blood lost in the intervention arm) with lower numbers indicating greater benefit, blood loss ratio>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

Figure 24: Forest plot, mean blood loss full population (OR< 1 favours intervention)

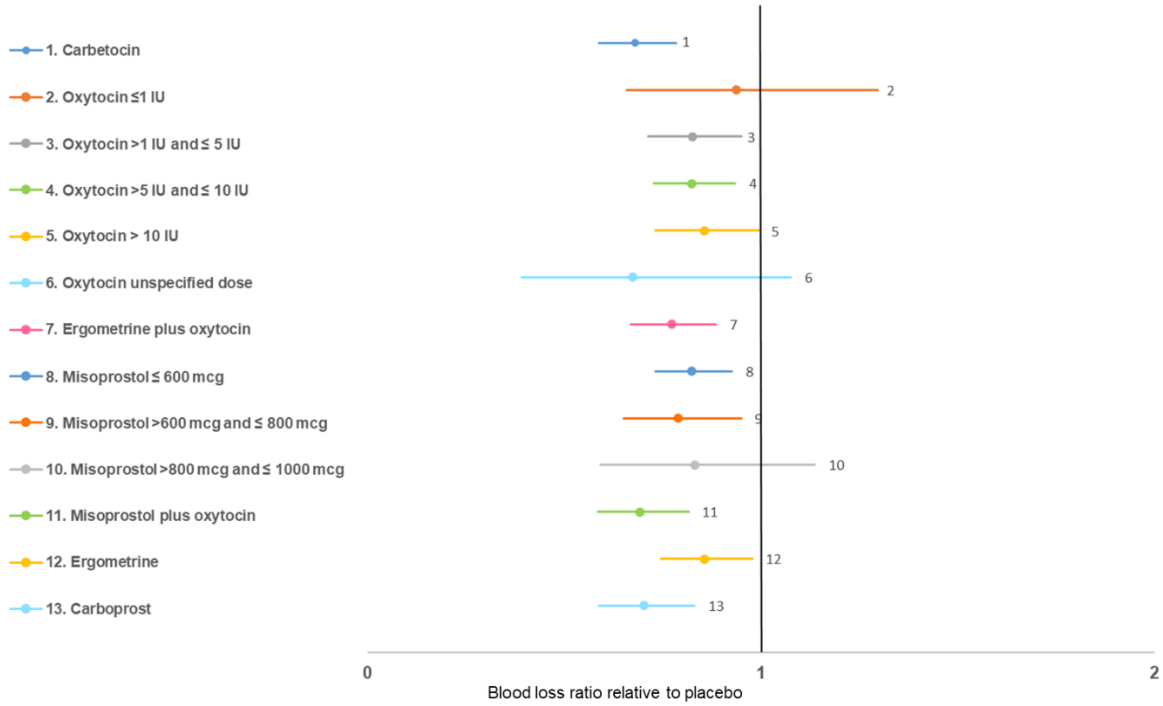


Table 23: Median treatment ranks and probability of being the best treatment for all interventions for mean blood loss

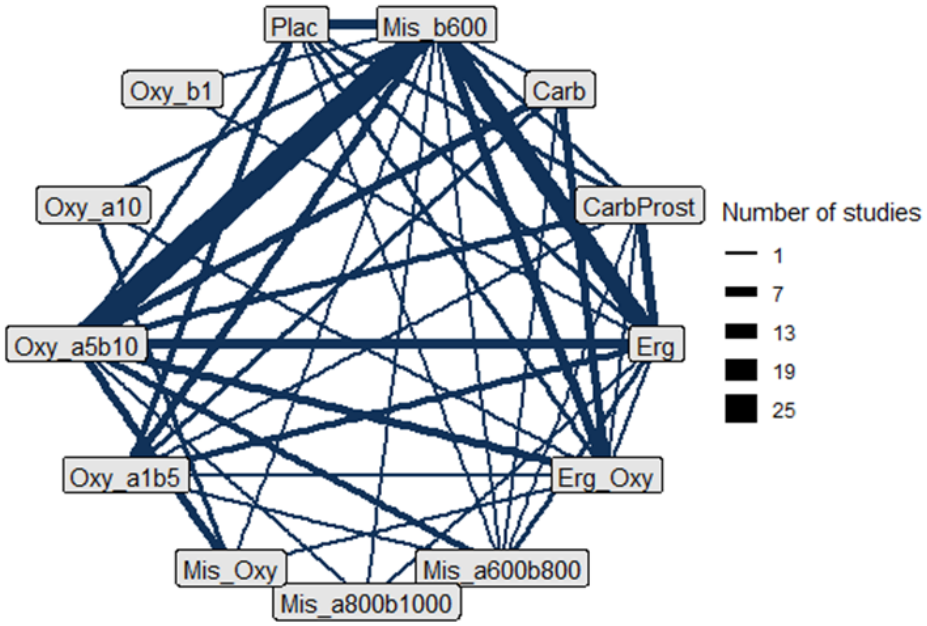
Intervention	Median (95% CrI) treatment rank	Probability of being best
Carbetocin	2 (1, 5)	15.75%
Misoprostol plus oxytocin	3 (1, 6)	14.32%
Carboprost	3 (1, 7)	13.26%
Oxytocin unspecified dose	2 (1, 14)	49.70%
Ergometrine plus oxytocin	6 (3, 10)	0.08%
Misoprostol >600 mcg and ≤ 800 mcg	6 (2, 12)	0.79%
Misoprostol >800 mcg and ≤ 1000 mcg	8 (1, 14)	4.70%
Misoprostol ≤ 600 mcg	9 (5, 12)	0.00%
Oxytocin >5 IU and ≤ 10 IU	9 (5, 12)	0.00%
Oxytocin >1 IU and ≤ 5 IU	9 (4, 13)	0.01%
Oxytocin > 10 IU	11 (6, 13)	0.00%
Ergometrine	11 (6, 13)	0.00%
Oxytocin ≤1 IU	13 (2, 14)	1.38%
Placebo	14 (12, 14)	0.00%

Vaginal birth subgroup analysis

109 studies comparing 13 treatments in 76,400 women were included in this subgroup analysis.

The network plot for this outcome is shown below at Figure 25, the odds ratios compared to placebo in Table 24, the Forest plot at Figure 26 and the median treatment ranks in Table 25.

Figure 25: Network of evidence for mean blood loss, vaginal birth subgroup



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; CarbProst, carboprost; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Mis_a800b1000, misoprostol >800mcg and ≤1000mcg; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU; Oxy_b1, oxytocin ≤1IU.

Table 24: blood loss ratio and 95% CrI for mean blood loss for all interventions compared with placebo, vaginal birth subgroup

Intervention	NMA blood loss ratio (95% CrI)	Number of studies providing direct evidence
Carbetocin	0.6817 (0.5584, 0.8251)	-
Carboprost	0.7038 (0.5772, 0.847)	2
Misoprostol plus oxytocin	0.7817 (0.6185, 0.9731)	-
Misoprostol >600 mcg and ≤ 800 mcg	0.7976 (0.6443, 0.9777)	1
Ergometrine plus oxytocin	0.7977 (0.6755, 0.9358)	2
Oxytocin >5 IU and ≤ 10 IU	0.8189 (0.7078, 0.9424)	2
Oxytocin >1 IU and ≤ 5 IU	0.8328 (0.693, 0.9924)	4
Misoprostol >800 mcg and ≤ 1000 mcg	0.8366 (0.5815, 1.163)	-
Misoprostol ≤ 600 mcg	0.8368 (0.7295, 0.9565)	7
Ergometrine	0.8626 (0.7373, 1.004)	2
Oxytocin ≤1 IU	0.8714 (0.4275, 1.519)	-
Oxytocin > 10 IU	0.9367 (0.7093, 1.209)	-

Results from the random effects NMA. Blood loss ratio <1 favours the intervention (lower amount of blood lost in the intervention arm) with lower numbers indicating greater benefit, blood loss ratio>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

Figure 26: Forest plot, mean blood loss vaginal birth (OR < 1 favours intervention)

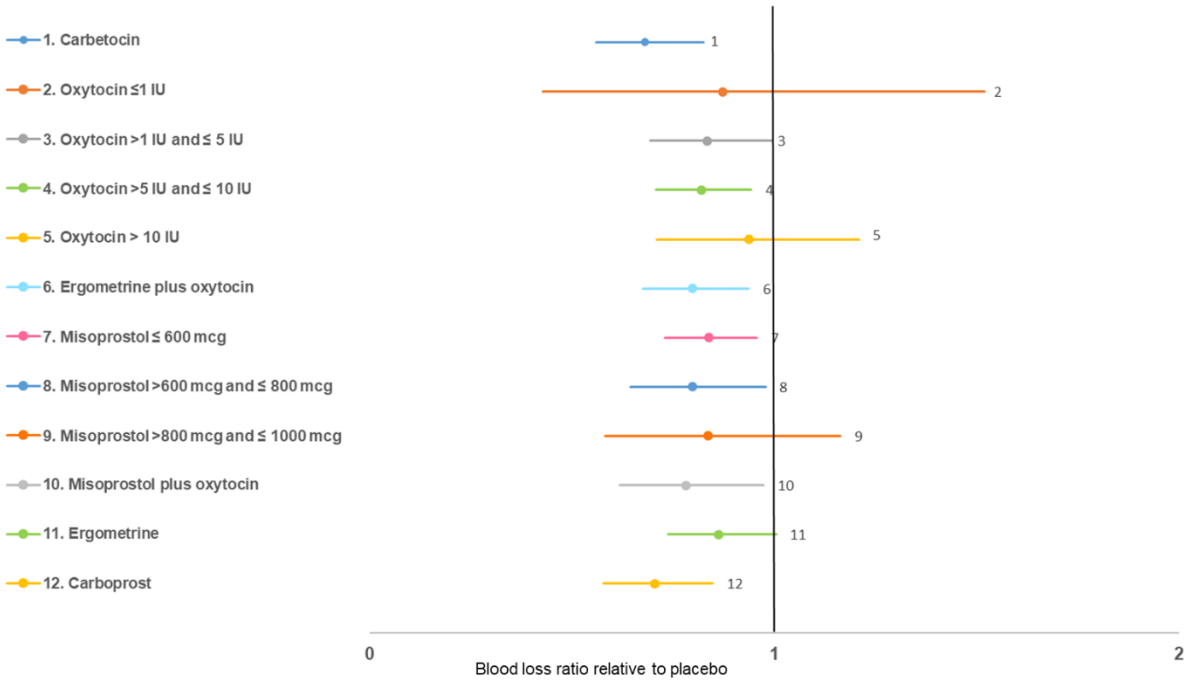


Table 25: Median treatment ranks and probability of being the best treatment for all interventions for mean blood loss, vaginal birth subgroup

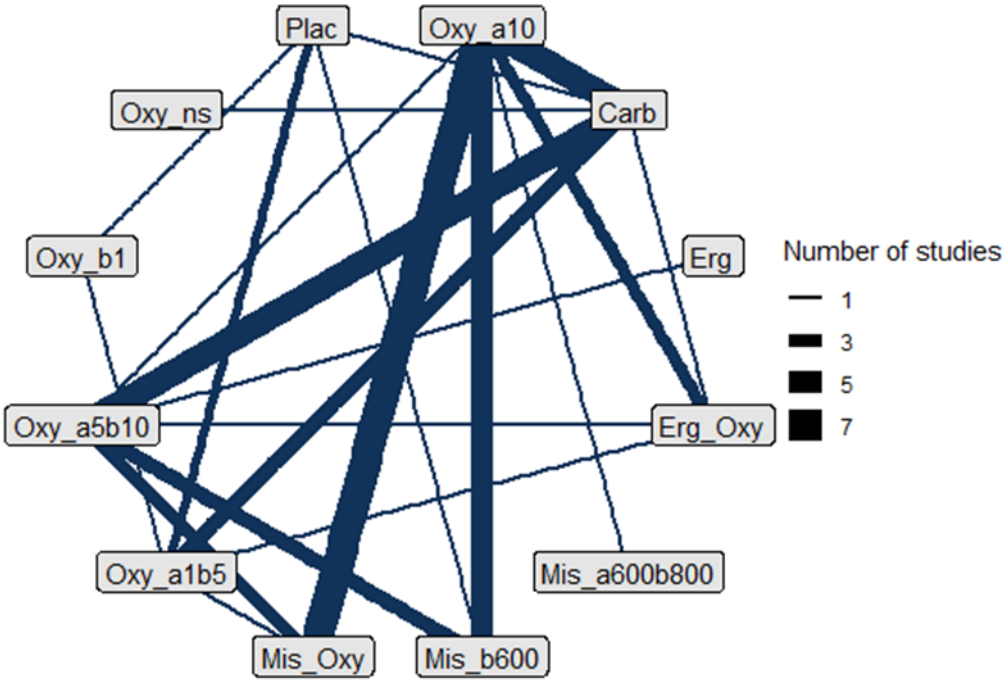
Intervention	Median (95% CrI) treatment rank	Probability of being best
Carbetocin	2 (1, 5)	39.21%
Carboprost	2 (1, 7)	23.97%
Misoprostol plus oxytocin	5 (1, 11)	4.72%
Ergometrine plus oxytocin	6 (2, 11)	0.20%
Misoprostol >600 mcg and ≤ 800 mcg	6 (2, 12)	1.88%
Oxytocin >5 IU and ≤ 10 IU	7 (4, 10)	0.00%
Misoprostol >800 mcg and ≤ 1000 mcg	7 (1, 13)	7.59%
Oxytocin ≤1 IU	8 (1, 13)	22.00%
Oxytocin >1 IU and ≤ 5 IU	8 (3, 12)	0.22%
Misoprostol ≤ 600 mcg	8 (5, 11)	0.00%
Ergometrine	9 (5, 12)	0.00%
Oxytocin > 10 IU	11 (4, 13)	0.22%
Placebo	12 (10, 13)	0.00%

Caesarean birth subgroup analysis

46 studies comparing 12 treatments in 8,585 women were included in this subgroup analysis.

The network plot for this outcome is shown below at Figure 27, the odds ratios compared to placebo in Table 26 , the Forest plot at Figure 28 and the median treatment ranks in Table 27.

Figure 27: Network of evidence for mean blood loss, caesarean birth subgroup



Abbreviations: Plac, placebo; Mis_b600, misoprostol ≤600mcg; Carb, carbetocin; Erg, ergometrine; Erg_Oxy, ergometrine plus oxytocin; Mis_a600b800, misoprostol >600mcg and ≤800mcg; Mis_Oxy, misoprostol plus oxytocin; Oxy_a1b5, oxytocin >1IU and ≤5IU; Oxy_a5b10, oxytocin >5IU and ≤10IU; Oxy_a10, oxytocin >10IU; Oxy_NS, oxytocin unspecified dose; Oxy_b1, oxytocin ≤1IU.

Table 26: blood loss ratio and 95% CrI for mean blood loss for all interventions compared with placebo, caesarean birth subgroup

Intervention	NMA blood loss ratio (95% CrI)	Number of studies providing direct evidence
Misoprostol plus oxytocin	0.6035 (0.4414, 0.8083)	-
Oxytocin unspecified dose	0.6484 (0.3743, 1.048)	-
Carbetocin	0.6605 (0.4926, 0.8652)	1
Misoprostol >600 mcg and ≤ 800 mcg	0.6722 (0.3892, 1.082)	-
Ergometrine plus oxytocin	0.6793 (0.482, 0.929)	-
Misoprostol ≤ 600 mcg	0.7539 (0.5607, 0.9983)	1
Oxytocin > 10 IU	0.7743 (0.5759, 1.02)	-
Oxytocin >1 IU and ≤ 5 IU	0.7866 (0.5919, 1.022)	2
Oxytocin >5 IU and ≤ 10 IU	0.8555 (0.6303, 1.136)	-
Ergometrine	0.8839 (0.5105, 1.415)	-
Oxytocin ≤1 IU	0.9617 (0.6401, 1.387)	1

Results from the random effects NMA. Blood loss ratio <1 favours the intervention (lower amount of blood lost in the intervention arm) with lower numbers indicating greater benefit, blood loss ratio>1 favours placebo. Abbreviations: OR, odds ratio; CrI, credible interval.

Figure 28: Forest plot, mean blood loss caesarean birth (OR < 1 favours intervention)

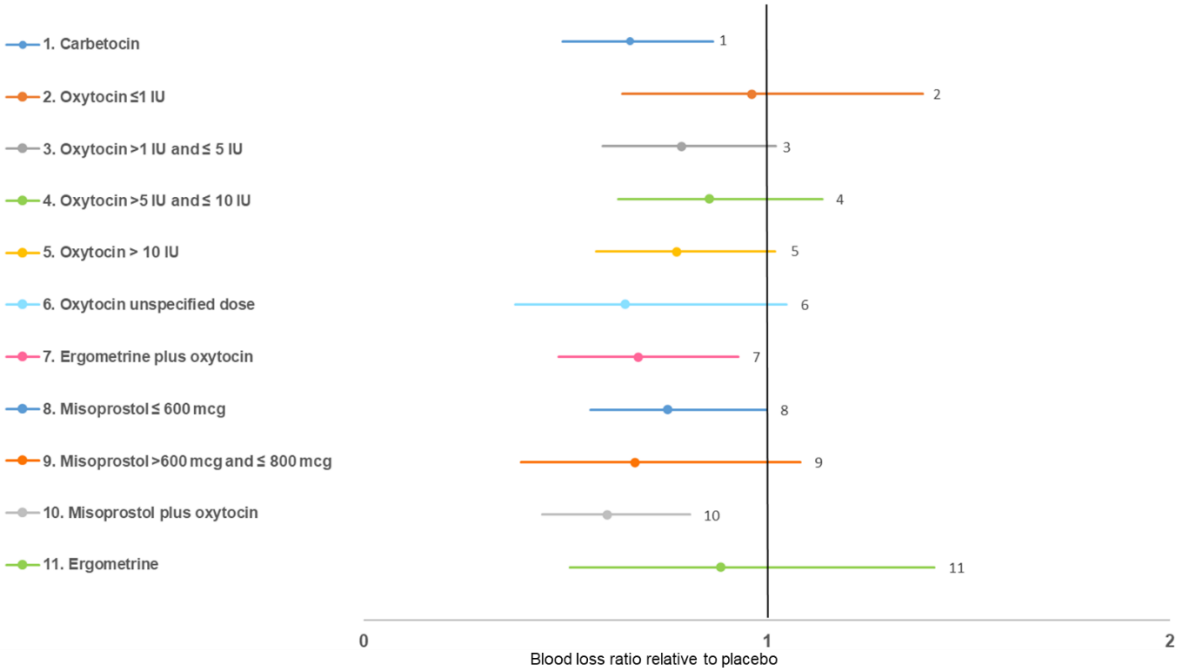


Table 27: Median treatment ranks and probability of being the best treatment for all interventions for mean blood loss, caesarean birth subgroup

Intervention	Median (95% CrI) treatment rank	Probability of being best
Misoprostol plus oxytocin	2 (1, 6)	28.40%
Carbetocin	4 (1, 7)	2.76%
Oxytocin unspecified dose	3 (1, 11)	30.46%
Ergometrine plus oxytocin	4 (1, 9)	4.88%
Misoprostol >600 mcg and ≤ 800 mcg	4 (1, 11)	24.50%
Misoprostol ≤ 600 mcg	6 (3, 10)	0.23%
Oxytocin > 10 IU	7 (4, 10)	0.00%
Oxytocin >1 IU and ≤ 5 IU	8 (4, 11)	0.12%
Ergometrine	10 (1, 12)	2.85%
Oxytocin >5 IU and ≤ 10 IU	9 (6, 12)	0.00%
Placebo	11 (1, 12)	5.20%
Oxytocin ≤1 IU	11 (3, 12)	0.60%

Economic evidence

Included studies

Two economic studies were identified which were relevant to this question (Gallos 2019 and Matthijsse 2022).

See the literature search strategy in Appendix B and economic study selection flow chart in Appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in Appendix J.

Summary of included economic evidence

See Table 28 for the economic evidence profile of the included studies.

Table 28: Economic evidence profile of a systematic review of economic evaluations of uterotonics for the prevention of postpartum haemorrhage

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
NICE guideline model 2023	Minor limitations[4]	Directly applicable[1]	Decision analytic model ICERs were calculated for non-QALY outcomes and interpreted by transforming the ICER using the NICE WTP threshold.	Incremental costs are relative to oxytocin 1-5 IU for the full population and caesarean subgroup, and to oxytocin 5-10 IU for vaginal birth **Full population** Oxytocin 5-10 IU £1.04 Oxytocin ≤1 IU £5.39 Oxytocin >10 IU £7.95 Carbetocin £65.66 Ergometrine plus oxytocin	Incremental effects (PPH≥1000mL avoided) are relative to oxytocin 1-5 IU for the full population and caesarean subgroup, and to oxytocin 5-10 IU for vaginal birth **Full population** [7] Oxytocin 5-10 IU 0.001 Oxytocin ≤1 IU 0.053 Oxytocin >10 IU 0.030 Carbetocin -0.015 Ergometrine plus oxytocin	**Full population** Oxytocin 5-10 IU Dominated Oxytocin ≤1 IU Dominated Oxytocin >10 IU Dominated Carbetocin £4,319 per PPH ≥1000mL avoided Ergometrine plus oxytocin Dominated	**Full population** Probabilistic average results and deterministic results were broadly similar. When AEs are excluded ergometrine plus oxytocin is most likely to be cost-effective. **Vaginal birth** Probabilistic average results and deterministic results were broadly

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				£105.97 **Vaginal birth** Oxytocin 1-5 IU £1.50 Oxytocin >10 IU £3.52 Oxytocin ≤1 IU £6.82 Ergometrine plus oxytocin £60.86 Carbetocin £68.76 **Caesarean birth** Carbetocin £23.24 Oxytocin >10 IU £70.74 Oxytocin 5-10 IU £123.26 Ergometrine plus oxytocin £151.08	-0.012 **Vaginal birth** Oxytocin 1-5 IU -0.001 Oxytocin >10 IU 0.030 Oxytocin ≤1 IU 0.060 Ergometrine plus oxytocin -0.012 Carbetocin -0.010 **Caesarean birth** Carbetocin -0.024 Oxytocin >10 IU 0.050 Oxytocin 5-10 IU 0.001 Ergometrine plus oxytocin -0.002	**Vaginal birth** Oxytocin 1-5 IU £1,139 per PPH ≥1000mL avoided Oxytocin >10 IU Dominated Oxytocin ≤1 IU Dominated Ergometrine plus oxytocin £5,423 per PPH ≥1000mL avoided Carbetocin Dominated **Caesarean birth** Carbetocin £951 per PPH ≥1000mL avoided Oxytocin >10 IU Dominated Oxytocin 5-10 IU Dominated Ergometrine plus oxytocin Dominated	similar. When AEs are excluded ergometrine plus oxytocin dominated over all other treatments. **Caesarean birth** Probabilistic average results and deterministic results were broadly similar.
Gallos 2019	Potentially serious	Partially applicable[5]	Decision analytic model	**Vaginal birth**	**Vaginal birth**	**Vaginal birth**	**Vaginal birth**

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
Uterotonic drugs to prevent postpartum haemorrhage	limitations[2,3,4]			Oxytocin £0 Ergometrine plus oxytocin -£7 Carbetocin £6 Misoprostol plus oxytocin -£6 Misoprostol £3 Ergometrine £6 **Caesarean birth** Misoprostol plus oxytocin £0 Oxytocin £29 Carbetocin £19 Misoprostol £25	Oxytocin 0 cases of PPH ≥ 500 ml Ergometrine plus oxytocin 0.028 cases of PPH ≥ 500 ml avoided Carbetocin 0.036 cases of PPH ≥ 500 ml avoided Misoprostol plus oxytocin 0.023 cases of PPH ≥ 500 ml avoided Ergometrine 0.017 cases of PPH ≥ 500 ml **Caesarean birth** Misoprostol plus oxytocin 0 cases of PPH ≥ 500 ml Oxytocin 0.133 cases of PPH ≥ 500 ml Carbetocin 0.033 cases of PPH ≥ 500 ml	carbetocin v ergometrine plus oxytocin £1,889 per PPH ≥ 500 ml avoided ergometrine plus oxytocin dominates all other interventions **Caesarean birth** Misoprostol plus oxytocin dominates	Carbetocin had a greater than 50% probability of being cost-effective relative to oxytocin for cost-effectiveness thresholds > £864 per PPH ≥ 500 ml avoided

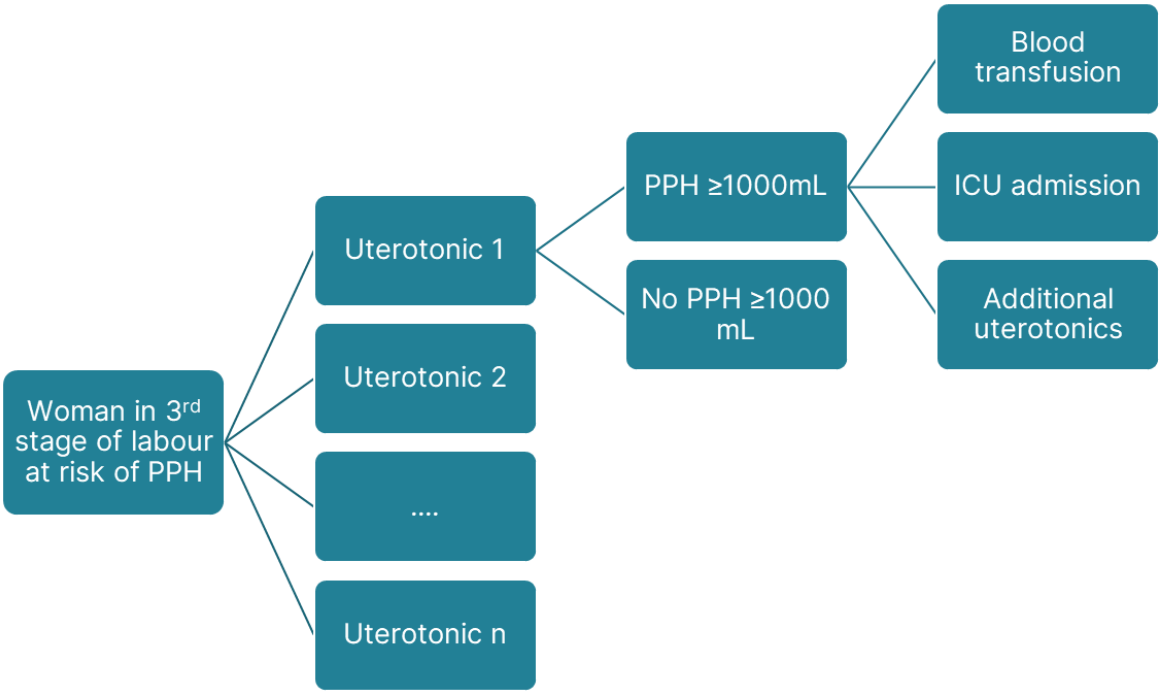
Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
					Misoprostol 0.152 cases of PPH ≥ 500 ml		
Matthijsse 2022 Carbetocin versus oxytocin for the prevention of postpartum hemorrhage following vaginal birth	Potentially serious limitations [2.6]	Partially applicable[5]	Decision analytic model	Carbetocin -£55	Carbetocin 0.0342 PPH events avoided	Carbetocin dominates	79.5% probability that carbetocin dominates

[1]This analysis was conducted specifically to answer this review question, QALYs were not used due to limited utility data but cost per outcome was compared with the NICE threshold using a conversion into healthy days lost.
[2]The authors noted that the trials including carbetocin in the NMA were small and of low quality and that there would be a need to update the NMA with the larger and better quality studies that have since been undertaken
[3] Probabilistic sensitivity analysis was restricted to the outcome of PPH ≥ 500 ml which was not identified by the guideline committee as either a primary or secondary outcome
[4] The authors identified missing data as the main limitation of this analysis
[5] Clinical effectiveness data from the NMA did not distinguish by dose
[6]The study was funded by the manufacturers of carbetocin
[7]Lower numbers of PPH events indicate more effective treatments

Economic model

A de-novo economic model was developed to answer this question, based on the outputs from the updated NMAs on PPH ≥1000 mL, additional uterotonics, ICU admission, and blood transfusions. The model utilised the decision tree structure as shown in Figure 29, with the time horizon only considering the immediate costs and outcomes in the third stage of labour. The model compares all uterotonics included in the NMAs (where data allows), and due to a lack of utility data in this area, costs are presented alongside outcomes such as number of PPH≥1000 mL events avoided rather than as cost per QALY gained.

Figure 29: Model schematic



Costs included in the model were; prophylactic drug costs, drug administration costs, treatment-related adverse event costs, cost of additional uterotonics, cost of blood transfusion, and cost of ICU admission (as a scenario analysis). In the base-case, ICU admission and the costs associated with this were excluded due to missing data in the NMA.

Results were generated separately for the full population and the subgroups of vaginal birth and caesarean birth, as agreed by the committee. Efficacy results for each population group were informed by the corresponding NMA.

Deterministic results were presented alongside a probabilistic sensitivity analysis (PSA) which involved repeated Monte Carlo simulation of model inputs from their corresponding probability distributions. This was done in order to capture the inherent uncertainty in the model inputs. In each simulation the total cost, and total number of outcomes was calculated for each uterotonic. These individual simulation values were then aggregated to determine the average total cost and total number of outcomes, to evaluate the cost per event avoided. The probabilistic results were broadly similar to the deterministic results, suggesting that the cost-effectiveness results are fairly stable to the parameter uncertainty.

Scenario analyses were conducted on inclusion of ICU admissions in the model, exclusion of adverse events, and route of administration for carbetocin, to determine the impact of these events in the economic results. These scenarios were selected as there were data gaps and therefore uncertainty in the data informing these aspects of the economic analysis.

For full details of the economic model and results are available in appendix I.

Unit costs

The drug costs used in the economic model are detailed in the table below. Where combinations (for example, misoprostol plus oxytocin) or different doses than those listed (for example, misoprostol >800 mcg and ≤ 1000 mcg) have been modelled, the costs have been calculated using the values shown in the table. Details of these calculations are available in appendix I, Table 34.

Resource	Unit costs	Source
Carbetocin 100mcg	£17.64 (per dose)	British National Formulary – January 2023
Oxytocin 5IU	£0.80 (per dose)	British National Formulary – January 2023
Oxytocin 10IU	£0.91 (per dose)	British National Formulary – January 2023
Ergometrine 500mcg	£1.50 (per dose)	British National Formulary – January 2023
Misoprostol 200mcg	£0.17 (per dose)	British National Formulary – January 2023
Carboprost 250mcg	£18.20 (per dose)	British National Formulary – January 2023
Syntometrine	£1.57 (per dose)	British National Formulary – January 2023

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee chose postpartum haemorrhage greater than or equal to 1000 mL as the critical outcome for this review. They agreed that this outcome directly informed the effectiveness of uterotonics to prevent postpartum haemorrhage. In addition, they agreed that this outcome indicated major haemorrhage which would impact the woman's birth experience, ability to bond with the baby, and could have a psychological impact on both her and her partner. They also agreed on important outcomes for the review as the need for additional uterotonics, intensive care admissions, number of blood transfusions, and mean blood loss volume. They agreed that these outcomes would provide further information to help understand which uterotonic would be the most effective to prevent postpartum haemorrhage, as they would demonstrate a reduction in other negative outcomes or need for further interventions. The committee discussed maternal mortality and agreed on the high importance of this outcome. However, they agreed that although postpartum haemorrhage accounts for many of maternal deaths, maternal mortality is still a very rare outcome and many studies would be underpowered to report this outcome with precision. Therefore the committee agreed that looking at postpartum haemorrhage as an outcome would be the best way of approaching this review question.

The quality of the evidence

The trials included for this evidence review were individually assessed using the Cochrane risk of bias tool, and the summarised quality of the evidence for each of the NMAs is presented in supplement 4. The main area where trials were at risk of bias was due to not blinding of assessors. There were also some concerns around allocation concealment, and unclear bias on selective reporting due to no protocol being available to review.

The data presented using pairwise analysis were assessed using GRADE. The majority of the comparisons were assessed as low to very low. The concerns were mainly due to imprecision and also some concerns around risk of bias.

The inconsistency checks highlighted moderate heterogeneity but little evidence of inconsistency (see appendix N for more information).

Benefits and harms

The committee discussed the network meta-analysis evidence on the use of a variety of uterotonics for the prevention of postpartum haemorrhage. They considered the evidence for the whole population for the critical outcome of PPH of 1000 mL or more and noted that the evidence indicated that, based on the odds ratios, all active treatments were better than placebo, although for 2 treatments the confidence intervals did cross the line of no effect. The committee therefore focussed their discussion on which of the treatments was most effective and noted that there were differences in the most effective uterotonic across the outcomes depending on mode of birth, and therefore agreed that they would consider the evidence broken down by modes of birth (vaginal or caesarean).

The committee also discussed that the evidence for ICU admission (as an indicator of maternal morbidity) was based on evidence from only 9 studies, the networks were sparsely populated, and in the case of the caesarean birth sub-group non-existent, so they agreed that the results from this outcome would be less influential in helping them make decisions.

The committee discussed the method of administration of the uterotonics and noted that both oxytocin and carbetocin could be administered by intravenous or intramuscular injection. They noted that the evidence for both oxytocin and carbetocin included both these routes of administration.

The committee discussed that in addition to the clinical effectiveness of the drugs it was also important to consider the route of administration, licensed status, cost effectiveness, side effects and heat stability.

The committee first discussed the evidence for the caesarean birth subgroup. They discussed that across the outcomes of postpartum haemorrhage of 1000 mL or more, need for additional uterotonics and blood transfusion, the evidence showed that misoprostol >600 mcg to ≤800 mcg and carbetocin were the best ranked drugs, although there was some uncertainty due to large credible intervals. For the outcome of mean blood loss, misoprostol plus oxytocin, or carbetocin were the best ranked drugs. As outlined above, the committee agreed that the evidence for intensive care admission was limited and they could not use it to guide their recommendations. The committee therefore discussed that misoprostol or carbetocin could be options for women who had had a caesarean birth but agreed that in theatre it would be easier to give intravenous carbetocin rather than misoprostol which has to be given orally or rectally, and also that misoprostol is not approved for this indication whereas carbetocin is approved. They also discussed the importance of side effects and noted that misoprostol often causes nausea and vomiting, diarrhoea and abdominal pain which would be extremely unpleasant for the woman, and may be difficult for woman being sutured and recovering from a caesarean birth. The committee also discussed the impact of these side-effects on the birth experience of the woman and her partner and agreed that although they might be short term, the postpartum period is a crucial period for bonding with the baby and it was important to ensure the best experience for the woman and her partner. The committee discussed that carbetocin was heat stable and did not require refrigeration, although this was unlikely to cause a problem in theatres where fridges for drug storage were likely to be available.

The committee then reviewed the cost-effectiveness data for the caesarean birth population (see more detailed discussion below) and agreed that due to its clinical and cost

effectiveness they would recommend intravenous carbetocin to prevent PPH in those women having a caesarean birth.

The committee then looked at the evidence for the vaginal birth subgroup and agreed that the results for this group were more varied. For the critical outcome of PPH of 1000 mL or more there was evidence that some doses of oxytocin, ergometrine, ergometrine plus oxytocin, carbetocin, some doses of misoprostol or misoprostol plus oxytocin were all effective. Similarly, a number of these treatments and carboprost seemed to demonstrate similar efficacy for the outcomes of additional uterotonics, blood transfusion and mean blood loss. The committee agreed not to recommend misoprostol because, as for caesarean birth, they were aware that misoprostol would have unpleasant side effects of nausea and vomiting, diarrhoea and abdominal pain and this would impact the woman's birth experience, and that it was not approved for this indication. The committee agreed that oxytocin or oxytocin plus ergometrine were already routinely used for prophylaxis of PPH, could be given intramuscularly in home births or midwife-led settings and that either of these options could be recommended. They also discussed the place of carbetocin but used the health economic analysis to inform their decision to not recommend carbetocin for use after vaginal birth as it was not cost-effective (see more detailed discussion below).

The committee discussed the evidence for oxytocin, and for oxytocin plus ergometrine, which both showed similar effectiveness for the outcomes of the review, although oxytocin plus ergometrine was marginally more effective with tighter credible intervals for the critical outcome of PPH of 1000 mL or more, and noted that oxytocin >5 units and ≤ 10 units and oxytocin plus ergometrine were cost-effective (see detailed discussion below). They agreed to offer women the option of either of these 2 drugs. The committee discussed that the side effect profiles differ between the two drugs, and that oxytocin plus ergometrine could be associated with more side effects (for example, nausea and vomiting) than oxytocin alone, and was contraindicated in women with severe hypertension, cardiac, hepatic or renal disease. Nevertheless, the committee agreed that it was important to give women the option for either drug given the potential increased effectiveness of oxytocin plus ergometrine, but that there needed to be careful consideration of the benefits and harms to allow women to make an informed decision. Based on their knowledge and experience the committee agreed that women receiving oxytocin plus ergometrine should be offered antiemetics as well.

The committee discussed that the evidence was not stratified by risk of postpartum haemorrhage and that the population in the evidence included a mixed population of high and low risk. They discussed that the recommendations would apply to a general mixed population but the committee agreed that due to the marginal greater effectiveness of oxytocin plus ergometrine they would advise this option in women who had been identified as at a higher risk of PPH.

Cost effectiveness and resource use

A health economic model was developed for this review question, comparing uterotonics for preventing postpartum haemorrhage. The committee also considered the two published studies identified for this review question (Gallos 2019 and Matthijsse 2022), but ultimately based their recommendations on the updated NMA and new economic model as that included the more recent clinical evidence including 2 large carbetocin trials, and also differentiated treatments by dose. The model was run separately for vaginal birth and caesarean birth since outcomes in the NMA were generated for each of these populations and the committee thought that there would be important differences between these groups and that recommendations may need to be considered separately.

The committee did not use the results of the full population analysis to make recommendations as they felt it was more appropriate to consider the mode-of-birth subgroups separately given the differences between them.

The results from the economic model included three outcomes alongside costs; PPH ≥ 1000 mL, need for additional uterotonics, and need for blood transfusions. The committee reviewed all results generated in the model, but primarily based their decisions on the PPH ≥ 1000 mL outcome as this was designated as the critical outcome for this review.

There was evidence in the caesarean birth subgroup suggesting carbetocin to be the most cost-effective option of the uterotonics the committee were considering. Carbetocin was more costly but more effective than oxytocin >1 iu and ≤ 5 iu, and dominant over other oxytocin doses and oxytocin plus ergometrine. Using the conversion method described in a published HTA (Gallos 2019), carbetocin would be considered cost effective compared with oxytocin if a person would be willing to trade 17 days in full health to avoid having a PPH ≥ 1000 mL. The committee agreed that this was a reasonable trade off and recommended that carbetocin be offered for women who have had a caesarean birth.

In the vaginal birth subgroup the committee agreed that oxytocin >5 iu and ≤ 10 iu was likely to be the most cost-effective option, and oxytocin plus ergometrine was more costly and more effective but would be considered cost-effective compared to oxytocin if a person was willing to trade 91 days of full health to avoid having a PPH ≥ 1000 mL. However, there was missing data in the information from the HTA informing the adverse events in the model and a scenario analysis was undertaken in which side-effects were excluded. The committee considered this scenario as they believed that some of the key side effects of treatments in the comparison (nausea and vomiting) could be mitigated by offering antiemetics. Under this scenario oxytocin plus ergometrine became the most likely cost-effective option, being least costly and most effective. Carbetocin was more costly and less effective than oxytocin plus ergometrine in the base case model and in the scenario where adverse events were included. In the scenario where the cost of intramuscular injection was used for carbetocin administration carbetocin was less costly and less effective than ergometrine plus oxytocin, but more costly and more effective than oxytocin >5 iu and ≤ 10 iu, however when carbetocin was assumed to be administered by intramuscular injection and adverse events were excluded carbetocin was still more costly and less effective than oxytocin plus ergometrine. The committee agreed that the cost-effectiveness evidence was not strong enough to recommend carbetocin for the prevention of postpartum haemorrhage following vaginal birth. Based on the evidence, the committee recommended a choice between oxytocin or oxytocin plus ergometrine and listed factors that should be discussed when making this decision. The committee also recommended that antiemetics are offered alongside oxytocin plus ergometrine due to the higher likelihood of nausea and vomiting. Offering antiemetics is not anticipated to have a substantial resource impact as these drugs are low cost and are expected to reduce downstream costs in terms of managing nausea and vomiting.

Other factors the committee took into account

The committee noted that the use of oxytocin for the prevention of postpartum haemorrhage was within the licensed indications and although the IM route is not strictly in line with the marketing authorisation, they recognised that this a well-established practice and licensed in several other countries.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.10.9 to 1.10.11 and 1.10.13.

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Effectiveness

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Vimala N, Mittal S, Kumar S, Dadhwal V, Mehta S. Sublingual misoprostol versus methylergometrine for active management of third stage of labor. International Journal of Gynecology & Obstetrics 2004;87:1-5.

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Vimala N, Mittal S, Kumar S. Sublingual misoprostol versus oxytocin infusion to reduce blood loss at cesarean section. International Journal of Gynecology & Obstetrics 2006;92(2):106-10.

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Walley RL, Wilson JB, Crane JM, Matthews K, Sawyer E, Hutchens D. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. BJOG: an international journal of obstetrics and gynaecology 2000;107(9):1111-5.

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Zgaya 2020

Zgaya, R., Ghadhab, I., Triki, M.A. et al. Randomized controlled trial comparing 400mug sublingual misoprostol versus placebo for prevention of primary postpartum hemorrhage. Pan African Medical Journal 2020; 36: 1-9

Economic

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Gallos I, Williams H, Price M et al. Uterotonic drugs to prevent postpartum haemorrhage: a network meta-analysis. Health Technol Assess. 2019 Feb;23(9):1-356.

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Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Table 29: Review protocol

Field	Content
PROSPERO registration number	Not applicable
Review title	Uterotonics for the prevention of PPH
Review question	What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?
Objective	To update the recommendations in CG190 (2014) for the use of uterotonics for prevention of postpartum haemorrhage
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE & MEDLINE In-Process • International Health Technology Assessment (IHTA) database Searches will be restricted by: • Date limitations: May 2018 (date when the search was last run for Gallos 2018) • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies for the MEDLINE database will be published in the final review. For each search,

Field	Content
	the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist. Key papers: ○ Cochrane NMA (Gallos 2018) https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011689.pub3/full ○ IMOX trial https://pubmed.ncbi.nlm.nih.gov/30606246/ ○ CHAMPION trial https://www.nejm.org/doi/full/10.1056/nejmoa1805489
Condition or domain being studied	Prevention of postpartum haemorrhage
Population	• Women in the third stage of labour following a vaginal or caesarean birth
Intervention	The following uterotonic agents: • Carbetocin • Ergometrine (includes also ergonovine, methylergonovine) • Injectable prostaglandins (carboprost, tromethamine, sulprostone) • Misoprostol ○ Dose ≤600 mcg ○ Dose >600 mcg to ≤800 mcg ○ Dose >800 mcg to ≤1000 mcg ○ Dose >1000 mcg • Oxytocin ○ Dose ≤1 iu ○ Dose >1 iu to ≤ 5 iu ○ Dose >5 iu to ≤ 10 iu ○ Dose > 10 iu • The following combination agents: ○ Syntometrine ® as a fixed-combination agent containing 5 international units (IU) of oxytocin and 500 mcg of ergometrine; any oxytocin dose and route when combined with any dose and

Field	Content
	route of ergometrine, ergonovine, or methylergonovine ○ Misoprostol plus oxytocin (any oxytocin dose and route when combined with any dose and route of misoprostol) The uterotonic or combination agents noted above will be eligible if they are administered systemically by a healthcare professional for preventing PPH at birth. Any dosage, route and regimen will be included.
Comparator	• Any uterotonic agent listed as part of the interventions compared to another • Placebo • No treatment
Types of study to be included	Include published full-text papers: • RCTs • Cluster RCTs • Conference abstracts in which sufficient information can be retrieved Quasi-randomised trials will be excluded
Other exclusion criteria	• Trials evaluating uterotonics agents not administered systemically, such as intrauterine administration, or not immediately after birth • Trials exclusively comparing different dosages, routes or regimens of the same uterotonic agent
Context	This review will update the following guideline: Intrapartum care for healthy women and babies (CG190) and it is based on the Cochrane NMA Gallos 2018 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011689.pub3/full
Primary outcome (critical outcome)	• Primary PPH ≥1000 mL
Secondary outcomes (important outcomes)	• Severe maternal morbidity: intensive care admissions • Additional uterotonics

Field	Content
	• Number of blood transfusions • Mean volumes of blood loss (mL)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies in excel. The following data will be extracted: study details (study ID, first author, publication year, number of arms, number randomised), participant characteristics, intervention characteristics, dose and route and relevant outcome data. Data will be extracted independently by 2 reviewers into a standardised form, and any disagreements will be resolved via discussion and consultation with senior staff. For dichotomous outcomes, an intention-to-treat (ITT) approach will be taken and where possible ITT data will be extracted; if both ITT and completer data are reported, the former will be preferred; completer data will be used only if ITT data are not reported. For continuous outcomes, completer data will be preferred, unless some method of adjusting for missing data has been used, in which case, an ITT approach will be preferred.
Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the relevant version of the Cochrane RoB tool, v1. checklist
Strategy for data synthesis	**Method of analysis** <u>Network meta-analysis (NMA)</u> • Network meta-analysis will be conducted within a Bayesian framework using WinBUGS. • The exact model structure will be agreed with the NICE Technical Support Unit (TSU) following the review of available clinical evidence. Fixed and random effects NMA models will be fitted to the data and

Field	Content
	compared based on the posterior mean residual deviance and DIC. The model with the best fit and meaningfully lower DIC will be selected. Differences of at least 3 will be considered meaningful. • For dichotomous outcomes, posterior median ORs and 95% credible intervals (CrIs) will be used to report the results • For continuous outcomes, mean differences will be used to report the results • Ranking of treatments will be provided (i.e. posterior median ranks and 95% CrIs, rankograms, probability being best). • Inconsistency checks will be conducted by comparing the posterior mean residual deviance, DIC, and where appropriate (i.e., random effects models), posterior median between study standard deviation, of the base case NMA model and unrelated mean effects (UME) model. Plots of contributions to the residual deviance for the UME vs the NMA model will be inspected to identify lack of consistency for particular studies / comparisons. If these checks indicate potential inconsistency, further checks will be conducted using node splitting analysis. Pairwise estimates will be obtained from the UME model to aid comparison of the direct estimates with the NMA estimates. • Threshold analysis will also be conducted if a clear decision rule between linking the recommendations to the NMA estimates can be identified. <u>Pairwise meta-analysis</u> For outcomes with insufficient data for NMA, standard pair-wise meta-analysis will be conducted using Cochrane Review Manager. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I^2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled.
Analysis of subgroups	Subgroup analysis: • Mode of birth:

Field	Content			
	○ Vaginal birth ○ Caesarean birth			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	Not applicable			
Anticipated completion date	Not applicable			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☑
	Piloting of the study selection process		☑	☑
	Formal screening of search results against eligibility criteria		☑	☑
	Data extraction		☑	☑
	Risk of bias (quality) assessment		☑	☑
	Data analysis		☑	☑

Field	Content
Named contact	5a. Named contact Guideline Development Team National Guideline Alliance (NGA) 5b. Named contact e-mail IPCupdate@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)
Review team members	From the Guideline Development Team: • Senior Systematic Reviewer • Systematic Reviewer
Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team NGA, Centre for Guidelines, which is part of the National Institute for Health and Care Excellence (NICE
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10174
Other registration details	None
URL for published protocol	Not applicable
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication

Field	Content	
	publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	[Give words or phrases that best describe the review.]	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	None	
Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CrIs: credible interval; DARE: Database of Abstracts of Reviews of Effects; Development and Evaluation; IHTA: International Health Technology Assessment; ITT: intention to treat; IU: international units; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; OR: odds ratio; PPH: postpartum haemorrhage; PRESS: Peer Review of Electronic Search Strategies; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation; TSU: technical support unit; UME: unrelated mean effects

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Database: Medline – OVID interface

Date of last search: 14/06/2022

#	Searches
1	POSTPARTUM HEMORRHAGE/
2	((postpartum or post partum) adj3 h?emorrhag*).ti,ab.
3	PPH.ti,ab.
4	or/1-3
5	exp ANTIFIBRINOLYTIC AGENTS/
6	(antifibrinoly* or anti-fibrinoly* or antiplasmin? or anti-plasmin? or plasmin inhibitor? or aminocaproic acid or tranexamic acid or vitamin k* or alpha-2-antiplasmin or aminomethylbenzoic acid).mp.
7	APROTININ/
8	aprotinin.mp.
9	or/5-8
10	uterotonic?.mp.
11	exp OXYTOCICS/
12	(oxytocic? or carbetocin or ergometrine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
13	exp PROSTAGLANDINS/
14	(prostaglandin? or carboprost).mp.
15	or/10-14
16	4 and 9
17	4 and 15
18	or/16-17
19	limit 18 to english language
20	LETTER/
21	EDITORIAL/
22	NEWS/
23	exp HISTORICAL ARTICLE/
24	ANECDOTES AS TOPIC/
25	COMMENT/
26	CASE REPORT/
27	(letter or comment*).ti.
28	or/20-27
29	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
30	28 not 29
31	ANIMALS/ not HUMANS/
32	exp ANIMALS, LABORATORY/
33	exp ANIMAL EXPERIMENTATION/
34	exp MODELS, ANIMAL/
35	exp RODENTIA/
36	(rat or rats or mouse or mice).ti.
37	or/30-36
38	19 not 37
39	META-ANALYSIS/
40	META-ANALYSIS AS TOPIC/
41	(meta analy* or metanaly* or metaanaly*).ti,ab.
42	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
43	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
44	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
45	(search* adj4 literature).ab.
46	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
47	cochrane.jw.
48	or/39-47
49	randomized controlled trial.pt.
50	controlled clinical trial.pt.
51	pragmatic clinical trial.pt.
52	randomi#ed.ab.
53	placebo.ab.
54	randomly.ab.
55	CLINICAL TRIALS AS TOPIC/
56	trial.ti.

#	Searches
57	or/49-56
58	38 and 48
59	38 and 57
60	or/58-59
61	limit 50 to yr="2018 -Current"

Database: Embase – OVID interface

Date of last search: 14/06/2022

#	Searches
1	POSTPARTUM HEMORRHAGE/
2	((postpartum or post partum) adj3 h?emorrhag*).ti,ab.
3	PPH.ti,ab.
4	or/1-3
5	exp ANTIFIBRINOLYTIC AGENT/
6	(antifibrinoly* or anti-fibrinoly* or antiplasmin? or anti-plasmin? or plasmin inhibitor? or aminocaproic acid or tranexamic acid or vitamin k* or alpha-2-antiplasmin or aminomethylbenzoic acid).mp.
7	aprotinin.mp.
8	or/5-7
9	exp UTEROTONIC AGENT/
10	uterotonic?.mp.
11	(oxytocic? or carbetocin or ergometrine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
12	exp *PROSTAGLANDIN/
13	(prostaglandin? or carboprost).mp.
14	or/9-13
15	4 and 8
16	4 and 14
17	or/15-16
18	limit 17 to english language
19	letter.pt. or LETTER/
20	note.pt.
21	editorial.pt.
22	CASE REPORT/ or CASE STUDY/
23	(letter or comment*).ti.
24	or/19-23
25	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
26	24 not 25
27	ANIMAL/ not HUMAN/
28	NONHUMAN/
29	exp ANIMAL EXPERIMENT/
30	exp EXPERIMENTAL ANIMAL/
31	ANIMAL MODEL/
32	exp RODENT/
33	(rat or rats or mouse or mice).ti.
34	or/26-33
35	18 not 34
36	SYSTEMATIC REVIEW/
37	META-ANALYSIS/
38	(meta analy* or metanaly* or metaanaly*).ti,ab.
39	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
40	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
41	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
42	(search* adj4 literature).ab.
43	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
44	((pool* or combined) adj2 (data or trials or studies or results)).ab.
45	cochrane.jw.
46	or/36-45
47	random*.ti,ab.
48	factorial*.ti,ab.
49	(crossover* or cross over*).ti,ab.
50	((doubl* or singl*) adj blind*).ti,ab.
51	(assign* or allocat* or volunteer* or placebo*).ti,ab.
52	CROSSOVER PROCEDURE/
53	SINGLE BLIND PROCEDURE/
54	RANDOMIZED CONTROLLED TRIAL/
55	DOUBLE BLIND PROCEDURE/
56	or/47-55

#	Searches
57	35 and 46
58	35 and 56
59	or/57-58
60	limit 59 to yr="2018 -Current"

Databases: Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials – Wiley interface

Date of last search: 14/06/2022

ID	Search
#1	MeSH descriptor: [Postpartum Hemorrhage] this term only
#2	((postpartum or "post partum") near/3 (hemorrhag* or haemorrhag*)):ti,ab
#3	PPH:ti,ab
#4	{or #1-#3}
#5	MeSH descriptor: [Antifibrinolytic Agents] this term only
#6	(antifibrinoly* or "anti-fibrinoly*" or antiplasmin* or "anti-plasmin*" or "plasmin inhibitor*" or "aminocaproic acid" or "tranexamic acid" or "vitamin k*" or "alpha-2-antiplasmin" or "aminomethylbenzoic acid"):ti,ab
#7	MeSH descriptor: [Aprotinin] this term only
#8	aprotinin:ti,ab
#9	{or #5-#8}
#10	uterotonic*:ti,ab
#11	MeSH descriptor: [Oxytocics] this term only
#12	(oxytocic* or carbetocin or ergometrine or misoprostrol or oxytocin or pitocin or syntometrine):ti,ab
#13	MeSH descriptor: [Prostaglandins] explode all trees
#14	(prostaglandin* or carboprost):ti,ab
#15	{or #10-#14}
#16	#4 and #9
#17	#4 and #15
#18	#16 or #17 with Cochrane Library publication date Between Jan 2018 and Jun 2022

Database: CINAHL – Ebsco interface

Date of last search: 14/06/2022

#	Query	Limiters/Expanders
S45	S27 AND S44	Limiters - Published Date: 20180101-20220631; English Language Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S44	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S43	AB (cluster W3 RCT)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S42	MH (crossover design) OR MH (comparative studies)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S41	AB (control W5 group)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S40	PT (randomized controlled trial)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S39	MH (placebos)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S38	MH (sample size) AND AB (assigned OR allocated OR control)	Expanders - Apply equivalent subjects

#	Query	Limiters/Expanders
		Search modes - Boolean/Phrase
S37	TI (trial)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S36	AB (random*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S35	TI (randomised OR randomized)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S34	(MH cluster sample)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S33	(MH pretest-posttest design)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S32	(MH random assignment)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S31	(MH single-blind studies)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S30	(MH double-blind studies)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S29	(MH randomized controlled trials)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S28	(TI (systematic* n3 review*)) or (AB (systematic* n3 review*)) or (TI (systematic* n3 bibliographic*)) or (AB (systematic* n3 bibliographic*)) or (TI (systematic* n3 literature)) or (AB (systematic* n3 literature)) or (TI (comprehensive* n3 literature)) or (AB (comprehensive* n3 literature)) or (TI (comprehensive* n3 bibliographic*)) or (AB (comprehensive* n3 bibliographic*)) or (TI (integrative n3 review)) or (AB (integrative n3 review)) or (JN “Cochrane Database of Systematic Reviews”) or (TI (information n2 synthesis)) or (TI (data n2 synthesis)) or (AB (information n2 synthesis)) or (AB (data n2 synthesis)) or (TI (data n2 extract*)) or (AB (data n2 extract*)) or (TI (medline or pubmed or psyclit or cinahl or (psycinfo not “psycinfo database”) or “web of science” or scopus or embase)) or (AB (medline or pubmed or psyclit or cinahl or (psycinfo not “psycinfo database”) or “web of science” or scopus or embase)) or (MH “Systematic Review”) or (MH “Meta Analysis”) or (TI (meta-analy* or metaanaly*)) or (AB (meta-analy* or metaanaly*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S27	S18 not S26	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S26	S19 OR S22 OR S23 OR S24 OR S25	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S25	TI (rat or rats or mouse or mice)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S24	(MH Rodents+)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S23	(MH Animals, Laboratory)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S22	S20 not S21	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

#	Query	Limiters/Expanders
S21	(MH human)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S20	(MH animals+)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S19	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S18	S16 OR S17	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S17	S4 AND S15	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S16	S4 AND S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S15	S10 OR S11 OR S12 OR S13 OR S14	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S14	TX (prostaglandin* or carboprost)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S13	(MH "Prostaglandins+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S12	TX (oxytocic* or carbetocin or ergometrine or misoprostrol or oxytocin or pitocin or syntometrine)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S11	(MH "Oxytocics+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S10	TX uterotonic*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S9	S5 OR S6 OR S7 OR S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S8	TX aprotinin	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S7	(MH "Aprotinin")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S6	TX (antifibrinoly* or "anti-fibrinoly*" or antiplasmin? or "anti-plasmin?" or "plasmin inhibitor?" or "aminocaproic acid" or "tranexamic acid" or "vitamin k*" or "alpha-2-antiplasmin" or "aminomethylbenzoic acid")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S5	(MH "Antifibrinolytic Agents+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S4	S1 OR S2 OR S3	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

#	Query	Limiters/Expanders
S3	TI PPH OR AB PPH	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S2	TI (((postpartum or post partum) N3 h?emorrhag*)) OR AB (((postpartum or post partum) N3 h?emorrhag*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S1	(MH "Postpartum Hemorrhage")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

Database: ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP)

Date of last search: 14/06/2022

List of search terms

Limited to 2018-

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

Health economics search strategies

Database: Medline – OVID interface

Date of last search: 09/03/2022

#	Searches
1	POSTPARTUM HEMORRHAGE/
2	((postpartum or post partum) adj3 h?emorrhag*).ti,ab.
3	PPH.ti,ab.
4	or/1-3
5	uterotonic?.mp.
6	exp OXYTOCICS/
7	(oxytocic? or carbetocin or ergometrine or ergonovine or methylergonovine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
8	exp PROSTAGLANDINS/

#	Searches
9	(prostaglandin? or carboprost or sulprostone).mp.
10	or/5-9
11	4 and 10
12	limit 11 to english language
13	LETTER/
14	EDITORIAL/
15	NEWS/
16	exp HISTORICAL ARTICLE/
17	ANECDOTES AS TOPIC/
18	COMMENT/
19	CASE REPORT/
20	(letter or comment*).ti.
21	or/13-20
22	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
23	21 not 22
24	ANIMALS/ not HUMANS/
25	exp ANIMALS, LABORATORY/
26	exp ANIMAL EXPERIMENTATION/
27	exp MODELS, ANIMAL/
28	exp RODENTIA/
29	(rat or rats or mouse or mice).ti.
30	or/23-29
31	12 not 30
32	ECONOMICS/
33	VALUE OF LIFE/
34	exp "COSTS AND COST ANALYSIS"/
35	exp ECONOMICS, HOSPITAL/
36	exp ECONOMICS, MEDICAL/
37	exp RESOURCE ALLOCATION/
38	ECONOMICS, NURSING/
39	ECONOMICS, PHARMACEUTICAL/
40	exp "FEES AND CHARGES"/
41	exp BUDGETS/
42	budget*.ti,ab.
43	cost*.ti,ab.
44	(economic* or pharmaco?economic*).ti,ab.
45	(price* or pricing*).ti,ab.
46	(financ* or fee or fees or expenditure* or saving*).ti,ab.
47	(value adj2 (money or monetary)).ti,ab.
48	resourc* allocat*.ti,ab.
49	(fund or funds or funding* or funded).ti,ab.
50	(ration or rations or rationing* or rationed).ti,ab.
51	ec.fs.
52	or/32-51
53	31 and 52

Database: Embase – OVID interface

Date of last search: 09/03/2022

#	Searches
1	POSTPARTUM HEMORRHAGE/
2	((postpartum or post partum) adj3 h?emorrhag*).ti,ab.
3	PPH.ti,ab.
4	or/1-3
5	exp UTEROTONIC AGENT/
6	uterotonic?.mp.
7	(oxytocic? or carbetocin or ergometrine or ergonovine or methylergonovine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
8	exp *PROSTAGLANDIN/
9	(prostaglandin? or carboprost or sulprostone).mp.
10	or/5-9
11	4 and 10
12	limit 11 to english language
13	letter.pt. or LETTER/
14	note.pt.
15	editorial.pt.

#	Searches
16	CASE REPORT/ or CASE STUDY/
17	(letter or comment*).ti.
18	or/13-17
19	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
20	18 not 19
21	ANIMAL/ not HUMAN/
22	NONHUMAN/
23	exp ANIMAL EXPERIMENT/
24	exp EXPERIMENTAL ANIMAL/
25	ANIMAL MODEL/
26	exp RODENT/
27	(rat or rats or mouse or mice).ti.
28	or/20-27
29	12 not 28
30	HEALTH ECONOMICS/
31	exp ECONOMIC EVALUATION/
32	exp HEALTH CARE COST/
33	exp FEE/
34	BUDGET/
35	FUNDING/
36	RESOURCE ALLOCATION/
37	budget*.ti,ab.
38	cost*.ti,ab.
39	(economic* or pharmaco?economic*).ti,ab.
40	(price* or pricing*).ti,ab.
41	(financ* or fee or fees or expenditure* or saving*).ti,ab.
42	(value adj2 (money or monetary)).ti,ab.
43	resourc* allocat*.ti,ab.
44	(fund or funds or funding* or funded).ti,ab.
45	(ration or rations or rationing* or rationed).ti,ab.
46	or/30-45
47	29 and 46

Database: Cochrane Central Register of Controlled Trials – Wiley interface

Date of last search: 09/03/2022

#	Searches
#1	MeSH descriptor: [Postpartum Hemorrhage] this term only
#2	((postpartum or "post partum") near/3 (hemorrhag* or haemorrhag*)):ti,ab
#3	PPH:ti,ab
#4	#1 or #2 or #3
#5	uterotonic*:ti,ab
#6	MeSH descriptor: [Oxytocics] explode all trees
#7	(oxytocic* or carbetocin or ergometrine or ergonovine or methylergonovine or misoprostrol or oxytocin or pitocin or syntometrine):ti,ab
#8	MeSH descriptor: [Prostaglandins] explode all trees
#9	(prostaglandin* or carboprost or sulprostone):ti,ab
#10	#5 or #6 or #7 or #8 or #9
#11	#4 and #10
#12	MeSH descriptor: [Economics] this term only
#13	MeSH descriptor: [Value of Life] this term only
#14	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#15	MeSH descriptor: [Economics, Hospital] explode all trees
#16	MeSH descriptor: [Economics, Medical] explode all trees
#17	MeSH descriptor: [Resource Allocation] explode all trees
#18	MeSH descriptor: [Economics, Nursing] this term only
#19	MeSH descriptor: [Economics, Pharmaceutical] this term only
#20	MeSH descriptor: [Fees and Charges] explode all trees
#21	MeSH descriptor: [Budgets] explode all trees
#22	budget*:ti,ab
#23	cost*:ti,ab
#24	(economic* or pharmaco?economic*):ti,ab
#25	(price* or pricing*):ti,ab
#26	(financ* or fee or fees or expenditure* or saving*):ti,ab
#27	(value near/2 (money or monetary)):ti,ab
#28	resourc* allocat*:ti,ab

#	Searches
#29	(fund or funds or funding* or funded):ti,ab
#30	(ration or rations or rationing* or rationed):ti,ab
#31	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#32	#11 and #31

Database: International Health Technology Assessment

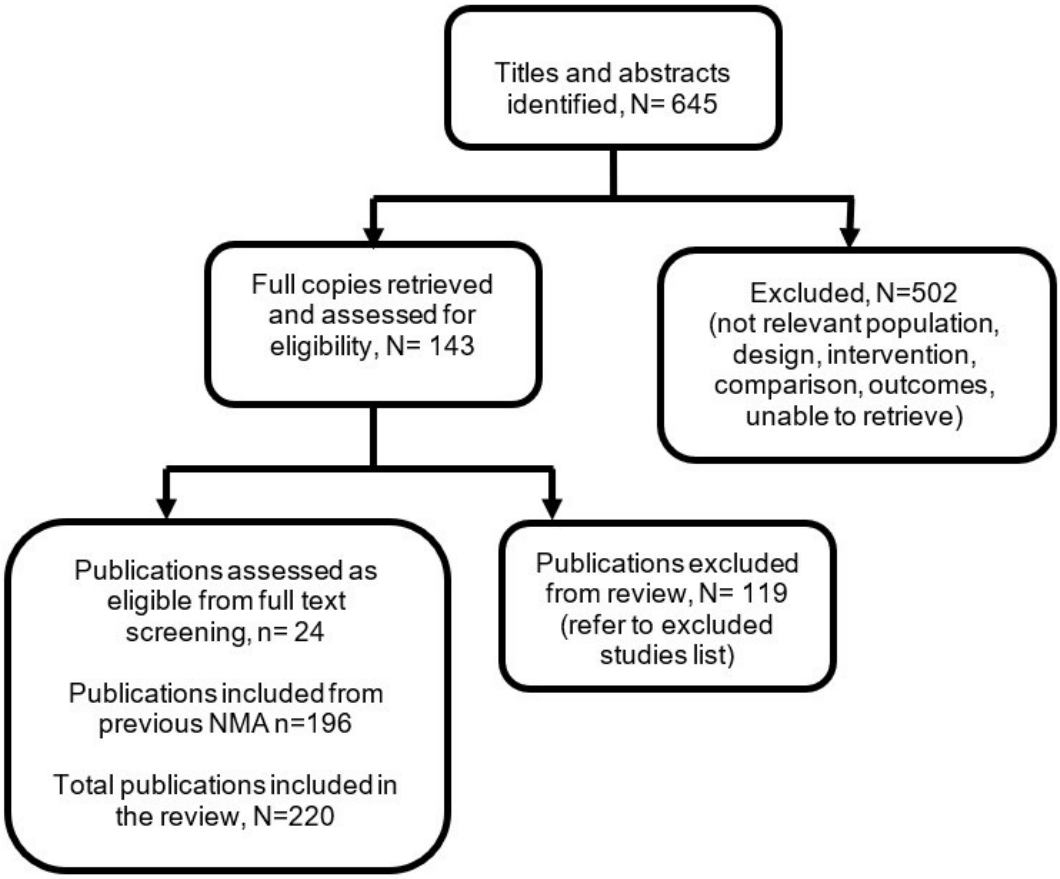
Date of last search: 09/03/2022

#	Searches
	"Postpartum Hemorrhage"[mh]
	OR All: postpartum hemorrrhage
	OR All: postpartum haemorrrhage
	OR All: post partum hemorrrhage
	OR All: post partum haemorrrhage

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Figure 30: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Due to the size and complexity of these tables they are provided in a separate document. See Supplement 4.

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

This section includes forest plots only for outcomes that are meta-analysed, but were not included in the NMA. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Postpartum haemorrhage ≥ 1000 mL

Figure 31: Ergometrine versus Misoprostol ≤600mcg – Vaginal birth

Study or Subgroup	Ergometrine Events	Ergometrine Total	Misoprostol 600 Events	Misoprostol 600 Total	Weight	Risk Difference M-H, Fixed, 95% CI
Chhabra 2008	0	100	0	200	26.8%	0.00 [-0.02, 0.02]
Humera 2016	0	50	0	50	10.0%	0.00 [-0.04, 0.04]
Jago 2007	0	254	0	256	51.2%	0.00 [-0.01, 0.01]
Vimala 2004	0	60	0	60	12.0%	0.00 [-0.03, 0.03]
Total (95% CI)		**464**		**566**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

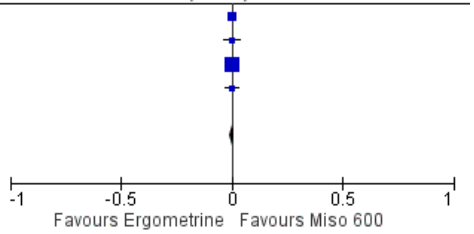


Figure 32: Misoprostol ≤600mcg versus Oxytocin >5 iu to ≤ 10 iu – Vaginal birth

Study or Subgroup	Misoprostol 600 Events	Misoprostol 600 Total	Oxytocin 5-10 Events	Oxytocin 5-10 Total	Weight	Risk Difference M-H, Fixed, 95% CI
Afolabi 2010	0	100	0	100	5.0%	0.00 [-0.02, 0.02]
Bellad 2012	0	321	0	331	16.4%	0.00 [-0.01, 0.01]
Bhatti 2014	0	60	0	60	3.0%	0.00 [-0.03, 0.03]
Gupta 2006	0	100	0	100	5.0%	0.00 [-0.02, 0.02]
Oboro 2003	0	247	0	249	12.5%	0.00 [-0.01, 0.01]
Sadiq 2011	0	900	0	900	45.4%	0.00 [-0.00, 0.00]
Tewatia 2014	0	50	0	50	2.5%	0.00 [-0.04, 0.04]
Walley 2000	0	202	0	196	10.0%	0.00 [-0.01, 0.01]
Total (95% CI)		**1980**		**1986**	**100.0%**	**0.00 [-0.00, 0.00]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 7 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

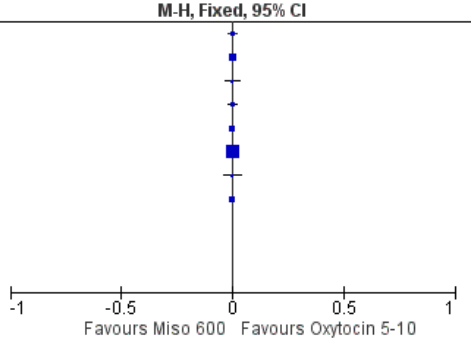


Figure 33: Oxytocin >1 iu to ≤ 5 iu versus Carbetocin

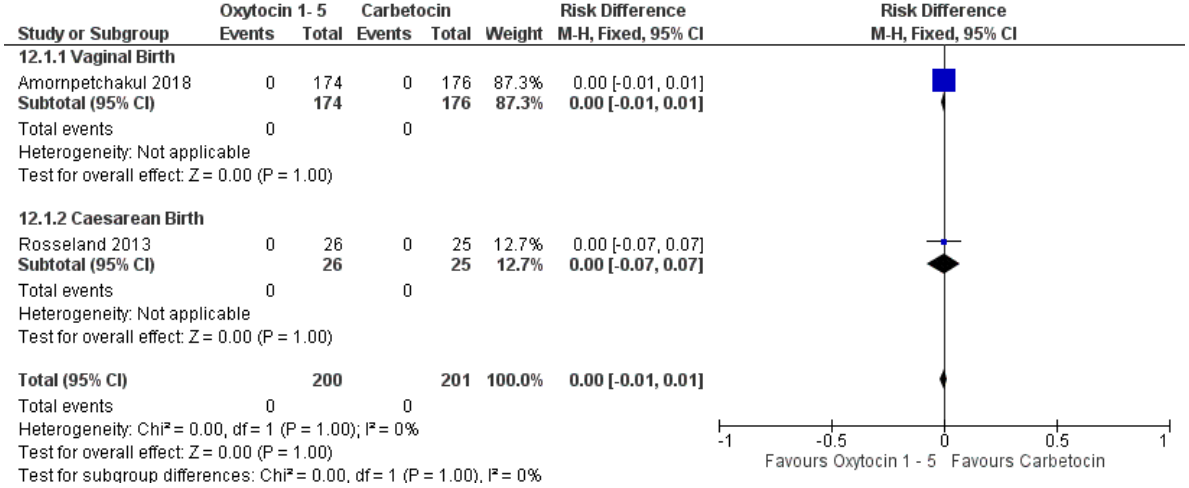
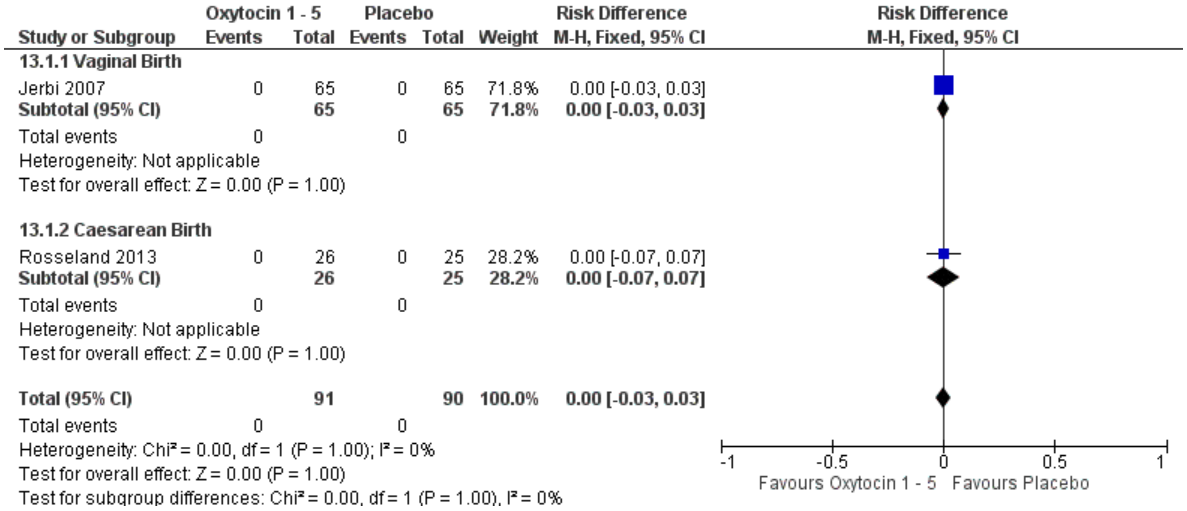


Figure 34: Oxytocin >1 iu to ≤ 5 iu versus Placebo



Severe maternal morbidity – intensive care admissions

Figure 35: Misoprostol >600 mcg to ≤800 mcg versus Oxytocin >1 iu to ≤ 5 iu – Vaginal birth

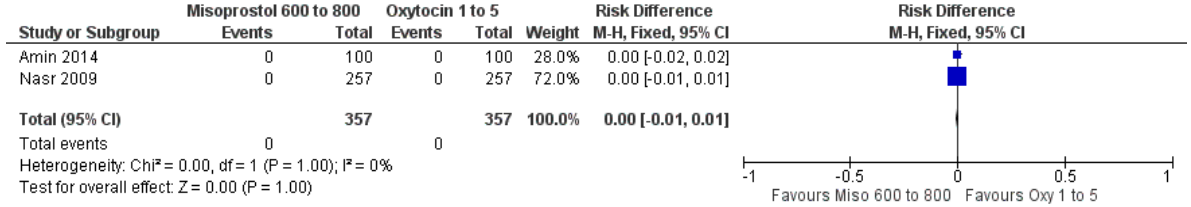


Figure 36: Misoprostol ≤600 mcg versus Oxytocin >5 iu to ≤ 10 iu – Vaginal birth

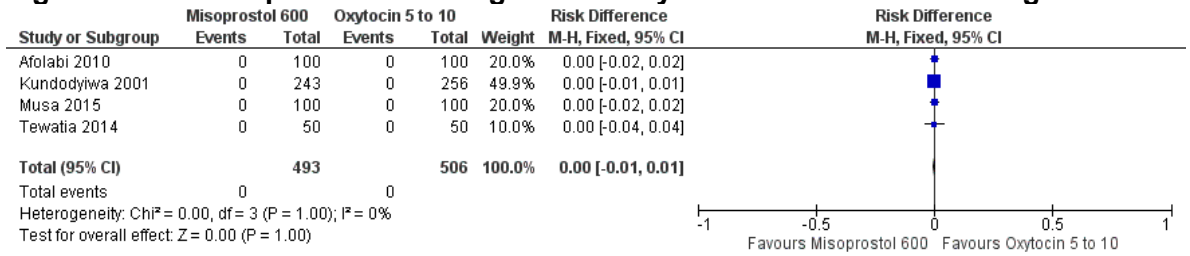
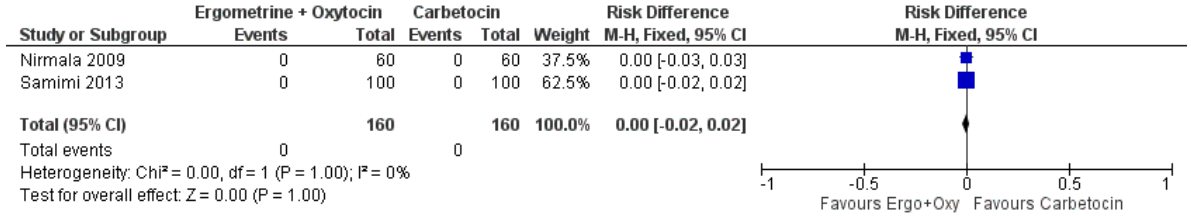


Figure 37: Ergometrine + Oxytocin versus Carbetocin – Vaginal birth



Need for blood transfusion

Figure 38: Ergometrine versus Misoprostol ≤600 mcg – Vaginal birth

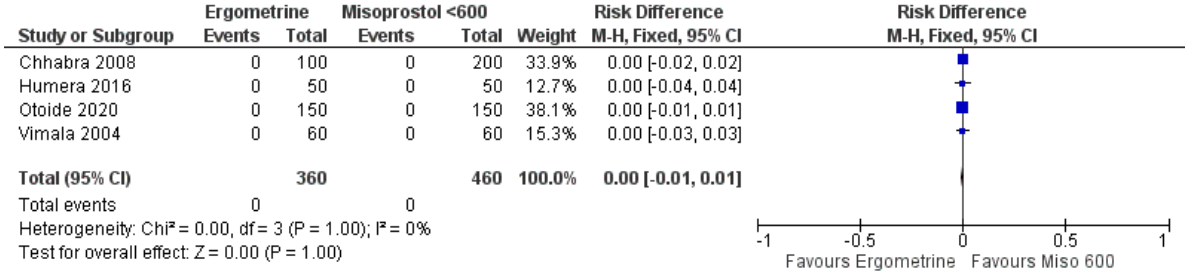


Figure 39: Misoprostol ≤600 mcg versus Ergometrine + Oxytocin – Vaginal birth

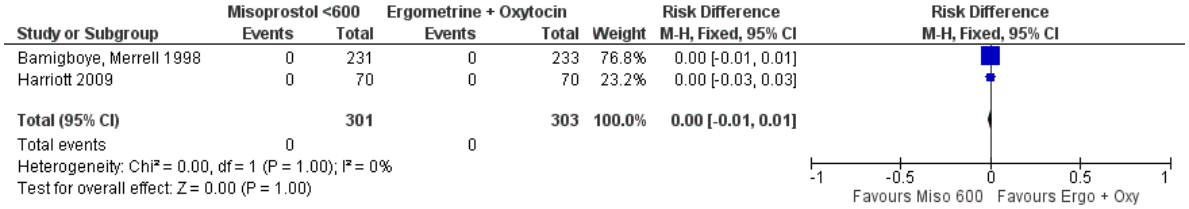


Figure 40: Misoprostol ≤600 mcg versus Oxytocin >5 iu to ≤ 10 iu

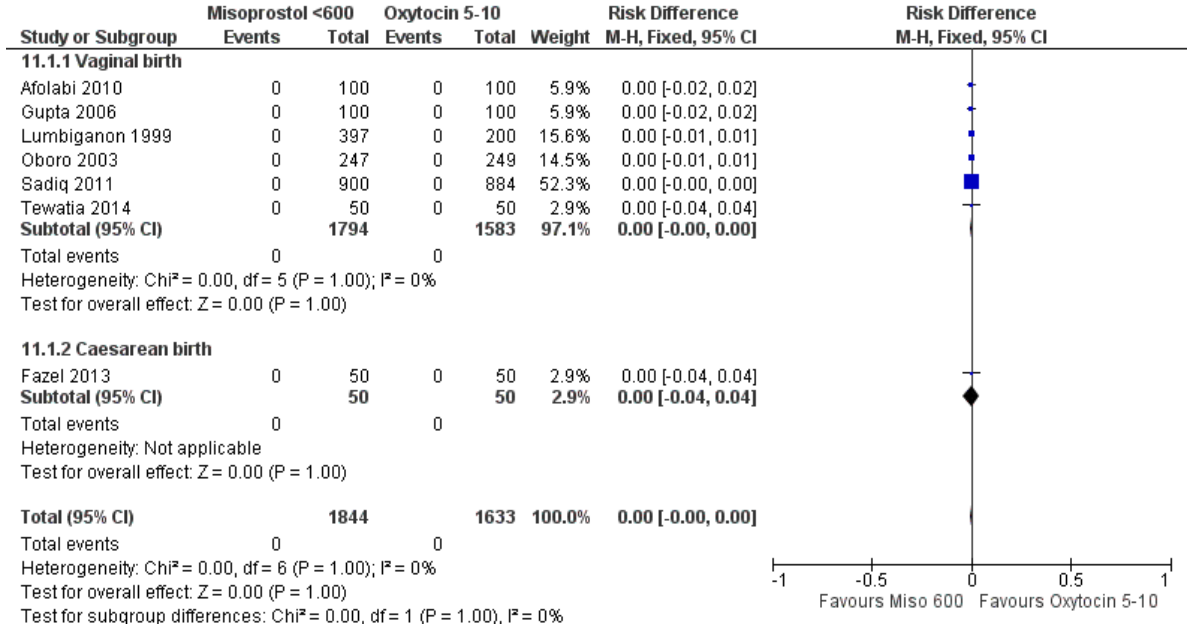


Figure 41: Misoprostol ≤600 mcg versus Oxytocin >1 iu to ≤ 5 iu – Vaginal birth

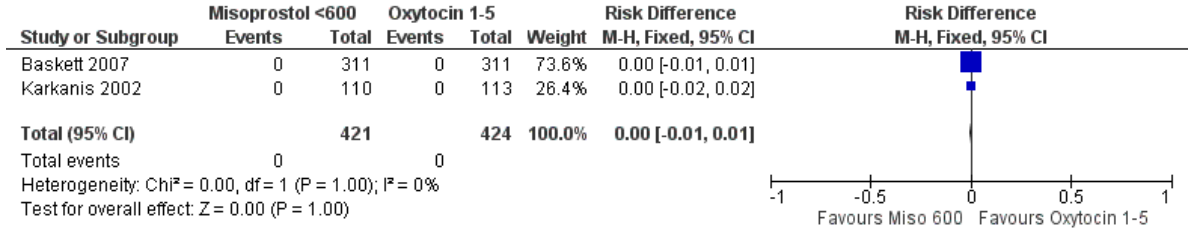


Figure 42: Oxytocin >10 iu versus Carbetocin

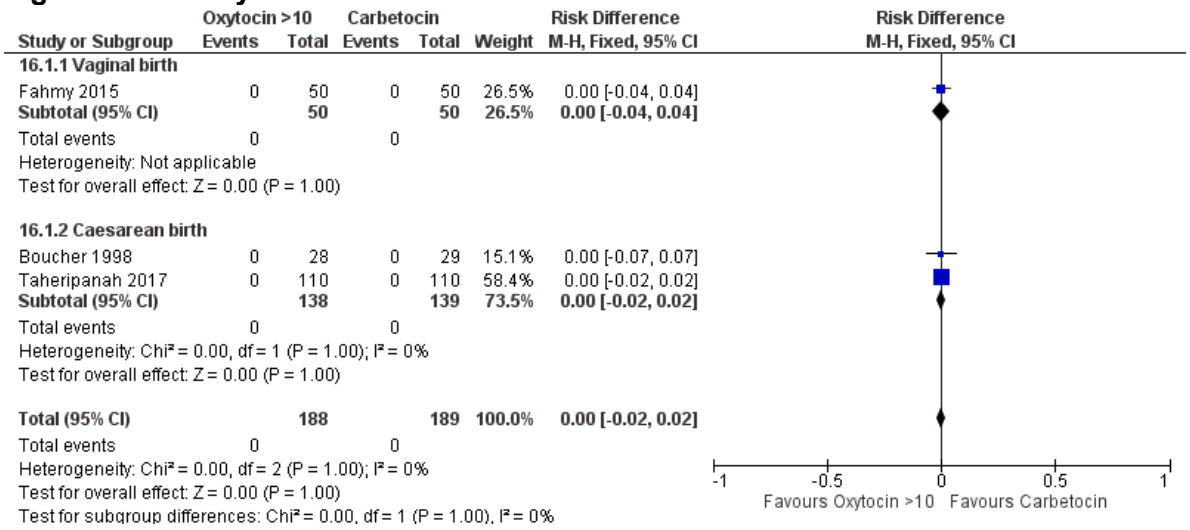


Figure 43: Oxytocin >5 iu to ≤ 10 iu versus Carbetocin

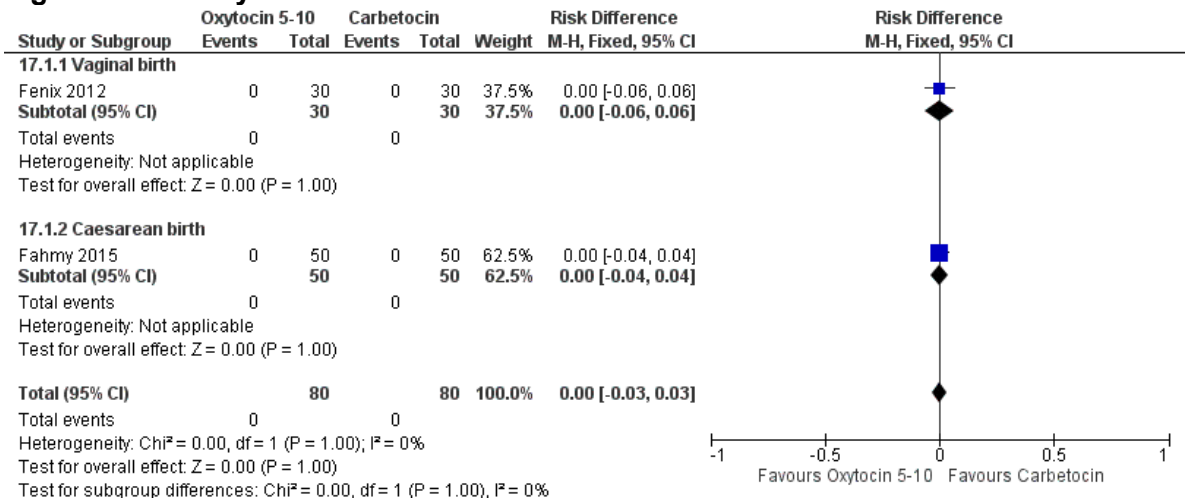
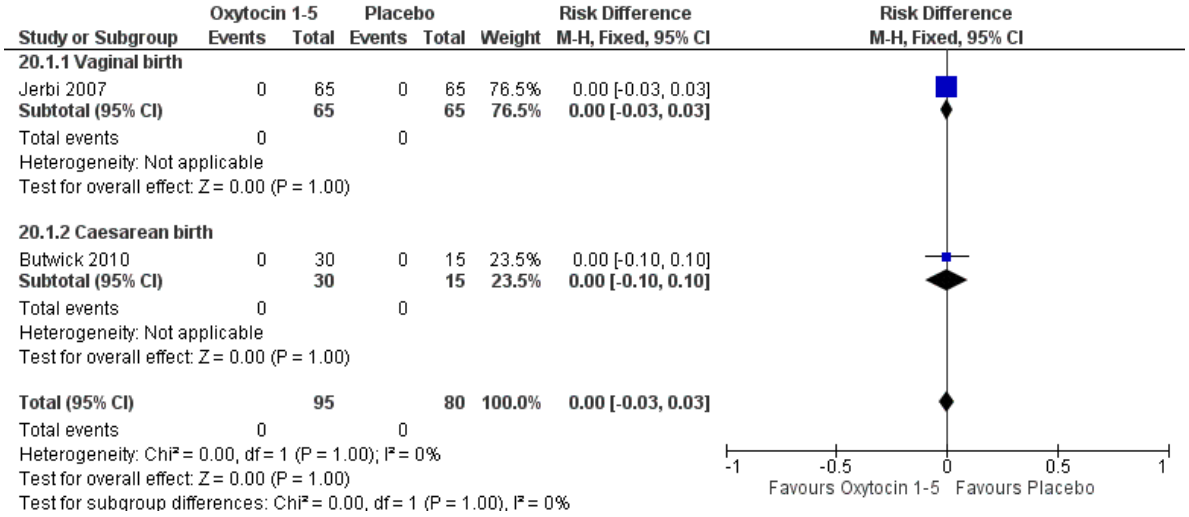


Figure 44: Oxytocin >1 iu to ≤ 5 iu versus Placebo



Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

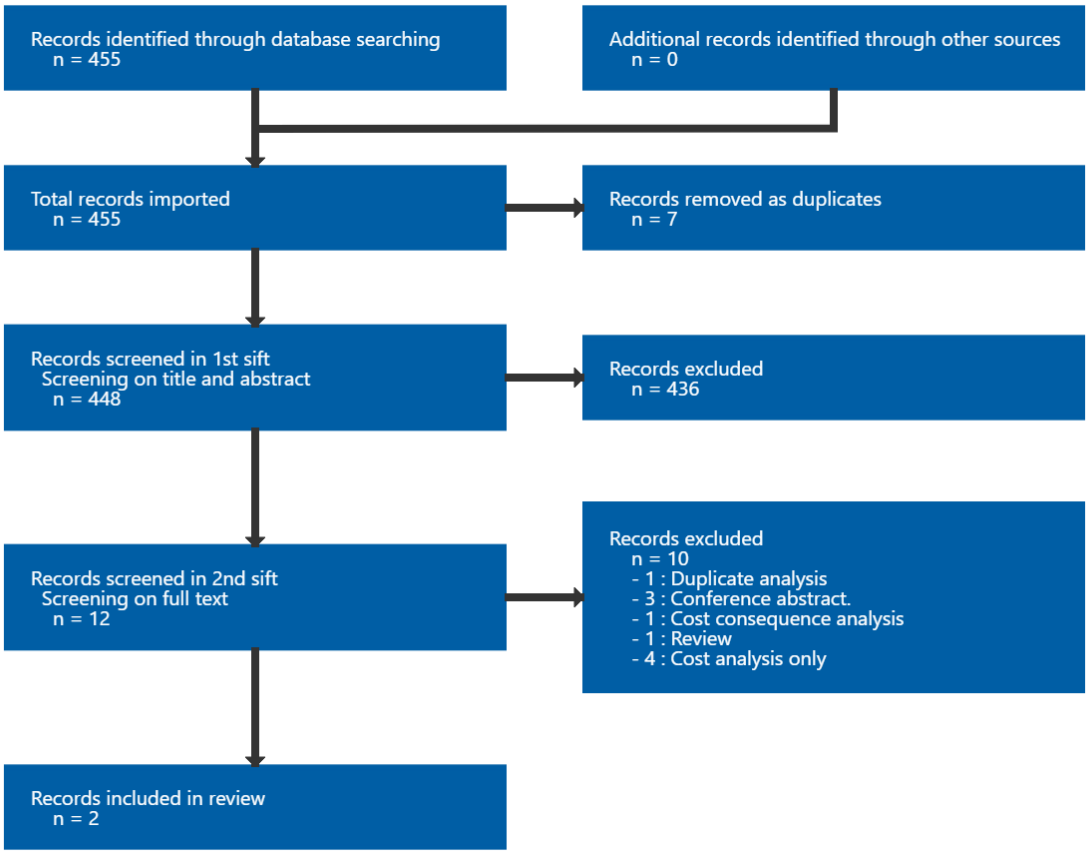
Due to the size and complexity of these tables they are provided in a separate document. See Supplement 5.

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Of 455 studies, 12 were assessed at full text level and of those 2 were included for this review.

Figure 45: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Table 30: Economic evidence tables for the effectiveness of uterotonics for the prevention of postpartum haemorrhage

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: Gallos 2019 **Country:** UK **Type of economic analysis:** Cost effectiveness analysis **Source of funding:** National Institute for Health Research (NIHR)	**Interventions in detail:** * ergometrine * ergometrine plus oxytocin * carbetocin * misoprostol * misoprostol plus oxytocin **Comparator in detail:** * oxytocin	**Population characteristics:** Women at risk of PPH after birth **Modelling approach:** Decision analytic model **Source of baseline data:** Oxytocin direct and indirect evidence from trials included in the NMA **Source of effectiveness data:** Direct and indirect evidence from trials included in the NMA **Source of cost data:** Birmingham Women's Hospital, Literature estimates **Source of unit cost data:** NHS Reference	***Vaginal births no adverse events*** **Mean cost per participant:** Oxytocin £2,545 Ergometrine plus oxytocin £2,538 Carbetocin £2,551 Misoprostol plus oxytocin £2,539 Misoprostol £2,548 Ergometrine £2,551 **Primary measure of outcome:** PPH ≥ 500 ml avoided **Mean outcome per participant:** Oxytocin 0.908 Ergometrine plus oxytocin 0.936	***Vaginal births no adverse events*** **ICERs:** carbetocin v ergometrine plus oxytocin £1,889 per PPH ≥ 500 ml avoided ergometrine plus oxytocin dominates all other interventions **Probability of being cost effective:** Carbetocin had a greater than 50% probability of being cost-effective relative to oxytocin for cost-effectiveness thresholds > £864 per PPH ≥ 500 ml avoided **Subgroup analysis:** ***Caesarean births with no adverse events and excluding ergometrine***	**Currency:** GBP **Cost year:** 2016 **Time horizon:** 6 days **Discounting:** N/A **Applicability:** Partially applicable **Limitations:** Potentially serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Costs 2014-15, BNF 71, NHS Electronic Drugs Tariff 2016	Carbetocin 0.944 Misoprostol plus oxytocin 0.931 Misoprostol 0.899 Ergometrine 0.891 :	***and ergometrine plus oxytocin*** Misoprostol plus oxytocin dominates **Sensitivity analysis:** ***Vaginal births with adverse events*** carbetocin v oxytocin £928 per PPH ≥ 500 ml avoided oxytocin dominates all other interventions ***Caesarean births with adverse events and excluding ergometrine and ergometrine plus oxytocin*** carbetocin v misoprostol plus oxytocin £2,480 per PPH ≥ 500 ml avoided carbetocin dominates all other interventions ***Caesarean births with adverse events and including ergometrine and ergometrine***	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				plus oxytocin ergometrine plus oxytocin dominates all other interventions ***Caesarean births with no adverse events and including ergometrine and ergometrine plus oxytocin*** ergometrine plus oxytocin dominates all other interventions	
Author and year: Matthijsse 2022 **Country:** UK **Type of economic analysis:** Cost effectiveness analysis **Source of funding:** Ferring Pharmaceuticals	**Interventions in detail:** 100 µg carbetocin given intramuscularly **Comparator in detail:** 10 IU bolus oxytocin	**Population characteristics:** Women at risk of PPH after vaginal birth **Modelling approach:** Decision analytic model **Source of baseline data:** Oxytocin direct and indirect evidence from trials included in the NMA **Source of effectiveness data:** Direct and indirect evidence from trials included in the NMA	**Mean cost per participant:** Intervention: £1,375 Control: £1,430 Difference: -£55 **Primary measure of outcome:** PPH event avoided **Mean outcome per participant:** Intervention: 0.0878 Control: 0.1220 Difference: -0.0342	**ICERs:** Carbetocin dominates **Probability of being cost effective:** 79.5% probability that carbetocin dominates Sensitivity analysis: A number of one-way sensitivity analyses presented as a Tornado diagram	**Currency:** GBP **Cost year:** 2019 **Time horizon:** 30 days **Discounting:** N/A **Applicability:** Partially applicable **Limitations:** Potentially serious limitations **Other comments:** Study funded by manufacturer of carbetocin

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of cost data: Survey of midwives in France, Italy, the Netherlands and the UK, expert opinion, North Bristol NHS Trust Postpartum Haemorrhage Study **Source of unit cost data:** NHS Reference Costs 2018-19, MIMS 2020, PSSRU 2019			

GBP = Pounds Sterling; ICER = Incremental cost effectiveness ratio; MIMS = Monthly Index of Medical Specialties; NMA = Network meta-analysis; PPH = Postpartum haemorrhage; PSSRU = Personal Social Services Research Unit

Appendix I Economic model

Economic model for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Cost-effectiveness analysis of different uterotonics

Introduction

Postpartum haemorrhage (PPH) can have significant physical and psychological impacts on a woman's health, as well as impacting the woman's birth experience and ability to bond with their baby. There are various uterotonic drugs that can be used prophylactically to reduce the risk of PPH, and the difference in effectiveness and downstream costs of these drugs is important to consider in the context of a resource constrained publicly funded health service and the potentially large resource impact given the number of women treated.

A recent UK health technology assessment (HTA) (Gallos 2019) synthesised clinical evidence comparing uterotonics for prevention of PPH using an NMA, and the HTA also included an economic evaluation. New evidence has been highlighted since this HTA was published including two large carbetocin trials, so it was decided the NMA and health economic model needed to be updated for the committee to make fully informed recommendations on uterotonics for prevention of PPH. The existing economic model included more of the pathway than could be informed by the new NMA evidence, so the NICE guideline developers constructed a new economic model for the purposes of this guideline.

Methods

Setting and population

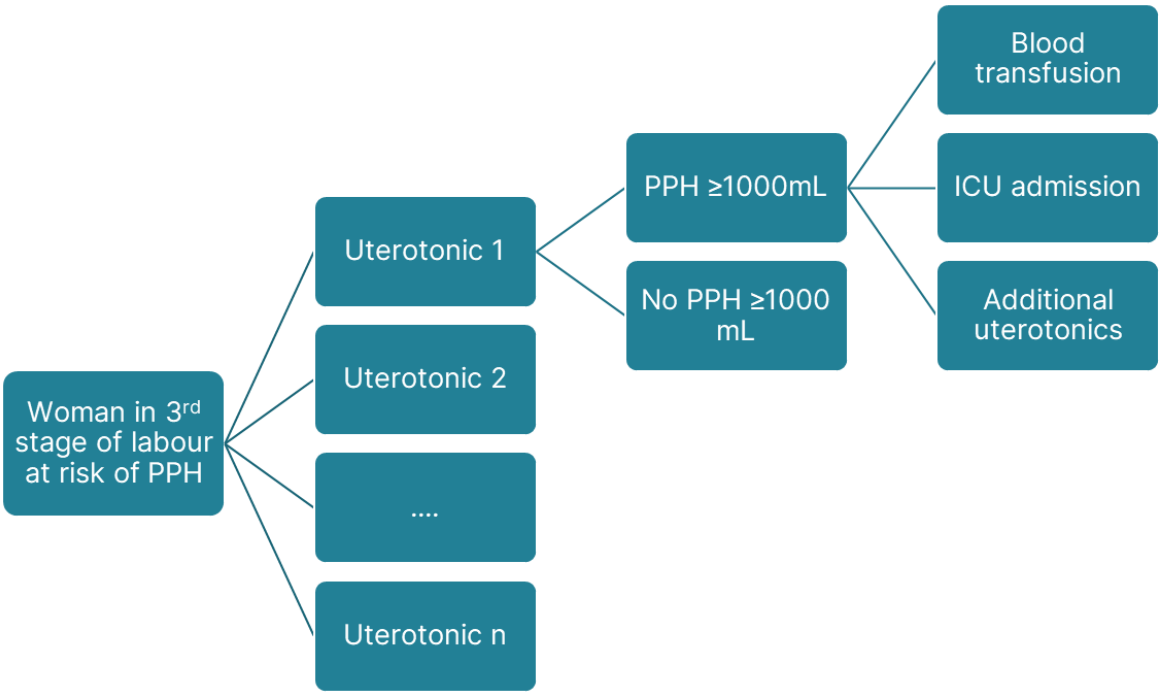
The model was in the NHS setting, and the population was women in the third stage of labour, who are all at risk of PPH. The time horizon was very short, only capturing the immediate postpartum period and the costs and outcomes in the third stage of labour. The model was run for the full population, and also for two mode-of-birth subgroups; vaginal birth and caesarean birth.

Model structure

A decision analytic model was developed in Microsoft Excel® to assess the cost-effectiveness of different uterotonics for prevention of PPH.

The model schematic is shown in Figure 46, and shows the four outcomes considered in the model, with the primary outcome being a PPH of 1000mL or more.

Figure 46: Model schematic



Clinical outcomes

The clinical outcomes incorporated into the model were the same as those considered in the NMA:

- PPH ≥1000mL
- Additional uterotonics
- ICU admission
- Blood transfusions

The continuous outcome of mean blood loss was not used in the economic model, as the committee felt this overlapped and would be correlated with the PPH ≥1000mL outcome. The relative treatment effects for each of these outcomes are informed by the NMAs for the entire population and mode-of-birth subgroups.

Interventions

The uterotonics included in the economic analysis reflected the interventions in which there was evidence from the NMAs, particularly for the PPH ≥1000mL outcome. The committee's clinical opinion was then used to select those uterotonics which were plausible clinical alternatives for PPH prophylaxis in an NHS setting.

The interventions included in the economic model were:

- Carbetocin
- Oxytocin ≤ 1 iu (full population and vaginal birth groups only)
- Oxytocin >1 iu and ≤ 5 iu
- Oxytocin >5 iu and ≤ 10 iu

- Oxytocin > 10 iu
- Ergometrine plus oxytocin

The network of evidence for the PPH ≥1000mL outcome in the caesarean birth subgroup did not include oxytocin ≤ 1 iu, so this dose level was not included in the economic model for the caesarean birth analysis.

There was limited NMA data for the ICU admission outcome, so this was included as a scenario only in the full population and vaginal birth subgroup, with the comparison restricted to just oxytocin >5 iu and ≤ 10 iu and carbetocin.

Baseline

The NMA provided evidence on the relative effectiveness of treatments relative to a reference treatment for each outcome. This analysis used the placebo arm as the reference for the majority of outcomes and population groups, but in two cases (caesarean birth; PPH≥1000mL and blood transfusion) the placebo arm was not included in the network and carbetocin was used as the reference instead.

Probabilities for each of the events in the reference arm were taken from trials included in that NMA that were considered to be in the most similar setting to the UK NHS perspective and are listed in Table 31.

Table 31: Baseline event probabilities

Outcome	Population	Study arm	Probability	Standard error[a]	Source
PPH ≥1000mL	Full	Placebo	11.9%	0.0004	Jans 2016
	VB	Placebo	11.9%	0.0004	Jans 2016
	CB	Carbetocin	4.8%	0.0011	Attilakos 2010
Additional uterotonics	Full	Placebo	23.5%	0.0005	Jans 2016
	VB	Placebo	23.5%	0.0005	Jans 2016
	CB	Placebo	92.0%	0.0106	Rosseland 2013
Blood transfusion	Full	Placebo	1.4%	0.0001	Jans 2016
	VB	Placebo	1.4%	0.0001	Jans 2016
	CB	Carbetocin	2.1%	0.0008	Attilakos 2010
ICU admission	Full	Placebo	0.2%	0.0001	Derman 2006
	VB	Placebo	0.2%	0.0001	Derman 2006

[a]Standard error calculated from the total number of individuals, total number of events, and mean probability Beta distribution used around all probabilities.

Treatment effectiveness

Treatment effect was incorporated in the model by using the outcomes from the NMAs. The NMAs generated relative effectiveness in the form of odds ratios, which are applied to the baseline probabilities detailed in the previous section to calculate the event probabilities specific to each treatment in the economic model. These odds ratios are listed for each treatment, mode-of-birth subgroup, and event, in the Clinical evidence profile for outcomes included in the network meta-analysis.

The odds ratios are applied to baseline probabilities using a logit function:

- Logit = ln (reference treatment probability / (1 – reference treatment probability))

- Log odds (treatment A) = logit + log odds ratio of treatment A
- Absolute probability (treatment A) = exp (log odds) / (1 + exp (log odds))

Adverse events

Treatment-related adverse events were included in the model and are informed by the Gallos 2019 HTA. The probabilities and standard errors used in the economic model are detailed in Table 32 and Table 33. Since the HTA only reported adverse events for the separate subgroups, the adverse event probabilities for the full population are assumed to be the average of the probabilities reported for the two subgroups, and this approach was informed by clinical opinion.

Assumptions have been made where there are evidence gaps. Carboprost was not included in the HTA analysis so adverse events were not reported, and therefore the event probabilities have been assumed equal to the probabilities of oxytocin based on clinical opinion on the similarities in those treatments. Where information was missing for carbetocin the probabilities were set equal to those in the oxytocin arm, given the similarities between the probabilities for carbetocin and oxytocin in other events and other subgroups. Where information was missing for any other treatment three options were considered; average of all other treatments, minimum from other treatments, or maximum from other treatments. The base-case assumed the average of probabilities from other treatments for that subgroup and event.

Table 32: Treatment-related adverse event probabilities (SE), vaginal births

Intervention	Nausea	Vomiting	Hypertension	Headache	Tachycardia	Hypotension	Fever	Shivering	Abdominal pain
Carbetocin	0.028 (0.341)	0.01 (0.305)	0.03 (0.808)	0.054 (0.382)	0.074 (0.498)	0.005* (0.005)	0.02* (0.003)	0.071* (0.007)	0.099 (0.307)
Oxytocin ≤ 1 iu	0.039 (0.005)	0.01 (0.002)	0.021 (0.005)	0.044 (0.009)	0.025 (0.014)	0.005 (0.005)	0.02 (0.003)	0.071 (0.007)	0.134 (0.043)
Oxytocin >1 iu and ≤ 5 iu	0.039 (0.005)	0.01 (0.002)	0.021 (0.005)	0.044 (0.009)	0.025 (0.014)	0.005 (0.005)	0.02 (0.003)	0.071 (0.007)	0.134 (0.043)
Oxytocin >5 iu and ≤ 10 iu	0.039 (0.005)	0.01 (0.002)	0.021 (0.005)	0.044 (0.009)	0.025 (0.014)	0.005 (0.005)	0.02 (0.003)	0.071 (0.007)	0.134 (0.043)
Oxytocin > 10 iu	0.039 (0.005)	0.01 (0.002)	0.021 (0.005)	0.044 (0.009)	0.025 (0.014)	0.005 (0.005)	0.02 (0.003)	0.071 (0.007)	0.134 (0.043)
Ergometrine plus oxytocin (syntometrine)	0.081 (0.202)	0.043 (0.099)	0.059 (0.633)	0.072 (0.294)	0.04 (0.551)	0.0037* (0.7014)	0.02 (0.336)	0.087 (0.282)	0.149 (0.245)
Misoprostol ≤ 600 mcg	0.058 (0.161)	0.029 (0.097)	0.033 (0.655)	0.068 (0.323)	0.036* (0.184)	0.002 (1.63)	0.105 (0.162)	0.271 (0.14)	0.127 (0.158)
Misoprostol >600 mcg and ≤ 800 mcg	0.058 (0.161)	0.029 (0.097)	0.033 (0.655)	0.068 (0.323)	0.036* (0.184)	0.002 (1.63)	0.105 (0.162)	0.271 (0.14)	0.127 (0.158)
Misoprostol >800 mcg and ≤ 1000 mcg	0.058 (0.161)	0.029 (0.097)	0.033 (0.655)	0.068 (0.323)	0.036* (0.184)	0.002 (1.63)	0.105 (0.162)	0.271 (0.14)	0.127 (0.158)
Misoprostol plus oxytocin	0.27 (0.891)	0.039 (0.255)	0.0444* (0.424)	0.0635* (0.2093)	0.036* (0.184)	0.0037* (0.7014)	0.09 (0.229)	0.261 (0.246)	0.1337* (0.1662)
Ergometrine	0.106 (0.226)	0.042 (0.148)	0.172 (0.814)	0.129 (0.412)	0.036* (0.184)	0.0037* (0.7014)	0.02 (0.303)	0.097 (0.265)	0.172 (0.464)
Carboprost	0.039* (0.005)	0.01* (0.002)	0.021* (0.005)	0.044* (0.009)	0.025* (0.014)	0.005* (0.005)	0.02* (0.003)	0.071* (0.007)	0.134* (0.043)

**Missing data, completed with assumptions*

Table 33: Treatment-related adverse event probabilities (SE), caesarean births

Intervention	Nausea	Vomiting	Hypertension	Headache	Tachycardia	Hypotension	Fever	Shivering	Abdominal pain
Carbetocin	0.092 (0.327)	0.049 (0.282)	0.167* (0.076)	0.083 (0.151)	0.12 (1.546)	0.157 (0.346)	0.026 (0.785)	0.035 (0.392)	0.178 (0.089)
Oxytocin ≤ 1 iu	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)	0.05 (0.01)	0.172 (0.071)
Oxytocin >1 iu and ≤ 5 iu	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)	0.05 (0.01)	0.172 (0.071)
Oxytocin >5 iu and ≤ 10 iu	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)	0.05 (0.01)	0.172 (0.071)
Oxytocin > 10 iu	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)	0.05 (0.01)	0.172 (0.071)
Ergometrine plus oxytocin (syntometrine)	0.453 (1.012)	0.337 (1.127)	0.042 (1.08)	0.0863* (0.2404)	0.018 (0.707)	0.141 (0.532)	0.042* (0.3329)	0.1252* (0.2104)	0.1998* (0.1168)
Misoprostol ≤ 600 mcg	0.043 (0.687)	0.048 (0.407)	0.142* (0.2768)	0.059 (0.451)	0.039* (0.386)	0.034 (1.077)	0.049 (0.639)	0.244 (0.4)	0.1998* (0.1168)
Misoprostol >600 mcg and ≤ 800 mcg	0.043 (0.687)	0.048 (0.407)	0.142* (0.2768)	0.059 (0.451)	0.039* (0.386)	0.034 (1.077)	0.049 (0.639)	0.244 (0.4)	0.1998* (0.1168)
Misoprostol >800 mcg and ≤ 1000 mcg	0.043 (0.687)	0.048 (0.407)	0.142* (0.2768)	0.059 (0.451)	0.039* (0.386)	0.034 (1.077)	0.049 (0.639)	0.244 (0.4)	0.1998* (0.1168)
Misoprostol plus oxytocin	0.164 (0.393)	0.085 (0.299)	0.142* (0.2768)	0.141 (0.576)	0.039* (0.386)	0.22 (0.672)	0.073 (0.274)	0.16 (0.262)	0.333 (0.328)
Ergometrine	0.1202* (0.3869)	0.0839* (0.2973)	0.142* (0.2768)	0.0863* (0.2404)	0.039* (0.386)	0.1296* (0.5041)	0.042* (0.3329)	0.1252* (0.2104)	0.1998* (0.1168)
Carboprost	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)	0.05* (0.01)	0.172* (0.071)

**Missing data, completed with assumptions*

Costs

In accordance with NICE methodology a NHS and Personal Social Services (PSS) perspective was adopted for this analysis. NHS Reference Costs were based on the 2019/20 published costs. Drug costs were taken from the British National Formulary (BNF) at the date of writing. The short time horizon of the model meant that all costs occurred within a few days, meaning that there were no future costs to discount.

Drug costs

Treatment costs for each uterotonic used for prophylaxis are summarised in Table 34. Where a dose range is specified the dose used for costing is assumed to be the upper limit of that range. Drug costs were treated deterministically in the model as the values are based on published prices which are not subject to sampling uncertainty.

Table 34: Drug costs of prophylactic uterotonics

Intervention	Cost	Notes	Source
Carbetocin	£17.64	1x 100mcg dose	BNF, January 2023
Oxytocin ≤ 1 iu	£0.80	1x 5 IU dose Wastage assumed for the rest of the 5 IU ampoule	BNF, January 2023
Oxytocin >1 iu and ≤ 5 iu	£0.80	1x 5 IU dose	BNF, January 2023
Oxytocin >5 iu and ≤ 10 iu	£0.91	1x 10 IU dose	BNF, January 2023
Oxytocin > 10 iu	£2.72	3x 10 IU dose Assumed to be 30 IU as observed in clinical trials	BNF, January 2023
Ergometrine plus oxytocin	£1.57	1x syntometrine (500mcg/5IU)	BNF, January 2023
Misoprostol ≤ 600 mcg	£0.50	3x 200mcg oral tablets	BNF, January 2023
Misoprostol >600 mcg and ≤ 800 mcg	£0.67	4x 200mcg oral tablets	BNF, January 2023
Misoprostol >800 mcg and ≤ 1000 mcg	£0.84	5x 200mcg oral tablets	BNF, January 2023
Misoprostol plus oxytocin	£1.24	2x 200mcg oral misoprostol 1x 10 IU dose oxytocin	BNF, January 2023
Ergometrine	£1.50	1x 500mcg dose	BNF, January 2023
Carboprost	£18.20	1x 250mcg dose	BNF, January 2023

Drug administration costs

Administration costs were informed by clinical opinion and are detailed in Table 35. These costs include staff time only. Misoprostol is assumed to have no administration costs as it is assumed to be given either orally, vaginally or rectally. Based on committee input carbetocin is assumed to be given intravenously in the base case, and all other treatments are given by intramuscular injection for administration costing purposes. A scenario was included in the vaginal birth subgroup where carbetocin was assumed to be given by intramuscular injection.

The cost per working hour for one midwife is assumed to be £51.00 which is the cost for an hour of band 6 nurse time, as reported in the most recently published PSSRU document.

Table 35: Drug administration costs

Route of administration	Staff requirements	Cost
Intravenous slow infusion	2x midwives	£25.50

Route of administration	Staff requirements	Cost
	15 minutes for drawing up, checking, and delivering the drug	
Intramuscular injection	2x midwives 10 minutes for drawing up, checking, and delivering the drug	£17.00

Treatment-related adverse event costs

Adverse event costs are applied to the proportions of women expected to experience the events for each treatment, as detailed in the earlier section. Management of each event is based on that reported in the Gallos 2019 HTA, and all costs have been recalculated with drug costs taken from the BNF (accessed January 2023) and excess bed day costs from the NHS reference costs. The costs applied in the economic model are detailed in Table 36.

Table 36: Adverse event costs

Event	Total cost	Notes[1][2][3]
Nausea	£5.45	2x 50mg injection of cyclizine (£3.45) 2x 4mg injection of ondansetron (£2.00)
Vomiting	£758.75	3x 12.5mg injection prochlorperazine (£1.57) 1x excess bed day (£757.18)
Hypertension	£784.87	200mg labetalol over 24 hours (£27.60) 20mg nifedipine over 24 hours (£0.09) 1x excess bed day (£757.18)
Headache	£1.29	Paracetamol for 24 hours (£0.60) Codeine for 24 hours (£0.69)
Tachycardia	£757.18	1x excess bed day (£757.18)
Hypotension	£757.18	1x excess bed day (£757.18)
Fever	£759.70	Paracetamol (£0.60) Amoxicillin (£1.92) 1x excess bed day (£757.18)
Shivering	£757.18	1x excess bed day (£757.18)
Abdominal pain	£1.76	Paracetamol for 24 hours (£0.60) Ibuprofen for 24 hours (£1.16)

[1]Drug costs are taken from the BNF, accessed in January 2023
[2]Excess bed days are costed as the weighted average of all currency codes related to delivery (normal, assisted, planned caesarean, and emergency caesarean) in the National schedule of NHS reference costs
[3]For drugs where the amount has not been specified the cost of a full pack has been used, taking the least costly pack price from the BNF

Cost of additional uterotonics

Based on clinical input, assumptions were made on which uterotonics could be used as second line. It was assumed that it was not appropriate for single agent or combinations of either misoprostol or ergometrine to be repeated whereas repeat oxytocin can be. The model uses an average cost of all potential second line treatments following each prophylactic uterotonic. The cost associated with second line uterotonics used in the model is summarised in Table 37.

Table 37: Cost of subsequent uterotonics

Uterotonic used as prophylaxis	Cost	Uterotonics included in average
Carbetocin	£3.95	All uterotonics

Uterotonic used as prophylaxis	Cost	Uterotonics included in average
Oxytocin ≤ 1 iu	£3.95	All uterotonics
Oxytocin >1 iu and ≤ 5 iu	£3.95	All uterotonics
Oxytocin >5 iu and ≤ 10 iu	£3.95	All uterotonics
Oxytocin > 10 iu	£3.95	All uterotonics
Ergometrine plus oxytocin	£4.43	All options except ergometrine and syntometrine
Misoprostol ≤ 600 mcg	£5.52	All options except misoprostol
Misoprostol >600 mcg and ≤ 800 mcg	£5.52	All options except misoprostol
Misoprostol >800 mcg and ≤ 1000 mcg	£5.52	All options except misoprostol
Misoprostol plus oxytocin	£5.52	All options except misoprostol
Ergometrine	£4.43	All options except ergometrine and syntometrine
Carboprost	£3.95	All uterotonics

Cost of blood transfusions

The cost of blood transfusions is calculated using the cost per unit, administration cost, and the estimated number of units required. The cost per unit is £153.30 and was taken from the NHS blood and transplant price list 2022/23. The mean number of units was assumed to be two units based on committee clinical opinion and is varied in a gamma distribution with a confidence interval of 1-4 units which allows for rare events where many more units are required. The administration cost is £586.85, taken as the cost of a single plasma exchange or other intravenous blood transfusion as reported in the National schedule of NHS reference costs. The total cost of blood transfusion used in the model is £893.45 and is applied to the proportion of women having this outcome, as reported in the NMA.

Cost of ICU admission

The cost of ICU admission is only applied in scenario analysis due to the limited NMA evidence on this outcome. The cost used in the analysis is £2,303.38 which is the weighted average of all codes for obstetric critical care (Service code CCU12 with currency codes XC02Z, XC03Z, XC04Z, XC05Z, XC06Z, XC07Z) in the National schedule of NHS reference costs.

Cost-effectiveness measure

In general NICE prefers a cost-utility approach in economic analyses, using QALYs to measure the health benefits of an intervention, however other approaches can be used if it is not possible to quantify benefits using QALYs. The Gallos 2019 HTA presented an analysis based on cost per PPH ≥500mL avoided, and noted that QALYs could not be used due to the lack of appropriate utility data in the literature. For this analysis a similar approach was taken, using cost per PPH ≥1000mL avoided, after a non-systematic review of the literature did not identify any utility data for PPH.

The Gallos 2019 HTA detailed a method of considering ICERs based on hard outcomes (i.e., PPH ≥1000mL) against a willingness-to-pay threshold of £30,000 per QALY gained, without having QALYs as an outcome of the analysis. This analysis also uses this approach to aid interpretation of the results for the committee given there isn't an agreed price that the NHS is willing to pay for avoidance of PPH. This analysis uses the ICER and a cost-effectiveness threshold of £20,000 per QALY to calculate how many days in perfect health must be considered acceptable to trade off to avoid one PPH event. An illustrative example of this calculation is given below.

Example:

- Suppose carbetocin is associated with £10 more costs and 0.01 less PPH≥1000mL events than oxytocin and therefore has an ICER of £1,000 per PPH≥1000mL avoided

- First, we divide the ICER by the cost-effectiveness threshold of £20,000 to calculate the QALYs needed in this scenario to justify the incremental cost (£1,000 / £20,000 = 0.05)
- We then calculate the number of "perfect health" days that would need to be traded off to avoid one PPH≥1000mL event i.e. the number of days in full health equivalent to the calculated number of QALYs (0.05 / (1 / 365.25) = 18.26 days)
- Therefore, for carbetocin to be considered cost-effective compared with oxytocin at an ICER of £1,000 per PPH≥1000mL avoided, we must be willing to trade off 18 days in full health to avoid having a PPH≥1000mL.

This calculation is also performed at the £30,000 per QALY threshold to provide a range of trade-off days for each result.

Cost-effectiveness was only based on the PPH≥1000mL event, not the additional outcomes included in the economic model.

Sensitivity analysis

All results are presented using PSA to reflect uncertainty with respect to the precise value of model parameters. This involved running a total of 10,000 Monte Carlo simulations where, with the exception of a small number of deterministic parameters, model inputs are sampled from a probability distribution. In each simulation the total costs and outcomes (PPH ≥1000mL, additional uterotonics, blood transfusions) are calculated for each uterotonic treatment, which are then used to calculate the average total costs and outcomes and subsequently the cost-effectiveness measure using the methods detailed above.

Simulations of relative treatment effectiveness were undertaken using Bayesian Markov chain Monte Carlo (MCMC) simulation, which sampled directly from the joint posterior distribution from the NMAs, thereby maintaining any correlation between them, in the WinBugs® package. The results output (CODA) was then imported into the Microsoft Excel® spreadsheet model. When running the simulations in Excel a random number was used to select a row of data (reflecting a single WinBugs® simulation) so that any correlation between the LORs would be preserved.

In addition to the probabilistic base case and the deterministic results, two scenarios were run around parameters the committee considered important; exclusion of adverse events, and inclusion of ICU admission as an outcome. In the vaginal birth subgroup a scenario was explored assuming that carbetocin is administered by intramuscular injection.

Results

Full population

The results of the base-case analysis in the full population are summarised in Table 38, with absolute costs and numbers of events from the probabilistic analysis presented for each treatment.

As Table 38 shows, carbetocin is considered cost-effective compared with ergometrine plus oxytocin, and would be considered cost-effective compared with oxytocin >1 iu and ≤ 5 iu if we are willing to trade off 79 days in full health to avoid one PPH ≥1000mL.

Table 38: Probabilistic (deterministic)* results, full population

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >1 iu and ≤ 5 iu	£274.80 (£274.16)	0.069 (0.069)	0.063 (0.061)	0.008 (0.007)	-	-	-	-	-
Oxytocin >5 iu and ≤ 10 iu	£275.85 (£275.63)	0.070 (0.069)	0.099 (0.097)	0.009 (0.008)	£1.04 (£1.47)	-0.0006 (-0.0007)	-0.0361 (-0.0363)	-0.0011 (-0.0014)	Dominated by oxytocin >1 iu and ≤ 5 iu
Oxytocin ≤ 1 iu	£280.20 (£281.01)	0.122 (0.100)	0.155 (0.121)	0.014 (0.014)	£5.39 (£6.86)	-0.0527 (-0.0308)	-0.0917 (-0.0599)	-0.0067 (-0.0074)	Dominated by oxytocin >1 iu and ≤ 5 iu
Oxytocin > 10 iu	£282.76 (£281.65)	0.099 (0.097)	0.128 (0.125)	0.014 (0.013)	£7.95 (£7.49)	-0.0296 (-0.0287)	-0.0650 (-0.0639)	-0.0063 (-0.0060)	Dominated by oxytocin >1 iu and ≤ 5 iu
Carbetocin	£340.46 (£339.01)	0.054 (0.054)	0.027 (0.026)	0.004 (0.003)	£65.66 (£64.86)	0.0152 (0.0147)	0.0360 (0.0347)	0.0040 (0.0036)	More costly but more effective than oxytocin>1 iu and ≤ 5 iu Cost-effective if willing to trade off 79 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 53 days at the £30,000 per QALY threshold.

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Ergometrine plus oxytocin	£380.77 (£390.66)	0.057 (0.057)	0.056 (0.055)	0.007 (0.006)	£40.31 (£51.64)	-0.0032 (-0.0029)	-0.0291 (-0.0287)	-0.0029 (-0.0028)	Dominated by carbetocin

**Deterministic results are given in parentheses for comparison.*

Table 39 and Table 40 summarise the results of the scenarios where adverse events were excluded and ICU events were included, respectively. The scenarios use the deterministic values only.

In the adverse events scenario (Table 39) the absolute costs are significantly lower and ergometrine plus oxytocin is likely to be cost-effective.

In the ICU admissions scenario (Table 40) only oxytocin >5 iu and ≤ 10 iu and carbetocin can be compared, and carbetocin would be considered cost-effective compared with oxytocin if we are willing to trade off 75 days in full health to avoid one PPH≥1000mL.

Table 39: Scenario results, adverse events excluded, full population

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >1 iu and ≤ 5 iu	£24.26	0.069	0.061	0.007	-	-	-	-	-
Ergometrine plus oxytocin	£24.35	0.057	0.055	0.006	£0.09	0.0118	0.0060	0.0008	More costly but more effective than oxytocin Cost-effective if willing to trade off 0.14 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 0.09 days at the £30,000 per QALY threshold.
Oxytocin >5 iu and ≤ 10 iu	£25.73	0.069	0.097	0.008	£1.38	-0.0126	-0.0423	-0.0021	Dominated by ergometrine plus oxytocin

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin ≤ 1 iu	£31.12	0.100	0.121	0.014	£6.77	-0.0427	-0.0659	-0.0082	Dominated by ergometrine plus oxytocin
Oxytocin > 10 iu	£31.75	0.097	0.125	0.013	£7.40	-0.0405	-0.0699	-0.0067	Dominated by ergometrine plus oxytocin
Carbetocin	£46.28	0.054	0.026	0.003	£21.93	0.0029	0.0287	0.0028	More costly but more effective than ergometrine plus oxytocin Cost-effective if willing to trade off 138 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 92 days at the £30,000 per QALY threshold.

Table 40: Scenario results, ICU admission events included, full population

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >5 iu and ≤ 10 iu	£280.07	0.069	0.097	0.008	-	-	-	-	-
Carbetocin	£343.69	0.054	0.026	0.003	£63.62	0.0155	0.0710	0.0049	More costly but more effective than oxytocin Cost-effective if

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									willing to trade off 75 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 50 days at the £30,000 per QALY threshold.

Vaginal birth subgroup

The results of the base-case analysis in the vaginal birth subgroup are summarised in Table 41, with absolute costs and numbers of events from the probabilistic analysis presented for each treatment.

The results in Table 41 suggest that oxytocin >5 iu and ≤ 10 iu was the most cost-effective option, and oxytocin plus ergometrine was more costly and more effective but would be cost-effective if we are willing to trade off 91 days in full health to avoid one PPH ≥1000mL.

Table 41: Probabilistic (deterministic)* results, vaginal birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >5 iu and ≤ 10 iu	£141.28 (£141.14)	0.070 (0.069)	0.104 (0.103)	0.008 (0.007)	-	-	-	-	-
Oxytocin >1 iu and ≤ 5 iu	£142.78 (£141.88)	0.069 (0.069)	0.095 (0.092)	0.009 (0.008)	£1.50 (£0.75)	0.0013 (0.0009)	0.0092 (0.0101)	-0.0015 (-0.0010)	More costly and marginally more effective than oxytocin >5 iu and ≤ 10 iu Cost-effective if willing to trade off 21 days in full health to

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 14 days at the £30,000 per QALY threshold.
Oxytocin > 10 iu	£144.80 (£143.74)	0.100 (0.093)	0.150 (0.142)	0.009 (0.008)	£2.02 (£1.85)	-0.0309 (-0.0244)	-0.0548 (-0.0500)	-0.0001 (0.0003)	Dominated by oxytocin >1 iu and ≤ 5 iu
Oxytocin ≤ 1 iu	£148.10 (£147.81)	0.130 (0.104)	0.235 (0.235)	0.014 (0.014)	£5.32 (£5.93)	-0.0609 (-0.0357)	-0.1397 (-0.1425)	-0.0052 (-0.0060)	Dominated by oxytocin >1 iu and ≤ 5 iu
Ergometrine plus oxytocin	£202.14 (£218.62)	0.058 (0.058)	0.065 (0.063)	0.007 (0.007)	£59.36 (£76.73)	0.0109 (0.011)	0.0306 (0.0295)	0.0023 (0.0018)	More costly and more effective than oxytocin >5 iu and ≤ 10 iu Cost-effective if willing to trade off 91 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 60 days at the £30,000 per QALY threshold. Dominant over carbetocin in PSA
Carbetocin	£210.03 (£209.70)	0.061 (0.059)	0.043 (0.041)	0.007 (0.007)	£7.89 (-£8.91)	-0.0026 (-0.0019)	0.0215 (0.0215)	-0.0005 (-0.0003)	Dominated (on PPH ≥1000mL) by ergometrine plus oxytocin in PSA

**Deterministic results are given in parentheses for comparison.*

Table 42 and Table 43 summarise the results of the scenarios where adverse events were excluded and ICU events were included, respectively. The scenarios use the deterministic values only.

In the adverse events scenario (Table 42) the absolute costs are significantly lower and ergometrine plus oxytocin is dominant over all other strategies.

In the ICU admissions scenario (Table 43) only oxytocin >5 iu and ≤ 10 iu and carbetocin can be compared, and carbetocin would be considered cost-effective compared with oxytocin if we are willing to trade off 125 days in full health to avoid one PPH≥1000mL.

Table 42: Scenario results, adverse events excluded, vaginal birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Ergometrine plus oxytocin	£24.72	0.058	0.063	0.007	-	-	-	-	-
Oxytocin >5 iu and ≤ 10 iu	£24.89	0.069	0.103	0.007	£0.17	0.0119	0.0396	0.0008	Dominated by ergometrine plus oxytocin
Oxytocin >1 iu and ≤ 5 iu	£25.64	0.069	0.092	0.008	£0.92	0.0110	0.0295	0.0018	Dominated by ergometrine plus oxytocin
Oxytocin > 10 iu	£27.49	0.093	0.142	0.008	£2.77	0.0354	0.0794	0.0015	Dominated by ergometrine plus oxytocin
Oxytocin ≤ 1 iu	£31.57	0.104	0.235	0.014	£6.85	0.0467	0.1720	0.0078	Dominated by ergometrine plus oxytocin
Carbetocin*	£49.40*	0.059	0.041	0.007	£24.68	0.0019	-0.0215	0.0003	Dominated by ergometrine plus oxytocin

**When intramuscular injection costs rather than intravenous costs are used for carbetocin administration the only change to results here is that the total cost is reduced to £40.90 for carbetocin.*

Table 43: Scenario results, ICU admission events included, vaginal birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >5 iu and ≤ 10 iu	£145.19	0.069	0.103	0.007	-	-	-	-	-
Carbetocin	£213.96	0.059	0.041	0.007	£68.76	0.0100	0.0611	0.0005	More costly but more effective than oxytocin Cost-effective if willing to trade off 125 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 84 days at the £30,000 per QALY threshold.

Table 44 summarises the results of the scenario where intramuscular injection costs are used for carbetocin administration. In this scenario carbetocin became slightly less costly than oxytocin plus ergometrine, but remained more costly and more effective than any dose of oxytocin, and could be considered cost-effective compared with oxytocin >1 iu and ≤ 5 iu if we are willing to trade off 79 days in full health to avoid one PPH ≥1000mL.

Table 44: Scenario results, intramuscular carbetocin, vaginal birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >5 iu and ≤ 10 iu	£141.14	0.069	0.103	0.007	-	-	-	-	-
Oxytocin >1 iu and ≤ 5 iu	£141.88	0.069	0.092	0.008	£0.75	-0.0009	-0.0101	0.0010	More costly and more effective than oxytocin >5 iu and ≤

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									10 iu Cost-effective if willing to trade off 15 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 10 days at the £30,000 per QALY threshold.
Oxytocin > 10 iu	£143.74	0.093	0.142	0.008	£1.85	0.0244	0.0398	0.0007	Dominated by oxytocin >1 iu and ≤ 5 iu
Oxytocin ≤ 1 iu	£147.81	0.104	0.235	0.014	£5.93	0.0357	0.1324	0.0070	Dominated by oxytocin >1 iu and ≤ 5 iu
Carbetocin	£201.20	0.059	0.041	0.007	£59.32	-0.0091	-0.0611	-0.0005	More costly and more effective than oxytocin >1 iu and ≤ 5 iu Cost-effective if willing to trade off 119 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 79 days at the £30,000 per QALY threshold.
Ergometrine plus oxytocin	£218.62	0.058	0.063	0.007	£17.41	-0.0019	-0.0396	-0.0008	More costly and more effective than carbetocin Cost-effective if

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									willing to trade off 169 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 113 days at the £30,000 per QALY threshold.

Caesarean birth subgroup

The results of the base-case analysis in the caesarean birth subgroup are summarised in Table 45, with absolute costs and numbers of events from the probabilistic analysis presented for each treatment.

The results in Table 45 indicate that carbetocin is the most cost-effective option of the uterotonics as carbetocin was more costly but more effective than oxytocin >1 iu and ≤ 5 iu, and dominant over other oxytocin doses and oxytocin plus ergometrine. Using the cost-effectiveness measure described, carbetocin would be considered cost effective compared with oxytocin if we are willing to trade off 17 days in full health to avoid one PPH ≥1000mL.

Table 45: Probabilistic (deterministic)* results, caesarean birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >1 iu and ≤ 5 iu	£464.42 (£446.45)	0.072 (0.068)	0.489 (0.430)	0.068 (0.049)	-	-	-	-	-
Carbetocin	£487.65 (£488.40)	0.048 (0.048)	0.354 (0.275)	0.021 (0.021)	£23.24 (£41.95)	0.0244 (0.0197)	0.1344 (0.1551)	0.0464 (0.0273)	More costly and more effective than oxytocin >1 iu and ≤ 5 iu Cost-effective if willing to trade off 17

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 12 days at the £30,000 per QALY threshold.
Oxytocin > 10 iu	£535.16 (£522.60)	0.123 (0.119)	0.703 (0.696)	0.145 (0.130)	£47.51 (£34.20)	-0.0749 (-0.0713)	-0.3492 (-0.4206)	-0.1237 (-0.1092)	Dominated by carbetocin
Oxytocin >5 iu and ≤ 10 iu	£587.68 (£576.75)	0.073 (0.069)	0.726 (0.723)	0.208 (0.193)	£100.03 (£88.34)	-0.0252 (-0.0215)	-0.3718 (-0.4482)	-0.1863 (-0.1717)	Dominated by carbetocin
Ergometrine plus oxytocin	£615.50 (£591.26)	0.071 (0.066)	0.553 (0.510)	0.063 (0.035)	£127.85 (£102.86)	-0.0228 (-0.0178)	-0.1990 (-0.2346)	-0.0415 (-0.0142)	Dominated by carbetocin

**Deterministic results are given in parentheses for comparison.*

Table 46 summarises the results of the scenario analysis where adverse events were excluded. The scenario uses the deterministic values only.

In the adverse events scenario (Table 46) all oxytocin doses are dominated, and carbetocin would be considered cost-effective compared with ergometrine plus oxytocin if we are willing to trade off 11 healthy days to avoid one PPH≥1000mL.

Table 46: Scenario results, adverse events excluded, caesarean birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Ergometrine plus oxytocin	£52.55	0.066	0.510	0.035	-	-	-	-	-
Oxytocin >1 iu and ≤ 5 iu	£62.90	0.068	0.430	0.049	£10.35	-0.0019	0.0795	-0.0131	Dominated by ergometrine plus oxytocin
Carbetocin	£63.24	0.048	0.275	0.021	£10.69	0.0178	0.2346	0.0142	More costly and more effective than ergometrine plus

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									oxytocin Cost-effective if willing to trade off 11 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 7 days at the £30,000 per QALY threshold.
Oxytocin > 10 iu	£139.05	0.119	0.696	0.130	£75.81	-0.0713	-0.4206	-0.1092	Dominated by carbetocin
Oxytocin >5 iu and ≤ 10 iu	£193.20	0.069	0.723	0.193	£129.96	-0.0215	-0.4482	-0.1717	Dominated by carbetocin

Conclusion

In the full population, the model indicated that carbetocin is considered cost-effective compared with ergometrine plus oxytocin and would be considered cost-effective compared with oxytocin >1 iu and ≤ 5 iu if we are willing to trade off 79 days in full health to avoid one PPH ≥1000mL. In the scenario where adverse events are excluded, oxytocin plus ergometrine is likely to be the most cost-effective, as compared with oxytocin we would only need to be willing to trade off 0.14 days in full health to avoid one PPH ≥1000mL.

In the base-case model for the vaginal birth subgroup there was evidence suggesting that oxytocin >5 iu and ≤ 10 iu was the most cost-effective option, and oxytocin plus ergometrine was more costly and more effective but would be cost-effective if we are willing to trade off 91 days in full health to avoid one PPH ≥1000mL. Oxytocin >1 iu and ≤ 5 iu was more costly and marginally more effective than the >5 iu and ≤ 10 iu dose range, and would be considered cost-effective compared with this dose if we are willing to trade off 21 days in full health to avoid one PPH ≥1000mL. If adverse events are excluded from the analysis then oxytocin plus ergometrine becomes likely to be the most cost-effective option, being less costly and more effective than the other strategies. Carbetocin is not likely to be considered cost-effective for the vaginal birth subgroup.

There was strong evidence in the caesarean birth subgroup suggesting carbetocin to be the most cost-effective option of the uterotonics. Carbetocin was more costly but more effective than oxytocin >1 iu and ≤ 5 iu, and dominant over other oxytocin doses and oxytocin plus ergometrine. Using the cost-effectiveness measure described, carbetocin would be considered cost effective compared with oxytocin if we are willing to trade off 17 days in full health to avoid one PPH ≥1000mL.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Excluded effectiveness studies

Table 47: Excluded studies and reasons for their exclusion. From the update search

Study	Reason
Carbetocin Versus Buccal Misoprostol Plus IV Tranexamic Acid for Prevention of Postpartum Hemorrhage at Cesarean Section.	- Study design not in PICO Clinical trial - no results posted or publication provided
Buccal Misoprostol Versus IV Oxytocin in Prevention of Postpartum Hemorrhage.	- Study design not in PICO Clinical trial - no results posted or publication provided
Carbetocin Versus Ergometrin in the Prevention of Postpartum Hemorrhage.	- Study design not in PICO Clinical trial - no results posted or publication provided
Carbetocin Versus Oral Tranexamic Acid Plus, Buccal Misoprostol on Blood Loss After Vaginal Delivery.	- Study design not in PICO Clinical trial - no results posted or publication provided
Carbetocin Versus Oxytocin and Ergometrine for the Prevention of Postpartum Hemorrhage.	- Study design not in PICO Clinical trial - no results posted or publication provided
Carbetocin Versus Oxytocin for Prevention of Postcesarean Hemorrhage in Pregnancy With High Risk for PPH.	- Study design not in PICO Clinical trial - no results posted or publication provided
Carbetocin Versus Oxytocin for the Prevention of Postpartum Hemorrhage in Emergency Caesarean Delivery.	- Study design not in PICO Clinical trial - no results posted or publication provided
Carbetocin Versus Oxytocin Infusion Plus Tranexamic Acid During Cesarean Section.	- Study design not in PICO Clinical trial - no results posted or publication provided
Carbetocin Versus Oxytocin Plus Sublingual Misoprostol in the Management of Atonic Postpartum Hemorrhage.	- Study design not in PICO Network meta analysis - checked for eligible studies
Carbetocin Versus Syntocinon for Prevention of Postpartum Hemorrhage in Cardiac Patients Undergoing Caesarean Section.	- Study design not in PICO Clinical trial - no results posted or publication provided
Carbetocin Versus Syntometrine in Obese Women Undergoing Elective Cesarean.	- Study design not in PICO Clinical trial - no results posted or publication provided
The Comparison of the Effect of Different Oxytocin Administrations on the Blood Loss During Cesarean Delivery.	- Study design not in PICO Clinical trial - no results posted or publication provided
Double Simultaneous Uterotonic Agents Versus Single Agent Regimen to Prevent Early Postpartum Hemorrhage.	- Study design not in PICO Clinical trial - no results posted or publication provided
The Effect of Labor Induction With Oxytocin on Early Postpartum Hemorrhage, Perineal Integrity	- Study design not in PICO

Study	Reason
and Breastfeeding.	Clinical trial - no results posted or publication provided
Misoprostol Before and After Cesarean Section.	- Study design not in PICO Clinical trial - no results posted or publication provided
Oxytocin at Elective Cesarean Deliveries: A Dose-finding Study in Women With BMI ≥ 40kg/m2.	- Study design not in PICO Clinical trial - no results posted or publication provided
Oxytocin i.m./i.v. Versus Carbetocin i.v. in Elective Cesarean Sections.	- Study design not in PICO Clinical trial - No results posted or publication provided
Oxytocin Versus, Sublingual Misoprostol in the Secondary Prevention of Postpartum Hemorrhage After Vaginal Delivery.	- Study design not in PICO Clinical trial - no results posted or publication provided
Oxytocin vs Carbetocin at Cesarean Delivery in Women With Morbid Obesity.	- Study design not in PICO Clinical trial - no results posted or publication provided
Preoperative and Postoperative Sublingual Misoprostol for Prevention of Postpartum Blood Loss in Cesarean Section.	- Study design not in PICO Clinical trial - no results posted or publication provided
Prevention of Primary Postpartum Haemorrhage.	- Study design not in PICO Clinical trial - no results posted or publication provided
Second-Line Uterotonics in Postpartum Hemorrhage: A Randomized Clinical Trial.	- Duplicate Duplicate from IS search
Sublingual Misoprostol With or Without Intravenous Tranexamic Acid During Hemorrhagic Cesarean Section.	- Study design not in PICO Clinical trial - no results posted or publication provided
Sublingual vs Intrauterine MISOPROSTOL Plus Oxytocin Infusion for Prevention of Post-cesarean Hemorrhage in High Risk Pregnant Women: A Double-blind Placebo RCT.	- Study design not in PICO Clinical trial - no results posted or publication provided
A Trial of Sublingual Misoprostol to Reduce Primary Postpartum Haemorrhage After Vaginal Delivery.	- Study design not in PICO Clinical trial - no results posted or publication provided
Carbetocin at Elective Cesarean Deliveries: A Dose-finding Study in Women With BMI ≥ 40kg/m2.	- Unavailable from IS search Journal information unavailable so could no be found
Carbetocin Versus Rectal Misoprostol for Management of Third Stage of Labor in Women at Low Risk of Postpartum Hemorrhage.	- Unavailable from IS search Journal information unavailable so could no be found
The Effect of Preoperative and Post Operative Misoprostol Administration on Intraoperative Blood Loss and Postpartum Hemorrhage in CS.	- Unavailable from IS search Journal information unavailable so could no be found
Intrauterine Misoprostol Versus Rectal Misoprostol in Reducing Blood Loss During Cesarean Section.	- Unavailable from IS search Journal information unavailable so could no be found
Randomization of Oxytocin, Oxytocin+Intrauterine Misoprostol and Carbetocin During C-section.	- Unavailable from IS search Journal information unavailable so could no be found
Multimodal Uterotonics at the Time of Cesarean Section in Laboring Patients.	- Study design not in PICO Conference abstract

Study	Reason
Abbas, Dina F, Mirzazada, Shafiq, Durocher, Jill et al. (2020) Testing a home-based model of care using misoprostol for prevention and treatment of postpartum hemorrhage: results from a randomized placebo-controlled trial conducted in Badakhshan province, Afghanistan. Reproductive health 17(1): 88	- Intervention not in PICO Intervention for treatment of PPH
Abdelaleem, Ahmed A, Abbas, Ahmed M, Thabet, Andrew L et al. (2019) The effect of initiating intravenous oxytocin infusion before uterine incision on the blood loss during elective cesarean section: a randomized clinical trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 32(22): 3723-3728	- Intervention not in PICO Only one uterotonic - intravenous oxytocin infusion before uterine incision versus late after umbilical cord clamping
Adnan, Nita, Conlan-Trant, Rebecca, McCormick, Ciara et al. (2018) Intramuscular versus intravenous oxytocin to prevent postpartum haemorrhage at vaginal delivery: randomised controlled trial. BMJ (Clinical research ed.) 362: k3546	- Intervention not in PICO Same drug intervention both arms only different routes of administration
Ahmadi, Fatemeh (2018) A comparative study on infusion of usual dose of oxytocin and 80 units dose of oxytocin in the prevention of postpartum hemorrhage in cesarean section. Journal of advanced pharmaceutical technology & research 9(3): 102-106	- Intervention not in PICO Only one uterotonic - different doses of oxytocin
Alalfy, Mahmoud, Lasheen, Yossra, Elshenoufy, Hossam et al. (2020) The efficacy of intrauterine misoprostol during cesarean section in prevention of primary PPH, a randomized controlled trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 33(9): 1459-1465	- Non systemic administration Intrauterine misoprostol
Anger, Holly A, Dabash, Rasha, Hassanein, Nevine et al. (2020) A cluster-randomized, non-inferiority trial comparing use of misoprostol for universal prophylaxis vs. secondary prevention of postpartum hemorrhage among community level births in Egypt. BMC pregnancy and childbirth 20(1): 317	- Intervention not in PICO Only one uterotonic - 600mcg oral misoprostol versus 800mcg sublingual misoprostol Primary vs secondary prevention (i.e. provided only to women with postpartum blood loss)
Ashwal, Eran, Amikam, Uri, Wertheimer, Avital et al. (2022) Route of postpartum oxytocin administration and maternal hemoglobin decline - A randomized controlled trial. European journal of obstetrics, gynecology, and reproductive biology 272: 134-138	- Intervention not in PICO Only one uterotonic - 1) Intramuscular 10units; 2) intravenous 10units in 100 ml 0.9%NaCl solution over 10-15 min; 3) combined IV + IM regimens
Awoleke, J.O., Adeyanju, B.T., Adeniyi, A. et al. (2020) Randomised Controlled Trial of Sublingual and Rectal Misoprostol in the Prevention of Primary Postpartum Haemorrhage in a Resource-Limited Community. Journal of	- Intervention not in PICO Same drug intervention both arms only different routes of administration - 600 mcg of misoprostol rectally or 600 mcg of misoprostol

Study	Reason
Obstetrics and Gynecology of India 70(6): 462-470	sublingually
Bahadur, Anupama, Khoiwal, Kavita, Bhattacharya, Namrata et al. (2019) The effect of intrauterine misoprostol on blood loss during caesarean section. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 39(6): 753-756	- Non systemic administration Intrauterine misoprostol
Baliuliene, Vilda; Vitartaite, Migle; Rimaitis, Kestutis (2021) Prophylactic Dose of Oxytocin for Uterine Atony during Caesarean Delivery: A Systematic Review. International journal of environmental research and public health 18(9)	- Intervention not in PICO Same drug intervention both arms but different IV doses of oxytocin
Barua HR, Barua R, Barua S EA (2017) Carbetocin and oxytocin in the active management of third stage of labor after vaginal birth of baby. Bangladesh Med J 1(46): 7-10	- Study design not in PICO Not a randomised trial
Begley, Cecily M, Gyte, Gillian Ml, Devane, Declan et al. (2019) Active versus expectant management for women in the third stage of labour. The Cochrane database of systematic reviews 2: cd007412	- Systematic review Checked for eligible studies - eligible studies included. Ineligible studies either did not meet inclusion criteria or already included in Gallos 2018
Beiranvand S, Karimi A, Vahabi S et al. (2019) Comparison of the Mean Minimum Dose of Bolus Oxytocin for Proper Uterine Contraction during Cesarean Section. Current clinical pharmacology 14(3): 208-213	- Study design not in PICO Cross sectional study
Biradar, A.M., Yaliwal, R.G., Kori, S.S. et al. (2021) Randomised control trial of 3 iu intravenous oxytocin bolus with 7 iu oxytocin infusion versus 10 iu intramuscular oxytocin in the third stage of labour in the prevention of postpartum hemorrhage. International Journal of Women's Health and Reproduction Sciences 9(3): 171-175	- Intervention not in PICO Same drug intervention all arms but different routes of administration and different doses - 3 IU IV bolus and 7 IU infusion of oxytocin or 10 IU of IM oxytocin
Caceda, Sonia Indacochea; Ramos, Richard Rubio; Saborido, Carlos Martin (2018) Pharmacoeconomic study comparing carbetocin with oxytocin for the prevention of hemorrhage following cesarean delivery in Lima, Peru. Journal of comparative effectiveness research 7(1): 49-55	- Study design not in PICO Pharmacoecnomic study
Carroli, G., Durocher, J., Dzuba, I. et al. (2018) Does route matter? intravenous versus intramuscular oxytocin for prevention of postpartum hemorrhage. International Journal of Gynecology and Obstetrics 143(supplement3): 236	- Intervention not in PICO Only one uterotonic - 10 IU oxytocin-IV versus IM-and a matching ampoule (saline)
Cecilia, Maria, Vijayaselvi, Reeta, Bansal, Ramandeep et al. (2018) Ten units intravenous oxytocin over 2-4 h is as effective as 30 units over 8-12 h in preventing postpartum hemorrhage after cesarean section: A randomized controlled trial. Indian journal of pharmacology 50(5): 279-283	- Intervention not in PICO Only one uterotonic - single-dose intravenous oxytocin over 2-4 h (total = 10 units) versus oxytocin maintenance infusion for 8-12 h (total = 30 units)
Charles D, Anger H, Dabash R et al. (2019) Intramuscular injection, intravenous infusion,	- Intervention not in PICO Same drug intervention both arms only different

Study	Reason
and intravenous bolus of oxytocin in the third stage of labor for prevention of postpartum hemorrhage: a three-arm randomized control trial. BMC pregnancy and childbirth 19(1): 38	routes of administration - 10 IU oxytocin administered as either IM injection; IV infusion or IV bolus
Charles, Dyanna, Anger, Holly, Dabash, Rasha et al. (2019) Intramuscular injection, intravenous infusion, and intravenous bolus of oxytocin in the third stage of labor for prevention of postpartum hemorrhage: a three-arm randomized control trial. BMC pregnancy and childbirth 19(1): 38	- Duplicate Duplicate from IS search
Drew T, Balki M, Farine D et al. (2020) Carbetocin at elective caesarean section: a sequential allocation trial to determine the minimum effective dose in obese women. Anaesthesia 75(3): 331-337	- Study design not in PICO Dose finding study - no comparative group
Durocher, Jill, Dzuba, Ilana G, Carroli, Guillermo et al. (2019) Does route matter? Impact of route of oxytocin administration on postpartum bleeding: A double-blind, randomized controlled trial. PloS one 14(10): e0222981	- Intervention not in PICO Only one uterotonic - 10 IU oxytocin via IV infusion versus IM injection and a matching saline ampoule
Ebada, Mahmoud Ahmed; Elmatboly, Abdelmagid M; Baligh, Galal (2020) Intravenous Oxytocin versus Intramuscular Oxytocin for the Management of Postpartum Hemorrhage: A Systematic Review and Meta-Analysis. Current drug research reviews 12(2): 150-157	- Intervention not in PICO One uterotonic only - IV versus IM oxytocin
El-Sherbini, Moutaz M, Maged, Ahmed M, Helal, Omneya M et al. (2021) A comparative study between preoperative rectal misoprostol and intraoperative intrauterine administration in the reduction of blood loss during and after cesarean delivery: A randomized controlled trial. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 153(1): 113-118	- Non systemic administration Rectal misoprostol versus intrauterine misoprostol
Feduniw S, Warzecha D, Szymusik I et al. (2020) Epidemiology, prevention and management of early postpartum hemorrhage - a systematic review. Ginekologia polska 91(1): 38-44	- Systematic review Checked for eligible studies - eligible studies included. Ineligible studies either did not meet inclusion criteria or already included in Gallos 2018
Gallos, Ioannis, Williams, Helen, Price, Malcolm et al. (2019) Uterotonic drugs to prevent postpartum haemorrhage: a network meta-analysis. Health technology assessment (Winchester, England) 23(9): 1-356	- Study design not in PICO Health technology assessment
Ibrahim ZM, Sayed Ahmed WA, Abd El-Hamid EM et al. (2020) Carbetocin versus oxytocin for prevention of postpartum hemorrhage in hypertensive women undergoing elective cesarean section. Hypertension in pregnancy 39(3): 319-325	- Duplicate Duplicate from IS search
Ibrahim, G. and Khalid, A. (2019) Is carbetocin as effective as oxytocin in preventing PPH in the third stage of labour in the emergency caesarean section?. Australian and New Zealand Journal of Obstetrics and Gynaecology	- Study design not in PICO Conference abstract

Study	Reason
59(supplement1): 32	
Islamy, N., Bernolian, N., Basir, F. et al. (2018) The effect of different doses of intraumbilical oxytocin on the third stage of labor. International Journal of Gynecology and Obstetrics 143(supplement3): 288-289	- Non systemic administration Intraumbilical administration
Jaafar, J.D., Ismail, H., Ishak, N.A. et al. (2019) Carbetocin versus syntometrine in the prevention of postpartum haemorrhage among women with risk factors following vaginal delivery. Medical Journal of Malaysia 74(supplement1): 24	- Study design not in PICO Conference abstract
Jaffer, Danish, Singh, Preet Mohinder, Aslam, Adam et al. (2022) Preventing postpartum hemorrhage after cesarean delivery: a network meta-analysis of available pharmacologic agents. American journal of obstetrics and gynecology 226(3): 347-365	- Study design not in PICO Conference abstract
Jiang, Danni, Yang, Yang, Zhang, Xinxin et al. (2022) Continued versus discontinued oxytocin after the active phase of labor: An updated systematic review and meta-analysis. PloS one 17(5): e0267461	- Intervention not in PICO Same drug intervention both arms only different routes of administration- continued versus discontinued oxytocin
Jin, Xin-Hang; Li, Dan; Li, Xia (2019) Carbetocin vs oxytocin for prevention of postpartum hemorrhage after vaginal delivery: A meta-analysis. Medicine 98(47): e17911	- Systematic review Checked for eligible studies - eligible studies included. Ineligible studies either did not meet inclusion criteria or already included in Gallos 2018
Kalafat, Erkan, Gokce, Ali, O'Brien, Pat et al. (2021) Efficacy of carbetocin in the prevention of postpartum hemorrhage: a systematic review and Bayesian meta-analysis of randomized trials. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 34(14): 2303-2316	- Systematic review Checked for eligible studies - eligible studies included. Ineligible studies either did not meet inclusion criteria or already included in Gallos 2018
Leas, B. and Umscheid, C. A. (2011) Active management and treatment of postpartum hemorrhage.	- Unavailable from IS search
Lewis, Lucy, Doherty, Dorota A, Conwell, Marion et al. (2021) Spontaneous vaginal birth following induction with intravenous oxytocin: Three oxytocic regimes to minimise blood loss post birth. Women and birth : journal of the Australian College of Midwives 34(3): e322-e329	- Intervention not in PICO Oxytocin used for induction of labour
Li, T, Wei, Q, Wu, L et al. (2022) Multicenter, Randomized, Double-Blind, and Positive Drug-Controlled Clinical Trial on Prevention of Postpartum Hemorrhage after Vaginal Delivery with Ergometrine Maleate. Sichuan da xue xue bao. Yi xue ban [Journal of Sichuan University. Medical science edition] 53(2): 316-320	- Unavailable from IS search Not available in English
Maged AM, Fawzi T, Shalaby MA et al. (2019) A randomized controlled trial of the safety and efficacy of preoperative rectal misoprostol for	- Intervention not in PICO Same drug intervention both arms - 400 µg rectal misoprostol at urinary catheter insertion

Study	Reason
prevention of intraoperative and postoperative blood loss at elective cesarean delivery. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 147(1): 102-107	plus 400 µg rectally after abdominal closure versus 800 µg of rectal misoprostol after abdominal closure
Maged, Ahmed M, Fawzi, Tarek, Shalaby, Mohamed A et al. (2019) A randomized controlled trial of the safety and efficacy of preoperative rectal misoprostol for prevention of intraoperative and postoperative blood loss at elective cesarean delivery. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 147(1): 102-107	- Duplicate Duplicate from IS search
Maged, Ahmed M, Wali, Ahmed A, Metwally, Ahmed A et al. (2022) The efficacy of misoprostol in reducing intraoperative blood loss in women undergoing elective cesarean section. A systematic review and meta-analysis. The journal of obstetrics and gynaecology research	- Intervention not in PICO Same drug intervention both arms - preoperative versus postoperative misoprostol
Maged, Ahmed M, Waly, Mohamed, Fahmy, Radwa M et al. (2020) Carbetocin versus rectal misoprostol for management of third stage of labor among women with low risk of postpartum hemorrhage. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 148(2): 238-242	- Duplicate Duplicate from IS search
Mannaerts, D, Van der Veeken, L, Coppejans, H et al. (2018) Adverse Effects of Carbetocin versus Oxytocin in the Prevention of Postpartum Haemorrhage after Caesarean Section: A Randomized Controlled Trial. Journal of pregnancy 2018: 1374150	- Included in Gallos 2018
Mansouri, H.A. and Bahkali, D. (2018) A randomized controlled trial of intra-umbilical vein ergometrine as compared to intramuscular oxytocin for management of third stage of labor. Clinical and Experimental Obstetrics and Gynecology 45(4): 567-569	- Non systemic administration Intraumbilical administration
Masse, N.; Wong, C.; Dexter, F. (2022) A Randomized Controlled Trial to Assess Prophylactic Methylergonovine in Patients Undergoing an Intrapartum Cesarean Section. American Journal of Obstetrics and Gynecology 226(1supplement): 34	- Duplicate Duplication from manual addition
Masuzawa, Yuko, Kataoka, Yaeko, Fujii, Kana et al. (2018) Prophylactic management of postpartum haemorrhage in the third stage of labour: an overview of systematic reviews. Systematic reviews 7(1): 156	- Systematic review Checked for eligible studies - eligible studies included. Ineligible studies either did not meet inclusion criteria or already included in Gallos 2018
Mirteimouri, M, Pourali, L, Akhlaghi, F et al. (2020) Effect of sublingual Misoprostol in combination with oxytocin in reducing blood loss during and after cesarean delivery: a randomized clinical trial. Tehran university	- Unavailable from IS search Not available in English

Study	Reason
medical journal 78(6): 357-365	
Mohta, Medha, Chowdhury, Rohit B, Tyagi, Asha et al. (2021) Efficacy of different infusion rates of oxytocin for maintaining uterine tone during elective caesarean section: A randomised double blind trial. Anaesthesia and intensive care 49(3): 183-189	- Intervention not in PICO Same drug intervention both arms only different doses - Initial 1 IU bolus, then oxytocin infusion for four hours at 1.25 IU/hour versus 2.5 IU/hour versus 5.0 IU/hour
Mohta, Medha, Siddiqui, Sheeba, Chilkoti, Geetanjali T et al. (2022) Oxytocin infusion rates for maintaining uterine tone during non-elective cesarean section in laboring patients: a randomized, controlled trial. Journal of anesthesia	- Intervention not in PICO Same drug intervention both arms only different doses - oxytocin infusions at rates of 2.5 IU/h versus 5 IU/h (Group 5) versus 10 IU/h (Group 10) following 3 IU slow bolus
Monte-Fenix AP, Vera TR GN (2011) Double-blind randomized controlled trial comparing the effect of carbetocin and oxytocin for the prevention of postpartum hemorrhage among high risk women following vaginal delivery. Philipp J Obstet Gynecol 35: 169-175	- Study design not in PICO Conference abstract
Moradan, S; Anaraki, RM; Mirmohammadkhani, M (2018) Prophylactic effect of misoprostol versus tranexamic acid in conjunction with oxytocin in reduction of post-partum hemorrhage after cesarean sectionin: a randomized clinical trial. Koomesh 20(4): 620-625	- Unavailable from IS search Not available in English
Muhammad, R., Isah, A., Agida, T. et al. (2019) A prospective study to compare the effectiveness of adjunctive rectal misoprostol or oxytocin titration in the prevention of primary post-partum haemorrhage in at risk patients. African Health Sciences 19(1): 1517-1524	- Study design not in PICO Case-control study
Naeem, M., Nawaz, F., Latif, M. et al. (2021) Compare the sublingual and per rectal routes of misoprostol administration in third stage of labor in terms of average blood loss. Medical Forum Monthly 32(3): 105-108	- Intervention not in PICO Same drug intervention both arms only different routes of administration - 400 micro grams of sublingual misoprostol versus 400 micro grams of rectal misoprostol
Neyshabour University of Medical, Sciences (2022) The comparison of low dose with high dose of oxytocin in prevention of postpartum hemorrhage.	- Unavailable from IS search Journal information unavailable so could no be found
Oladapo, O.T., Okusanya, B.O., Abalos, E. et al. (2020) Intravenous versus intramuscular prophylactic oxytocin for reducing blood loss in the third stage of labour. Cochrane Database of Systematic Reviews 2020(12): cd009332	- Intervention not in PICO Same drug intervention both arms only different routes of administration -IV versus IM oxytocin
Oladapo, Olufemi T, Okusanya, Babasola O, Abalos, Edgardo et al. (2020) Intravenous versus intramuscular prophylactic oxytocin for the third stage of labour. The Cochrane database of systematic reviews 11: cd009332	- Duplicate Duplicate from IS search
Onwochei, D N, Van Ross, J, Singh, P M et al. (2019) Carbetocin reduces the need for additional uterotonics in elective caesarean delivery: a systematic review, meta-analysis and trial sequential analysis of randomised controlled trials. International journal of obstetric anesthesia 40: 14-23	- Systematic review Checked for eligible studies - eligible studies included. Ineligible studies either did not meet inclusion criteria or already included in Gallos 2018

Study	Reason
Onwochei, Desire N, Owolabi, Adetokunbo, Singh, Preet Mohinder et al. (2020) Carbetocin compared with oxytocin in non-elective Cesarean delivery: a systematic review, meta-analysis, and trial sequential analysis of randomized-controlled trials. Canadian journal of anaesthesia = Journal canadien d'anesthesie 67(11): 1524-1534	- Systematic review Checked for eligible studies - eligible studies included. Ineligible studies either did not meet inclusion criteria or already included in Gallos 2018
Peska, E., Balki, M., Maxwell, C. et al. (2021) Oxytocin at elective caesarean delivery: a dose-finding study in women with obesity. Anaesthesia 76(7): 918-923	- Study design not in PICO Dose finding study - no comparison/control group
Phung, Laura C, Farrington, Elise K, Connolly, Mairead et al. (2021) Intravenous oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery: a systematic review and meta-analysis. American journal of obstetrics and gynecology 225(3): 250e1-250e38	- Intervention not in PICO Same drug intervention both arms only different doses of IV oxytocin
Qian XW, Drzymalski DM, Lv CC et al. (2019) The ED50 and ED95 of oxytocin infusion rate for maintaining uterine tone during elective caesarean delivery: a dose-finding study. BMC pregnancy and childbirth 20(1): 6	- Intervention not in PICO Only one uterotonic - oxytocin infusion at a rate of 0, 1, 2, 3, 5, or 8 IU h- 1, to be given for a total of 1 hour
Salati, J.A., Leathersich, S.J., Williams, M.J. et al. (2019) Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database of Systematic Reviews 2019(4): cd001808	- Systematic review Checked for eligible studies - eligible studies included. Ineligible studies either did not meet inclusion criteria or already included in Gallos 2018
Shah, M., Urooj, H., Shah, S. et al. (2021) EFFICACY OF RECTAL MISOPROSTOL VS INTRAVENOUS OXYTOCIN IN PREVENTING POSTPARTUM HEMORRHAGE FOLLOWING ELECTIVE CAESAREAN SECTION. Journal of Postgraduate Medical Institute 35(3): 131-135	- Intervention not in PICO In one of the arms uterotonics were not administered as part of the third stage of labour
Slowiczek, L., Hein, D., Lozicki, A. et al. (2018) Methylergonovine versus prostaglandins for postpartum hemorrhage: A systematic review and meta-analysis. Journal of the American Pharmacists Association 58(3): e83	- Study design not in PICO Conference abstract
Somjit, Monsicha, Surojananon, Jaruta, Kongwattanakul, Kiattisak et al. (2020) Comparison of Low Dose versus High Dose of Oxytocin for Initiating Uterine Contraction During Cesarean Delivery: A Randomized, Controlled, Non-Inferiority Trial. International journal of women's health 12: 667-673	- Intervention not in PICO Same drug intervention both arms only different doses - intravenous injections of high-dose (10 IU) and low-dose (5 IU) oxytocin
Sun, Haiyan, Xu, Lei, Li, Yu et al. (2022) Effectiveness and safety of carboxytocin versus oxytocin in preventing postpartum hemorrhage: A systematic review and meta-analysis. The journal of obstetrics and gynaecology research 48(4): 889-901	- Systematic review Checked for eligible studies - eligible studies included. Ineligible studies either did not meet inclusion criteria or already included in Gallos 2018
Suzhou Municipal, Hospital (2018) Therapeutic efficacy and safety of carbetocin on postpartum hemorrhage.	- Unavailable from IS search Not available in English

Study	Reason
Sweed, Mohamed, El-Said, Mourad, Abou-Gamrah, Amgad et al. (2019) Comparison between 200, 400 and 600 microgram rectal misoprostol before cesarian section: A randomized clinical trial. The journal of obstetrics and gynaecology research 45(3): 585-591	- Intervention not in PICO Same drug intervention both arms only different doses - 200-, 400- or 600-mug misoprostol rectally
Tabl, S, Balki, M, Downey, K et al. (2019) Uterotonics in elective caesarean delivery: a randomised non-inferiority study comparing carbetocin 20 mug and 100 mug. Anaesthesia 74(2): 190-196	- Intervention not in PICO Only one uterotonic - intravenous carbetocin (20mug and 100mug)
Taheripanah, Robabeh, Shoman, Amal, Karimzadeh, Mohammad Ali et al. (2018) Efficacy of oxytocin versus carbetocin in prevention of postpartum hemorrhage after cesarean section under general anesthesia: a prospective randomized clinical trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 31(21): 2807-2812	- Included in Gallos 2018
Tan YQ, Liu SJ, Cao SY, Wang TT CL (2018) Comparison of the effectiveness and safety of carbetocin and oxytocin in preventing postpartum hemorrhage after vaginal delivery: a meta-analysis. Chin J Evid Based Med 10: 1093-1100	- Unavailable from IS search Not available in English
Torloni, Maria Regina, Siaulys, Monica, Riera, Rachel et al. (2021) Timing of oxytocin administration to prevent post-partum hemorrhage in women delivered by cesarean section: A systematic review and metanalysis. PloS one 16(6): e0252491	- Intervention not in PICO Same drug intervention both arms only different timing of oxytocin
Torloni, Maria Regina, Siaulys, Monica, Riera, Rachel et al. (2021) Route of oxytocin administration for preventing blood loss at caesarean section: a systematic review with meta-analysis. BMJ open 11(9): e051793	- Duplicate Duplication from IS search
University College of Mediacl Sciences and GTb, Hospital (2019) Comparison between mothers at high or low risk of uterine bleeding, with regards to the effective dose of oxytocin during cesarean surgery.	- Unavailable from IS search Unavailable from IS search as no journal information
University of, Liverpool (2018) Carboprost vs Oxytocin as the First Line Treatment of Primary Postpartum Haemorrhage: A phase IV, double-blind, double-dummy, randomised controlled trial.	- Unavailable from IS search Unavailable from IS search as no journal information
van der Nelson, H, O'Brien, S, Burnard, S et al. (2021) Intramuscular oxytocin versus Syntometrine R versus carbetocin for prevention of primary postpartum haemorrhage after vaginal birth: a randomised double-blinded clinical trial of effectiveness, side effects and	- Duplicate Duplication from IS search

Study	Reason
quality of life. BJOG : an international journal of obstetrics and gynaecology 128(7): 1236-1246	
Vernekar, Sunil S, Goudar, Swati S, Metgud, Mrityunjay et al. (2021) Effect of heat stable carbetocin vs oxytocin for preventing postpartum haemorrhage on post delivery hemoglobin-a randomized controlled trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians: 1-8	- Study design not in PICO Sub analysis CHAMPION trial
Vice chancellor for Research, Tabriz University Of Medical Sciences (2021) Comparison of the effects of misoprostol and oxytocine on postpartum Hemorrhage.	- Unavailable from IS search Journal information unavailable so could not be found
Voon HY, Suharjono HN, Shafie AA et al. (2018) Carbetocin versus oxytocin for the prevention of postpartum hemorrhage: A meta-analysis of randomized controlled trials in cesarean deliveries. Taiwanese journal of obstetrics & gynecology 57(3): 332-339	- Systematic review Checked for eligible studies - eligible studies included. Ineligible studies either did not meet inclusion criteria or already included in Gallos 2018
Wan SQ, Pan CY, Yin HZ ZY (2018) Meta-analysis of the effectiveness and safety of carbetocin versus oxytocin in preventing post-cesarean hemorrhage. Drug Eval Res 8: 1504-1511	- Unavailable from IS search Not available in English
Wang, L.; Jiang, H.-M.; Yang, R.-R. (2020) Carboprost tromethamine prevents caesarean section-associated postpartum hemorrhage. Tropical Journal of Pharmaceutical Research 19(4): 899-904	- Non systemic administration Intrauterine administration
Wei, Lin; Yang, Haiping; Sun, Xiaoli (2022) The Effect of Oxytocin plus Carboprost Methylate in Preventing Postpartum Hemorrhage in High-Risk Pregnancy and Its Effect on Blood Pressure. Evidence-based Complementary & Alternative Medicine (eCAM): 1-4	- Intervention not in PICO Oxytocin versus Oxytocin plus carboprost methylate
Widmer, M., Piaggio, G., Nguyen, T.M.H. et al. (2018) Heat-Stable Carbetocin Versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. Obstetrical and Gynecological Survey 73(11): 613-614	- Included in Gallos 2018
Widmer, M, Piaggio, G, Nguyen, TMH et al. (2018) Heat-Stable Carbetocin Versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. Obstetrical & gynecological survey 73(11): 613-614	- Duplicate Duplication from IS search
Widmer, Mariana, Piaggio, Gilda, Nguyen, Thi M H et al. (2018) Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. The New England journal of medicine 379(8): 743-752	- Duplicate Duplication from IS search
Wu, Yu, Wang, Huan, Wu, Qi-Yan et al. (2020) A meta-analysis of the effects of intramuscular and intravenous injection of oxytocin on the third stage of labor. Archives of gynecology and	- Intervention not in PICO Same drug intervention both arms only different routes of administration- IV versus IM oxytocin

Study	Reason
obstetrics 301(3): 643-653	
Xu, Renmei, Guo, Yongjie, Zhang, Qinggui et al. (2022) Comparison of Clinical Efficacy and Safety between Misoprostol and Oxytocin in the Prevention of Postpartum Hemorrhage: A Meta-Analysis. Journal of healthcare engineering 2022: 3254586	- Systematic review Checked for eligible studies - eligible studies included. Ineligible studies either did not meet inclusion criteria or already included in Gallos 2018
Yildirim, Dogukan and Ozyurek, Sefik Eser (2018) Intramuscular oxytocin administration before vs. after placental delivery for the prevention of postpartum hemorrhage: A randomized controlled prospective trial. European journal of obstetrics, gynecology, and reproductive biology 224: 47-51	- Intervention not in PICO Same drug intervention both arms only different timings - 10 IU of oxytocin intramuscularly within the first minute following the delivery of the fetus versus 10 IU of intramuscular oxytocin immediately following placental delivery.
Zgaya, Rym, Ghadhab, Imen, Triki, Mohamed Amine et al. (2020) Randomized controlled trial comparing 400mug sublingual misoprostol versus placebo for prevention of primary postpartum hemorrhage. The Pan African medical journal 36: 186	- Duplicate Duplication from IS search
Zhou, Yuan-Hong, Xie, Yan, Luo, You-Zhen et al. (2020) Intramuscular versus intravenous oxytocin for the third stage of labor after vaginal delivery to prevent postpartum hemorrhage: a meta-analysis of randomized controlled trials. European journal of obstetrics, gynecology, and reproductive biology 250: 265-271	- Intervention not in PICO Same drug intervention both arms only different routes of administration - IV versus IM oxytocin

Excluded economic studies

Table 48: Excluded studies and reasons for their exclusion

Study	Reason
Barrett, Jon; Ko, Samuel; Jeffery, William (2021) Cost Implications of Using Carbetocin Injection to Prevent Postpartum Hemorrhage in a Canadian Urban Hospital. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC	- Cost analysis only
Lawrie, Theresa A., Rogozinska, Ewelina, Sobiesuo, Pauline et al. (2019) A systematic review of the cost-effectiveness of uterotonic agents for the prevention of postpartum hemorrhage. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 146(1): 56-64	- Review
Luni, Yasmin, Borakati, Aditya, Matah, Arti et al. (2017) A prospective cohort study evaluating the cost-effectiveness of carbetocin for prevention of postpartum haemorrhage in caesarean sections. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 37(5): 601-604	- Cost analysis only
Mills, F., Siu, E., Poinas, A. C. et al. (2014) A	- Cost analysis only

Study	Reason
cost-minimization analysis of carbetocin for the prevention of postpartum hemorrhage in Canada. Value in Health 17(3): a161	
Patel, B. and Haloob, R. (2014) Carbitocin: A cost-effective tool to save lives. BJOG: An International Journal of Obstetrics and Gynaecology 121(suppl2): 88-89	- Conference abstract.
Pickering, Karen, Gallos, Ioannis D., Williams, Helen et al. (2019) Uterotonic Drugs for the Prevention of Postpartum Haemorrhage: A Cost-Effectiveness Analysis. PharmacoEconomics - open 3(2): 163-176	- Duplicate analysis
Shaw, L., Morris, C., Baekgaard, E. et al. (2013) Cost comparison of routine carbetocin use at caesarean section. BJOG: An International Journal of Obstetrics and Gynaecology 120(suppl1): 119-120	- Conference abstract.
van der Nelson, Helen A., Draycott, Tim, Siassakos, Dimitrios et al. (2017) Carbetocin versus oxytocin for prevention of post-partum haemorrhage at caesarean section in the United Kingdom: An economic impact analysis. European journal of obstetrics, gynecology, and reproductive biology 210: 286-291	- Cost consequence analysis. In addition it was considered that this study could not helpfully inform recommendations as there was more recent research and a de Novo model produced for the guideline which included a broader range of uterotonic comparators as well as more recent clinical evidence which was synthesised through a network meta-analysis
Wohling, J., Edge, N., Pena, Leal D. et al. (2018) Cost comparison of carbetocin compared to oxytocin as primary postpartum haemorrhage (PPH) prophylaxis at caesarean section. Australian and New Zealand Journal of Obstetrics and Gynaecology 58(supplement1): 88	- Conference abstract.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

No research recommendations were made for this review question.

Appendix L Network meta-analysis methods

Network meta-analysis methods for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Introduction

The results of conventional pairwise meta-analyses of direct evidence alone are not sufficient to fully inform a number of outcomes for the review on the effectiveness of uterotonics for the prevention of postpartum haemorrhage.

Each pairwise comparison does not fully inform the choice between the different treatments and having a series of discrete pairwise comparisons can be incoherent and difficult to interpret.

In addition, direct comparisons of treatments of clinical interest are not fully available, for all comparisons.

To overcome these issues, a Bayesian NMA was performed. Advantages of performing this type of analysis are as follows.

- It allows the synthesis of evidence on multiple treatments to be compared directly and indirectly without breaking randomisation. If treatment A has never been compared to treatment B in a head-to-head trial, but these two interventions have been compared to a common comparator, then an indirect treatment comparison can be derived using the relative effects of the two treatments versus the common comparator. Indirect estimates can be calculated whenever there is a path linking two treatments through a set of common comparators. There does not have to be a common comparator to which all treatments have been compared merely a connected network of treatments. All the randomised evidence is considered simultaneously within the same model.
- For every intervention in a connected network, a relative effect estimate (with its 95% CrIs) between any two interventions can be estimated. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on all relevant evidence, whilst appropriately accounting for uncertainty. Ranks of interventions may also be calculated.
- Estimates from the NMA can be used to directly parameterise treatment effectiveness in cost-effectiveness modelling of multiple treatments.

Conventional fixed effect meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

NMA assumes that the included studies are similar in terms of factors that might interact with the intervention effects (effect modifiers). So, the relative effect of intervention B vs intervention A would be expected to be similar in all of the studies (if they had included A and B interventions). This assumption is the same as that made in conventional pairwise meta-analysis, but we have to be particularly careful that the studies making different comparisons do not differ in effect modifiers (the data are consistent). We can assess this assumption by measuring statistical heterogeneity, and also by checking if the direct and indirect estimates are in agreement when there are loops of evidence in the network.

Study selection and data collection

For full details see analysis protocol in appendix A.

Outcome measures

The protocol for this review stated that NMA would be considered for five outcomes, if feasible. Based on the availability of data and the formation of a connected network, all five outcomes were deemed suitable for synthesis using NMA: PPH ≥ 1000ml, additional uterotonics, blood transfusion, ICU admission (morbidity) and mean blood loss (ml). NMAs were performed on these outcomes for all women, and for subgroups of women based on the mode of birth (vaginal or caesarean). The committee agreed it was important to consider results separately according to subgroups based on the mode of birth as their clinical experience suggested that different treatments are likely to be effective depending on the mode of birth.

For the outcome of ICU admissions (morbidity) there were fewer studies, particularly in the caesarean birth subgroup where there was only one study comparing two treatments. Therefore an NMA was not conducted for this outcome in the caesarean birth subgroup.

PPH ≥ 1000ml

Data for PPH ≥ 1000ml was reported as number of women experiencing an event in the RCTs. The probability of PPH ≥ 1000ml in each arm of a trial was estimated as the number of women who had PPH ≥ 1000ml, divided by the total number of women in this arm. The results are presented as posterior mean ORs.

Additional uterotonics

Data for additional uterotonics was reported as number of women requiring additional uterotonics in the RCTs. The probability of requiring additional uterotonics in each arm of a trial was estimated as the number of women who required this, divided by the total number of women in this arm. The results are presented as posterior mean ORs.

Blood transfusion

Data for blood transfusions was reported as number of women requiring transfusion in the RCTs. The probability of blood transfusion in each arm of a trial was estimated as the number of women requiring transfusion, divided by the total number of women in this arm. The results are presented as posterior mean ORs.

ICU admission (morbidity)

Data for ICU admissions was reported as number of women experiencing an event in the RCTs. The probability of having an ICU admission in each arm of a trial was estimated as the number of women who had an ICU admission, divided by the total number of women in this arm. The results are presented as posterior mean ORs.

Mean blood loss (ml)

Data for mean blood loss was reported as a continuous variable of the mean blood loss in ml as measured in the RCTs. The results are presented as posterior mean blood loss ratios.

Methodology

Model description

For four of the outcomes with dichotomous data, Binomial models with logit link were used for the synthesis. For mean blood loss Normal models with a log-link were used to estimate treatment effects as ratios of mean blood loss. The log-link was used as this gave an improved fit with less inconsistency, suggesting a multiplicative rather than additive effect of treatment. In both cases both fixed and random effects models were fitted for the full population, and for both subgroups of women who had vaginal birth and women who had a caesarean birth, and model choice based on goodness of fit.

The full description of standard fixed and random effects models using binomial likelihood with logit link, and the normal identity models can be found in NICE DSU Technical Support Document 2 (Dias 2011). The normal identity model was adapted for a log-link. Examples of the WinBUGS codes used to synthesise data can also be found in Appendix N.

Analysis was undertaken following Bayesian statistics principles and conducted using MCMC simulation techniques implemented in WinBUGS 1.4.3. (Lunn 2000; Spiegelhalter 2001).

For baseline and treatment effects non informative priors were used Normal(mean=0, variance=10000), Normal(mean=0, variance=1000) respectively, and a non-informative prior uniform (0,5) was specified for the between study SD for all outcomes except mean blood loss which used uniform (0,10000).

Each model was run until convergence was satisfactory and then the results were based on a further sample of iterations on three chains, the following iterations were used:

	Full population		Vaginal birth		Caesarean birth	
Outcome	**Burn-ins**	**Post-convergence**	**Burn-ins**	**Post-convergence**	**Burn-ins**	**Post-convergence**
PPH ≥ 1000ml	120,000	20,000	100,000	20,000	20,000	20,000
Additional uterotonics	10,000	20,000	10,000	20,000	30,000	20,000
Blood transfusion	20,000	20,000	40,000	20,000	400,000	20,000
ICU admission (morbidity)	10,000	20,000	10,000	20,000	-	-
Mean blood loss (ml)	10,000	20,000	10,000	20,000	10,000	20,000

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model. Smaller values are preferred and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point) (Spiegelhalter 2002).

In addition to comparing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean of the residual deviance and the effective number of parameters and thus penalizes model fit with model complexity. Lower values are preferred and typically differences of 3-5 points are considered meaningful (Spiegelhalter 2002).

For each analysis fixed and random effects models were compared and the best fitting model was chosen based on the criteria described above.

An important assumption made in NMA concerns the consistency, that is, the agreement of the direct and indirect evidence informing the treatment contrasts and there should be no meaningful differences between these two sources of evidence. The consistency checks were undertaken by TSU and are summarised in in Appendix N.

NMA methods references

Dias 2011

Dias S, Welton N, Sutton A, Ades A. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials, 2011, last updated September 2016, available from http://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/evidence-synthesis-tsd-series/

Lunn 2000

Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility, Statistics and Computing, 10, 325-337, 2000

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Spiegelhalter D, Best N, Carlin B, van der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B, 64, 583-616, 2002

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Spiegelhalter DJ,Thomas A,Best NG, et al. WinBUGS User Manual: Version 5.1.4. Cambridge: MRC Biostatistics Unit, 2001

Turner 2015

Turner R, Jackson D, Wei Y, Thompson S, Higgins J. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in Medicine 2015;34:984-98.

Appendix M Model fit results

Model fit characteristics for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Model selection was based on the posterior mean residual deviance (a measure of model fit),and the Deviance Information Criteria (DIC), where smaller values are preferred and differences of between 3-5 are considered meaningful. The chosen model for each analysis is noted in the first column of each of the tables below, and results from the selected model are reported in the main text of this evidence review. For the selected model, results from an inconsistency model are reported. Comparing the NMA and inconsistency models provides a global test of inconsistency and, where inconsistency was identified it was explored further in Appendix N.

Model fit characteristics for PPH ≥ 1000ml: whole population

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	0.22 (0.03, 0.41)	247.2	1073.0
Random effects - inconsistency	0.22 (0.04, 0.44)	239.0	1077.8
Fixed effects – consistency	-	270.0	1078.7

CrI: credible interval; DIC: deviance information criterion
(a) Compare 212 data points

Model fit characteristics for PPH ≥ 1000ml: vaginal birth subgroup

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	0.20 (0.02, 0.45)	190.5	795.1
Random effects - inconsistency	0.21 (0.02, 0.47)	178.9	791.9
Fixed effects – consistency	-	205.9	798.4

CrI: credible interval; DIC: deviance information criterion
(a) Compare 157 data points

Model fit characteristics for PPH ≥ 1000ml: caesarean birth subgroup

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected	0.34 (0.03, 0.81)	56.3	276.9

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
– all results reported in this guideline are based on this model)			
Random effects - inconsistency	0.26 (0.01, 0.79)	55.4	277.3
Fixed effects – consistency	-	61.6	276.6

CrI: credible interval; DIC: deviance information criterion
(a) Compare 53 data points

Model fit characteristics for additional uterotonics: whole population

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	0.83 (0.71, 0.98)	366.5	2035.7
Random effects - inconsistency	0.91 (0.76, 1.08)	360.4	2039.6
Fixed effects – consistency	-	1162.0	2715.7

CrI: credible interval; DIC: deviance information criterion
(a) Compare 345 data points

Model fit characteristics for additional uterotonics: vaginal birth subgroup

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	0.73 (0.58, 0.90)	254.0	1414.4
Random effects - inconsistency	0.74 (0.57, 0.94)	249.3	1415.3
Fixed effects – consistency	-	682.1	1768.3

CrI: credible interval; DIC: deviance information criterion
(a) Compare 236 data points

Model fit characteristics for additional uterotonics: caesarean birth subgroup

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	1.03 (0.76, 1.39)	111.5	617.9
Random effects - inconsistency	1.20 (0.85, 1.68)	110.8	620.6

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Fixed effects – consistency	-	315.7	788.3

CrI: credible interval; DIC: deviance information criterion
(a) Compare 107 data points

Model fit characteristics for blood transfusion: whole population

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	0.74 (0.51, 1.02)	270.1	1074.6
Random effects - inconsistency	0.75 (0.45, 1.11)	268.1	1082.0
Fixed effects – consistency	-	381.5	1142.9

CrI: credible interval; DIC: deviance information criterion
(a) Compare 242 data points

Model fit characteristics for blood transfusion: vaginal birth subgroup

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	0.53 (0.25, 0.84)	200.4	782.7
Random effects - inconsistency	0.54 (0.21, 0.93)	196.5	789.7
Fixed effects – consistency	-	243.9	803.0

CrI: credible interval; DIC: deviance information criterion
(a) Compare 175 data points

Model fit characteristics for blood transfusion: caesarean birth subgroup

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	1.11 (0.45, 1.99)	67.95	283.9
Random effects - inconsistency	1.50 (0.48, 3.09)	67.59	286.8
Fixed effects – consistency	-	94.73	299.0

CrI: credible interval; DIC: deviance information criterion

(a) Compare 65 data points

Model fit characteristics for ICU admission: whole population

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Fixed effects - consistency (selected – all results reported in this guideline are based on this model)	-	17.2	72.9
Fixed effects - inconsistency	-	14.8	70.6
Random effects – consistency	1.87 (0.06, 4.75)	16.3	73.4

CrI: credible interval; DIC: deviance information criterion
(a) Compare 18 data points

Model fit characteristics for ICU admission: vaginal birth subgroup

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Fixed effects - consistency (selected – all results reported in this guideline are based on this model)	-	16.0	68.7
Fixed effects - inconsistency	-	13.5	66.4
Random effects – consistency	1.83 (0.06, 4.72)	15.0	69.0

CrI: credible interval; DIC: deviance information criterion
(a) Compare 16 data points

Model fit characteristics for mean blood loss: whole population

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	0.24 (0.23, 0.27)	336.1	2883.0
Random effects - inconsistency	0.23 (0.20, 0.26)	334.2	2884.0
Fixed effects – consistency	-	5125.0	7526.2

CrI: credible interval; DIC: deviance information criterion
(a) Compare 332 data points

Model fit characteristics for mean blood loss: vaginal birth subgroup

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	0.25 (0.21, 0.29)	239.6	1936.4
Random effects - inconsistency	0.24 (0.20, 0.28)	238.1	1937.6
Fixed effects – consistency	-	2961.0	4553.8

CrI: credible interval; DIC: deviance information criterion
(a) Compare 235 data points

Model fit characteristics for mean blood loss: caesarean birth subgroup

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	0.21 (0.16, 0.27)	93.9	926.5
Random effects - inconsistency	0.19 (0.14, 0.25)	94.4	927.3
Fixed effects – consistency	-	1706.0	2506.8

CrI: credible interval; DIC: deviance information criterion
(a) Compare 95 data points

Appendix N Inconsistency checks

Inconsistency checks for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Guidelines Technical Support Unit (TSU), University of Bristol (Beatrice Downing, Nicky J. Welton)

Introduction

The purpose of this analysis was to assess the consistency assumption in the NMA model used to estimate the comparative effectiveness uterotonics for the prevention of postpartum haemorrhage. The outcomes included in this analysis were 1) PPH ≥ 1000ml, 2) additional uterotonics, 3) blood transfusion, 4) ICU admission (morbidity), and 5) mean blood loss (ml).

Methods

Inconsistency checks

NMA assumes that the included studies are similar in terms of factors that might interact with the intervention effects (effect modifiers). So, the relative effect of intervention B vs intervention A would be expected to be similar in all of the studies (if they had included A and B interventions). This assumption is the same as that made in conventional pairwise meta-analysis, but we have to be particularly careful that the studies making different comparisons do not differ in effect modifiers (the data are consistent). We can assess this assumption by measuring statistical heterogeneity, and also by checking if the direct and indirect estimates are in agreement when there are loops of evidence in the network.

To conduct inconsistency checks, an appropriate base-case model (fixed or random effects) must be determined beforehand. We assessed and compared the fit of a fixed effect model and a random effects model with a standard, uninformative prior distribution for all outcomes on the between-study standard deviation. The vague prior used on the between-study standard deviation was either Uniform (0,5) (for PPH ≥ 1000ml, additional uterotonics, blood transfusion, ICU admission (morbidity)), or Uniform (0, 10,000) (for mean blood loss). To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an “inconsistency”, or unrelated mean effects (UME), model (Dias 2013, Dias 2014). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that the consistency assumption can only be assessed when there are closed loops of direct evidence on 3 treatments that are informed by at least 3 independent sources of evidence (Van Valkenhoef 2016).

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model (Spiegelhalter 2002). Smaller values are preferred and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point on average) (Spiegelhalter 2002).

Where the base-case model assumes random effects, if the inconsistency model has smaller heterogeneity (measured by the posterior median between-study standard deviation) compared to the consistency model, then this may also indicate potential inconsistency in the data.

We performed further checks for evidence of inconsistency through node-splitting. The node-splitting method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared (Dias 2014, Dias 2010).

There are some small differences between the NMA estimates produced by the NMA models (presented in the main results) and those produced by the node-splitting models for exploring inconsistency (presented in forest plot below), due to small differences in the software used (WinBUGS or the GeMTC package in R). The NMA estimates presented in the main results were used to compare the safety and effectiveness of the interventions. In a separate exercise, the direct, indirect, and NMA estimates produced by the node-splitting modelling were used to assess how potential inconsistency between the direct and indirect estimates impacted the NMA estimates.

Results

Outcome: PPH >1000ml

Summary

We identified moderate heterogeneity in both full and mode-of-delivery subgroup datasets for this outcome, but little evidence of inconsistency. There was some indication of inconsistency between the studies comparing treatments on the oxytocin (>5 IU and ≤ 10 IU) vs carboprost v ergometrine loop, however these findings were driven by very small numbers of events in the Modi 2014 study.

Full data set

Global inconsistency check

Analysis of the full dataset for the outcome post-partum haemorrhage (>1000ml) included 98 studies (212 arms) of 13 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Comparing fixed (FE) and random-effect (RE) network meta-analysis (NMA) models indicated support for the random-effect model on the basis of a small decrease in DIC and a sizeable decrease in residual deviance (**Error! Reference source not found.**).

Total residual deviance was lower in the inconsistency UME model than in the NMA model; however, DIC was lower for the NMA model and the estimate of between-study SD was similar in the NMA and UME models (Table 49). This suggests that there is little evidence of inconsistency but moderate heterogeneity between study estimates.

Table 49: Model fit statistics for fixed- and random-effect NMA and UME models of the outcome PPH >1000ml, full dataset.

Outcome	Pop.	Model	Posterior total residual deviance[1]	Between-study SD Mean, 95% credible interval	pD	DIC[2]

[1] Posterior mean residual deviance compared to 212 total data points
[2] Deviance information criteria (DIC) – lower values preferred

PPH	Full	FE NMA	270.0	-	106.3	1078.7
PPH	Full	RE NMA	247.2	0.22 (0.03, 0.41)	123.7	1073.0
PPH	Full	FE UME	257.1	-	122.8	1082.3
PPH	Full	RE UME	239.0	0.22 (0.04, 0.44)	136.3	1077.8

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 47), shows that two studies showed inconsistency with the rest of the dataset:

- Begley, 1990
    - Compares Ergometrine (coded 12) and placebo (coded 1)
- Modi, 2014
    - Compares Oxytocin [>5 IU and ≤ 10 IU] (coded 5), Misoprostol ≤600mcg (coded 8), Ergometrine (coded 12) and Carboprost (coded 13)
    - In this four-armed trial events were rare with only two events observed, both on the carboprost arm, which likely explains the high deviance contribution for this study under the NMA model.

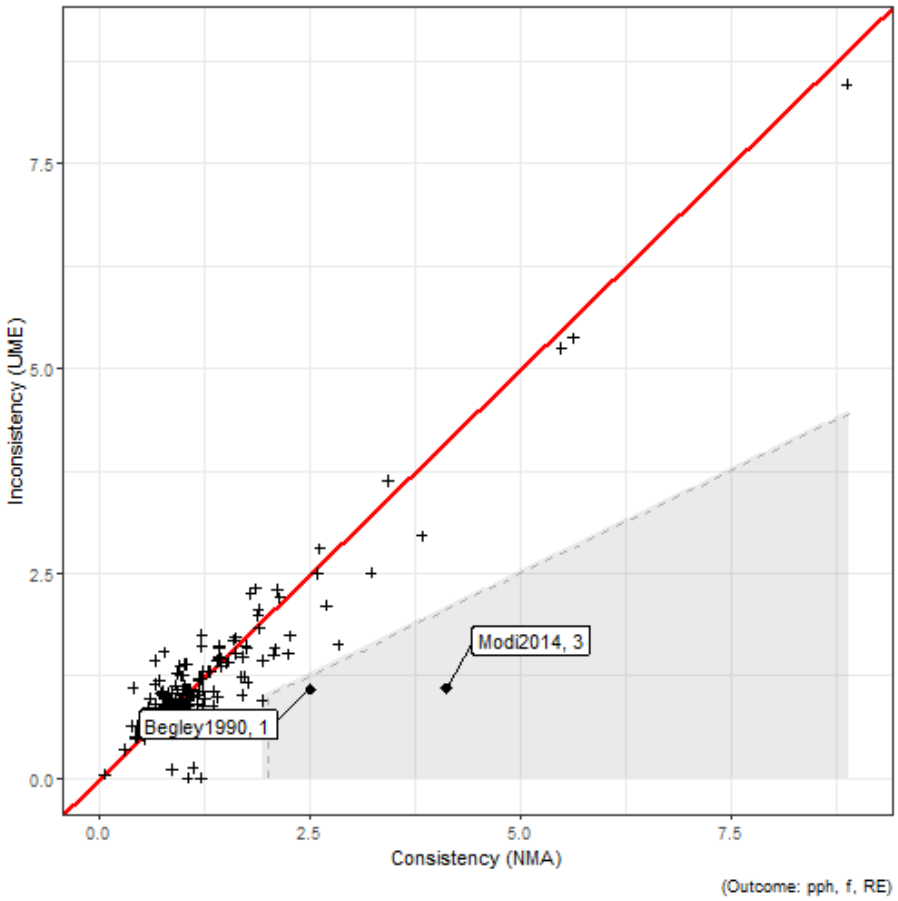

Figure 47. Dev-dev plot of each study arm's residual deviance under the standard and inconsistency models (RE model structure) for PPH >1000ml, full dataset. Labels indicate study arms with high deviance in the NMA model, relative to their deviance in the UME model. The dotted line and grey shaded area denotes where study arms fit poorly in the NMA model but well in the UME model, suggesting that they are predicted poorly when the model enforces consistency in treatment differences.

Checking inconsistency within individual treatment comparisons (Node-splitting)

Node-splitting procedures indicated no evidence of a difference between direct and indirect evidence on most treatment comparisons. Evidence conflicted on five comparisons (Table 50), including treatment comparisons where study arms were identified as inconsistent:

- Placebo and Ergometrine
- Carbetocin and Oxytocin >5 IU and ≤ 10 IU
- Ergometrine and Carboprost
- Carboprost and Oxytocin >5 IU and ≤ 10 IU
- Carboprost and Misoprostol ≤ 600 mcg

Given multiple testing of 33 contrasts, we would expect p-values below a 5% threshold in at least 1 case. Applying a Bonferroni correction suggests that only comparisons between carboprost and misoprostol (≤ 600 mcg) and oxytocin (>5 IU and ≤ 10 IU).

Forest plots for the comparisons where direct evidence conflicts with indirect evidence are presented (Figure 48 and Figure 49). We note that carboprost is only linked to treatments Oxytocin >5 IU and ≤ 10 IU, ergometrine and misoprostol ≤ 600 mcg by a single study (Modi 2014) in which no events were observed on 3 arms, leaving very little evidence with which to reach an estimate of the treatment effect and leading to extremely large treatment differences.

Table 50. Model fit statistics for node-split model (PPH >1000ml, full dataset). Comparisons where there is an indication of inconsistency between direct and indirect estimates (p-values <0.001 following application of a Bonferroni correction) are highlighted in orange.

Comparison	Total Residual Deviance	p-value
Carboprost vs Oxytocin >5 IU and ≤ 10 IU	240.9	<0.001
Carboprost vs Misoprostol ≤ 600 mcg	240.0	<0.001
Placebo vs Ergometrine	246.6	0.029
Carbetocin vs Oxytocin >5 IU and ≤ 10 IU	245.6	0.038
Ergometrine vs Carboprost	240.2	0.015
Placebo vs Oxytocin >1 IU and ≤ 5 IU	244.1	0.741
Placebo vs Oxytocin >5 IU and ≤ 10 IU	246.2	0.922
Placebo vs Ergometrine plus oxytocin	246.8	0.843
Placebo vs Misoprostol ≤ 600 mcg	242.7	0.526
Placebo vs Carboprost	247.8	0.653
Carbetocin vs Oxytocin >1 IU and ≤ 5 IU	246.9	0.863

Carbetocin vs Oxytocin > 10 IU	246.1	0.471
Carbetocin vs Ergometrine plus oxytocin	242.1	0.157
Carbetocin vs Misoprostol ≤ 600 mcg	247.3	0.471
Oxytocin >1 IU and ≤ 5 IU vs Ergometrine plus oxytocin	247.1	0.434
Oxytocin >1 IU and ≤ 5 IU vs Misoprostol ≤ 600 mcg	244.1	0.393
Oxytocin >5 IU and ≤ 10 IU vs Ergometrine plus oxytocin	238.9	0.543
Oxytocin >5 IU and ≤ 10 IU vs Misoprostol ≤ 600 mcg	236.8	0.578
Oxytocin >5 IU and ≤ 10 IU vs Misoprostol >600 mcg and ≤ 800 mcg	248.5	0.779
Oxytocin > 10 IU vs Ergometrine plus oxytocin	247.0	0.256
Oxytocin > 10 IU vs Misoprostol ≤ 600 mcg	247.1	0.870
Oxytocin > 10 IU vs Misoprostol >600 mcg and ≤ 800 mcg	247.6	0.390
Ergometrine plus oxytocin vs Misoprostol ≤ 600 mcg	239.9	0.417
Misoprostol ≤ 600 mcg vs Misoprostol >600 mcg and ≤ 800 mcg	245.7	0.037
Misoprostol plus oxytocin vs Oxytocin >5 IU and ≤ 10 IU	251.4	0.061
Misoprostol plus oxytocin vs Oxytocin > 10 IU	250.3	0.074
Misoprostol plus oxytocin vs Ergometrine plus oxytocin	246.6	0.991
Misoprostol plus oxytocin vs Misoprostol ≤ 600 mcg	244.8	0.067
Ergometrine vs Oxytocin >5 IU and ≤ 10 IU	239.9	0.082
Ergometrine vs Misoprostol ≤ 600 mcg	242.8	0.054
Ergometrine vs Misoprostol >600 mcg and ≤ 800 mcg	245.7	0.508
Carboprost vs Oxytocin >1 IU and ≤ 5 IU	246.8	0.715
Carboprost vs Ergometrine plus oxytocin	245.7	0.250
NMA (no nodes split)	**246.6**	**-**

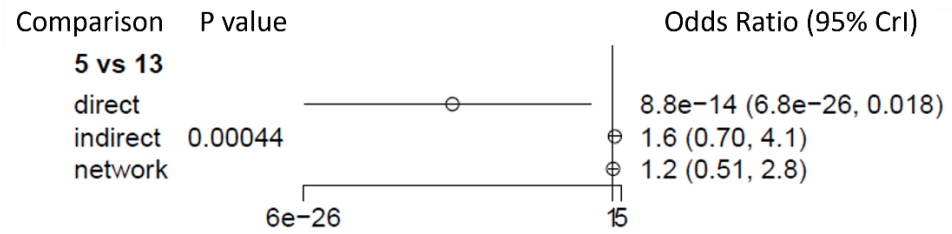

Figure 48. Treatment effect estimates separated by direct and indirect evidence: Oxytocin >5 IU and ≤ 10 IU (5) vs carboprost (13).

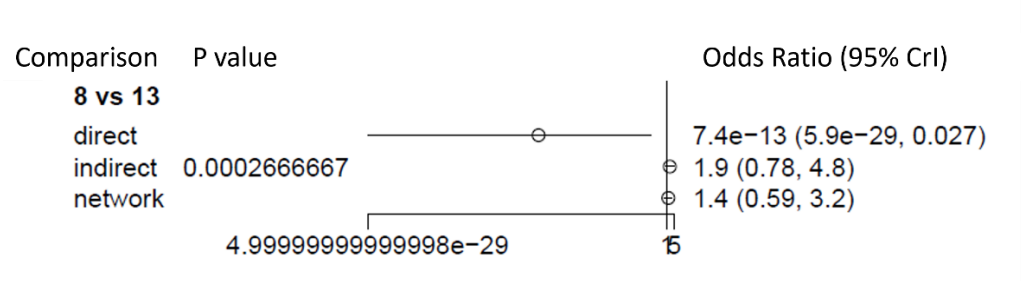

Figure 49. Treatment effect estimates separated by direct and indirect evidence: Misoprostol ≤ 600 mcg (8) vs carboprost (13).

Vaginal birth subgroup

Global inconsistency check

Analysis of the dataset for the vaginal birth subgroup for the outcome post-partum haemorrhage (>1000ml) included 71 studies (157 arms) of 13 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Fitting of both fixed and random-effect network meta-analysis (NMA) models indicated support for the random-effect model on the basis of a small decrease in DIC and a sizeable decrease in residual deviance (Table 51).

Total residual deviance and DIC were lower in the inconsistency UME model than in the NMA model and the estimate of between-study SD was the similar in the NMA and UME models (Table 51). This suggests no evidence of inconsistency, but that there is moderate heterogeneity between study estimates.

Table 51. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome PPH >1000ml, vaginal birth subgroup.

Outcome	Pop.	Model	Posterior total residual deviance[3]	Between-study SD Mean, 95% credible interval	pD	DIC[4]
PPH	VD	FE NMA	205.9	-	79.5	798.4
PPH	VD	RE NMA	190.5	0.20 (0.02, 0.45)	91.6	795.1
PPH	VD	FE UME	190.8	-	90.5	794.2
PPH	VD	RE UME	178.9	0.21 (0.02, 0.47)	100.1	791.9

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 50), shows that two studies showed inconsistency with the rest of the dataset:

- Begley, 1990
  - Compares Ergometrine (coded 12) and placebo (coded 1)
- Modi, 2014
  - Compares Oxytocin [>5 IU and ≤ 10 IU] (coded 5), Misoprostol ≤600mcg (coded 8), Ergometrine (coded 12) and Carboprost (coded 13)
  - In this four-armed trial events were rare with only two events observed, both on the carboprost arm, which likely explains the high deviance contribution for this study under the NMA model.

[3] Posterior mean residual deviance compared to 157 data points
[4] Deviance information criteria (DIC) – lower values preferred

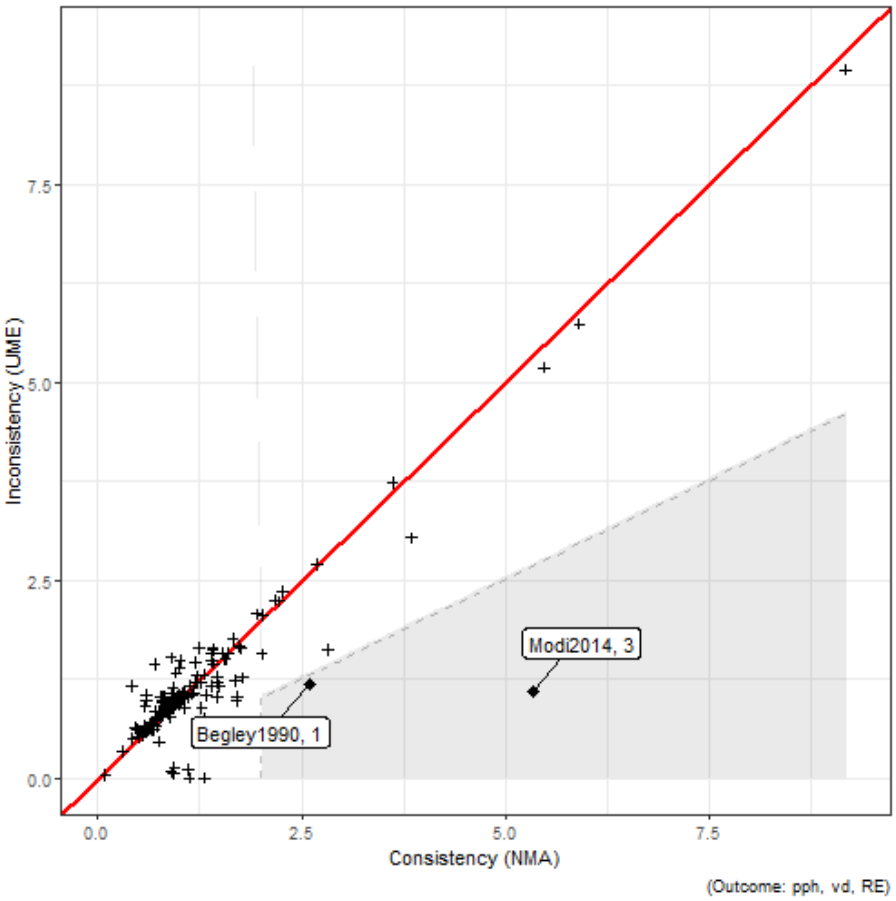

Figure 50. Dev-dev plot of each study arm's residual deviance under the consistency (NMA) and inconsistency models with RE structure for PPH >1000ml, vaginal birth subgroup. Labels indicate study arms with high deviance in the NMA model, relative to their deviance in the UME model. The dotted line and grey shaded area outline a region where study arms fit poorly in the NMA model but well in the UME model, suggesting that they are predicted poorly when the model enforces consistency in treatment differences.

Checking inconsistency within individual treatment comparisons (Node-splitting)

Node-splitting procedures indicate that direct and indirect evidence on most treatment comparisons agree. Evidence conflicted on 1 comparison following Bonferroni correction: Carboprost vs Misoprostol (<600mcg) (Table 52). The direct evidence for this comparison conflicts with indirect evidence (Figure 51), though the direct evidence is weak, being drawn from a single study (Modi 2014) in which no events were observed on 3 arms.

Table 52. Model fit statistics for node-split model (PPH >1000ml, vaginal birth subgroup). Comparisons where there is an indication of inconsistency between direct and indirect estimates (p-values <0.002 [p<0.05 following Bonferroni correction for 29 comparisons]) are highlighted in orange.

Comparison	Total Residual Deviance	p-value
CarbProst vs Mis_b600	186.4	<0.001

Plac vs Erg	189.0	0.019
Plac vs CarbProst	191.5	0.880
Erg vs CarbProst	187.4	0.004
Plac vs Oxy_a1b5	189.8	0.790
CarbProst vs Oxy_a1b5	190.2	0.997
Carb vs Oxy_a1b5	185.7	0.088
Plac vs Oxy_a5b10	191.2	0.928
Erg vs Oxy_a5b10	190.4	0.093
CarbProst vs Oxy_a5b10	189.2	0.002
Carb vs Oxy_a5b10	188.0	0.263
Mis_Oxy vs Oxy_a5b10	182.7	0.988
Mis_Oxy vs Oxy_a10	182.0	0.939
Plac vs Erg_Oxy	186.2	0.801
Oxy_a1b5 vs Erg_Oxy	188.7	0.035
Mis_Oxy vs Erg_Oxy	190.6	0.607
CarbProst vs Erg_Oxy	182.0	0.070
Carb vs Erg_Oxy	187.2	0.409
Oxy_a5b10 vs Erg_Oxy	182.3	0.539
Plac vs Mis_b600	189.0	0.528
Mis_Oxy vs Mis_b600	188.9	0.224
Erg vs Mis_b600	188.7	0.055
Oxy_a1b5 vs Mis_b600	185.9	0.410
Erg_Oxy vs Mis_b600	184.6	0.385
Oxy_a5b10 vs Mis_b600	179.1	0.872
Oxy_a10 vs Mis_b600	190.7	0.903
Erg vs Mis_a600b800	190.5	0.592
Oxy_a5b10 vs Mis_a600b800	184.0	0.280
Mis_b600 vs Mis_a600b800	190.0	0.041
NMA (no nodes split)	**190.5**	**-**

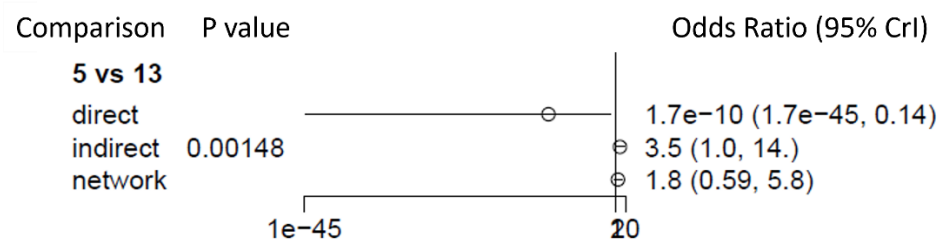

Figure 51. Treatment effect estimates separated by direct and indirect evidence: Misoprostol ≤600mcg (5) vs Carboprost (13) for the vaginal birth subgroup.

Caesarean Section birth subgroup

Global inconsistency check

Analysis of the dataset for the CS birth subgroup for the outcome post-partum haemorrhage (>1000ml) included 26 studies (53 arms) of 8 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Fitting both fixed (FE) and random-effect (RE) network meta-analysis (NMA) models gave similar values for DIC. However, residual deviance was lower by 5.3 for the RE NMA (Table 53) suggesting support for the RE model for these data.

Total residual deviance and DIC were lower in the inconsistency UME model than in the NMA model and the estimate of between-study SD was the similar in the NMA and UME models (Table 53). This suggests that there is no evidence of inconsistency, but moderate heterogeneity between study estimates.

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 52), showed no study arms to have high deviance in the NMA model, relative to their deviance in the UME model. Taken together, the model fit and dev-dev plots suggest there was little evidence of inconsistency in these data. Therefore, node-splitting models were not required.

Table 53. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome PPH >1000ml, CS birth subgroup.

Outcome	Pop.	Model	Posterior total residual deviance[5]	Between-study SD Mean, 95% credible interval	pD	DIC[6]
PPH	CS	FE NMA	61.6	-	32.6	276.6
PPH	CS	RE NMA	56.3	0.34 (0.03, 0.81)	38.1	276.9
PPH	CS	FE UME	56.7	-	36.6	275.7
PPH	CS	RE UME	55.4	0.26 (0.01, 0.79)	39.5	277.3

[5] Posterior mean residual deviance compared to 53 data points
[6] Deviance information criteria (DIC) – lower values preferred

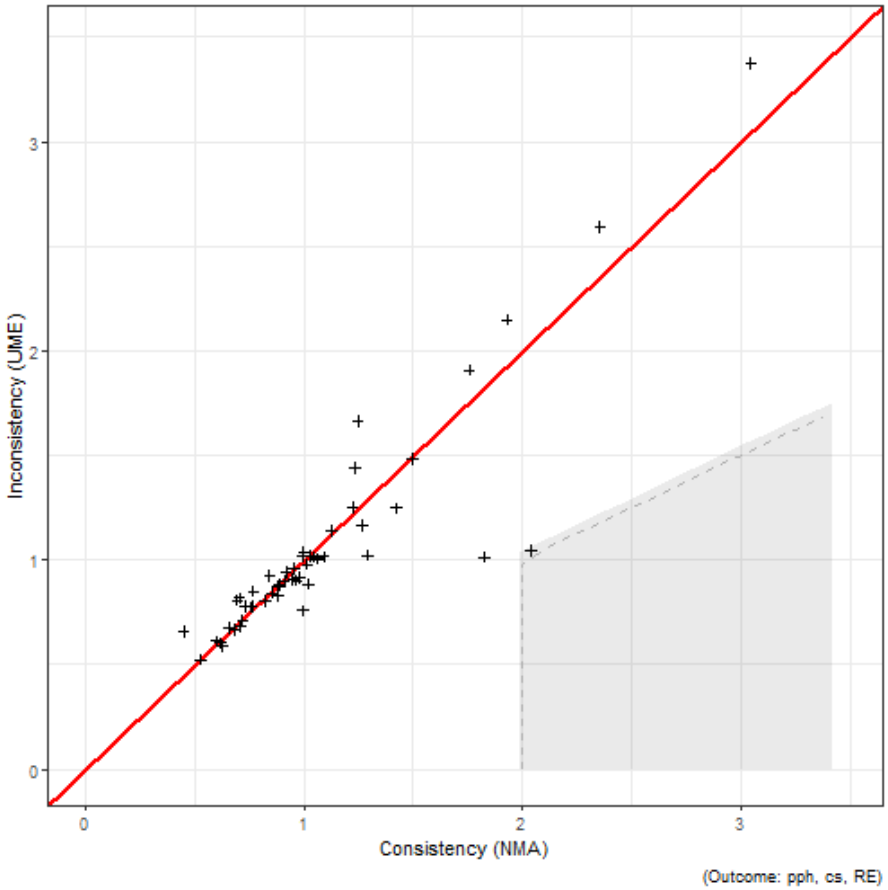

Figure 52. Dev-dev plot of each study arm's residual deviance under the consistency (NMA) and inconsistency models with RE structure for PPH >1000ml, CS birth subgroup. No study arms were identified as inconsistent (i.e. points in the shaded region).

Outcome: Additional uterotonics

Summary

We identified strong heterogeneity in study estimates for this outcome, but little evidence of inconsistency in both the full population and either of the mode-of-delivery subgroups. Estimates from two study arms, Supe 2016 (carboprost arm) and Maged 2020 (carbetocin arm), which were present in the full dataset and the vaginal birth subgroup datasets, were found to have a poor fit to the NMA model. Further investigation using node-splitting showed that although there was some evidence of inconsistency on the carboprost-carbetocin-misoprostol (>600mcg and <800mcg)-placebo loop, this was likely driven by a lack of data and hence very imprecise estimates. Global inconsistency tests detected no inconsistency in the CS birth subgroup.

Full dataset

Global inconsistency check

Analysis of the full dataset for the outcome additional uterotonics included 161 studies (345 arms) of 14 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Fitting of both fixed and random-effect network meta-analysis (NMA) models indicated strong support for the random-effect model on the basis of large reductions in DIC and residual deviance (Table 54**Error! Reference source not found.**). Between-study SD was estimated to be 0.83 (95% CrI 0.71, 0.98), which is large on the odds ratio scale. Modelling treatment differences with a random effects structure results in good model fit, with the total residual deviance equivalent to the number of study arms. Total residual deviance was slightly lower in the inconsistency UME model than in the NMA model, however DIC was lower for the NMA model and the estimate of between-study SD was similarly large in both NMA and UME models. This suggests that there is no evidence of inconsistency but there is evidence of substantial heterogeneity between study estimates.

Table 54. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome additional uterotonics, full dataset.

Outcome	Pop.	Model	Posterior total residual deviance[7]	Between-study SD Mean, 95% credible interval	pD	DIC[8]
Uterotonics	Full	FE NMA	1162.0	-	173.1	2715.7
Uterotonics	Full	RE NMA	366.5	0.83 (0.71, 0.98)	288.3	2035.7
Uterotonics	Full	FE UME	1035.0	-	198.0	2614.0
Uterotonics	Full	RE UME	360.4	0.91 (0.76, 1.08)	298.4	2039.6

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 53), shows that two studies showed inconsistency with the rest of the dataset:

- Supe 2016
    - Compares misoprostol (>600mcg and <800mcg) (coded 10), ergometrine (coded 13), carboprost (coded 14) and placebo (coded 1)

[7] Posterior mean residual deviance compared to 345 total data points
[8] Deviance information criteria (DIC) – lower values preferred

- This trial reports relatively small numbers of events on each arm (with a total of 12 events in 200 participants across all four arms)

- Maged 2020
  - Compares carbetocin (coded 2) and ergometrine plus oxytocin (coded 8)

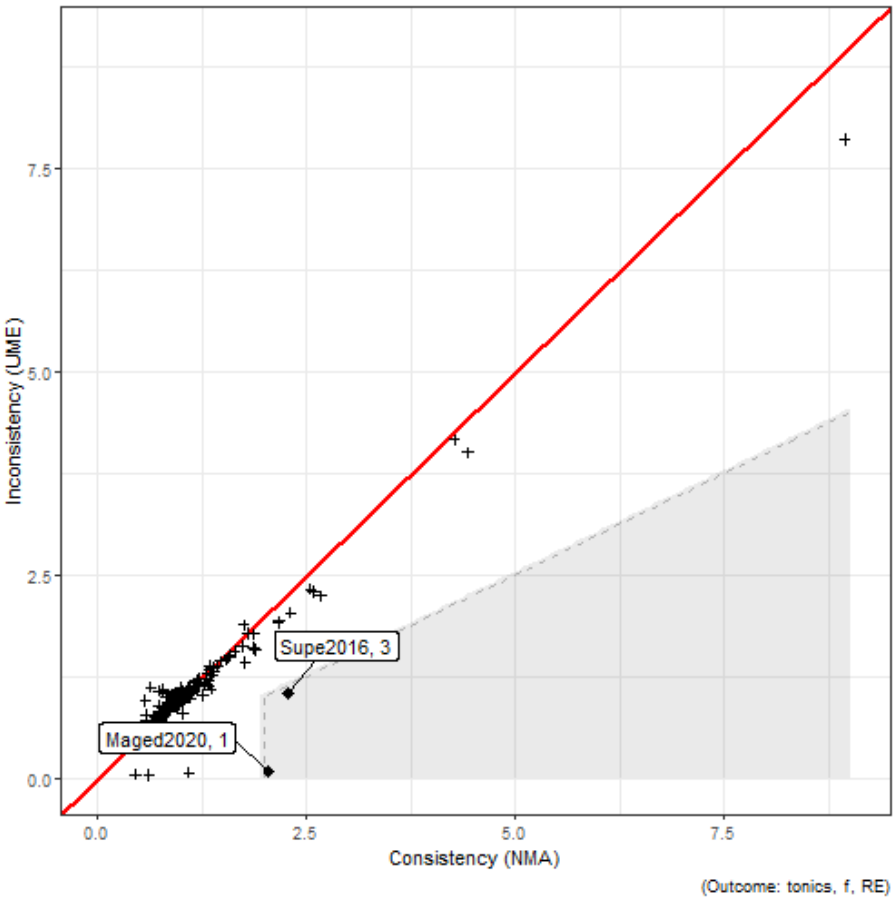

Figure 53. Dev-dev plot of each study arm's residual deviance under the standard and inconsistency models (RE model structure) for additional uterotonics, full dataset. Labels indicate study arms with high deviance in the NMA model, relative to their deviance in the UME model. The dotted line and grey shaded area denotes where study arms fit poorly in the NMA model but well in the UME model, suggesting that they are predicted poorly when the model enforces consistency in treatment differences.

Checking inconsistency within individual treatment comparisons (Node-splitting)

Node-splitting procedures indicate that direct and indirect evidence on most treatment comparisons agree. Applying a Bonferroni correction suggests that there are no comparisons where direct and indirect evidence is inconsistent, given 42 comparisons (Table 55). However, we note a p-value of 0.003 when comparing estimates from direct and indirect evidence for the comparison between misoprostol (>6000mcg and <8000mcg) and carbetocin and present the forest plot for this comparison (Figure 54), as well as for the comparison between misoprostol (>6000mcg and <8000mcg) and carboprost.

Table 55. Model fit statistics for node-split model (additional uterotonics, full dataset). No comparisons had p<0.0012 (Bonferroni correction of p <0.05 given 42 tests) when testing consistency between estimates from direct and indirect evidence.

Comparison	Total Residual Deviance	p-value
Mis_a600b800 vs Carb	365.3	0.003
Plac vs Mis_a600b800	365.8	0.831
Plac vs Erg	367.5	0.340
Plac vs CarbProst	366.6	0.271
Plac vs Carb	366.3	0.184
Plac vs Oxy_a1b5	363.1	0.758
Plac vs Oxy_a5b10	366.7	0.704
Plac vs Erg_Oxy	367.0	0.458
Plac vs Mis_b600	365.2	0.270
Mis_a600b800 vs Erg	366.7	0.955
Mis_a600b800 vs CarbProst	366.9	0.055
Mis_a600b800 vs Oxy_a1b5	366.8	0.988
Mis_a600b800 vs Oxy_a5b10	367.0	0.509
Mis_a600b800 vs Oxy_a10	366.9	0.981
Mis_a600b800 vs Mis_b600	364.1	0.720
Mis_Oxy vs Carb	366.2	0.526
Mis_Oxy vs Oxy_a1b5	366.3	0.866
Mis_Oxy vs Oxy_a5b10	366.3	0.465

Mis_Oxy vs Oxy_a10	365.1	0.323
Mis_Oxy vs Erg_Oxy	366.8	0.501
Mis_Oxy vs Mis_b600	365.2	0.793
Erg vs CarbProst	362.5	0.081
Erg vs Oxy_a1b5	366.4	0.162
Erg vs Oxy_a5b10	362.3	0.963
Erg vs Mis_b600	362.0	0.519
CarbProst vs Oxy_a1b5	364.5	0.567
CarbProst vs Oxy_a5b10	365.1	0.346
CarbProst vs Erg_Oxy	367.3	0.863
CarbProst vs Mis_b600	362.7	0.274
Carb vs Oxy_a1b5	364.7	0.422
Carb vs Oxy_a5b10	365.3	0.886
Carb vs Oxy_a10	364.1	0.643
Carb vs Erg_Oxy	365.3	0.607
Carb vs Mis_b600	364.9	0.644
Oxy_a1b5 vs Oxy_a10	365.0	0.318
Oxy_a1b5 vs Erg_Oxy	366.9	0.944
Oxy_a1b5 vs Mis_b600	364.7	0.489
Oxy_a5b10 vs Erg_Oxy	364.3	0.185
Oxy_a5b10 vs Mis_b600	360.2	0.459
Oxy_a10 vs Erg_Oxy	366.7	0.776
Oxy_a10 vs Mis_b600	364.1	0.854
Erg_Oxy vs Mis_b600	365.6	0.606
NMA (no nodes split)	366.7	**-**

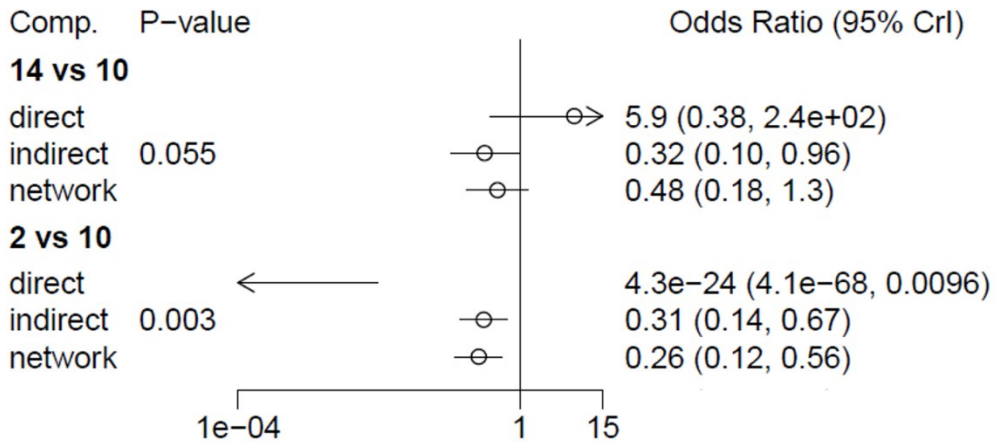

Figure 54. Treatment effect estimates separated by direct and indirect evidence for two comparisons: misoprostol (>600mcg and <800mcg) (10) vs carboprost (14) and misoprostol (>600mcg and <800mcg) (10) vs carbetocin (2).

Vaginal birth subgroup

Global inconsistency check

Analysis of the dataset for the vaginal birth subgroup for the outcome additional uterotonics included 109 studies (236 arms) of 12 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Comparing fixed and random-effect network meta-analysis (NMA) models indicated strong support for the random-effect model on the basis of large decreases in DIC and residual deviance (Table 56). Between-study SD was estimated to be large at 0.73 (95% CrI 0.58, 0.90), suggesting that there is heterogeneity in study estimates of treatment effect for the same treatment comparison. There was no reduction in DIC or between studies SD for the RE UME relative to the RE NMA, however there was an improvement in overall fit (residual deviance) for the RE UME suggesting there may be evidence of inconsistency, which we explore further below.

Table 56. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome additional uterotonics, vaginal birth subgroup.

Outcome	Pop.	Model	Posterior total residual deviance[9]	Between-study SD Mean, 95% credible interval	pD	DIC[10]
Uterotonics	VD	FE NMA	682.1	-	119.1	1768.3
Uterotonics	VD	RE NMA	254.0	0.73 (0.58, 0.90)	193.3	1414.4
Uterotonics	VD	FE UME	579.2	-	137.4	1683.8
Uterotonics	VD	RE UME	249.3	0.74 (0.57, 0.94)	198.8	1415.3

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 55), shows that two studies showed inconsistency with the rest of the dataset:

- Supe 2016
    - Compares misoprostol a600b800 (coded 10), ergometrine (coded 13), carboprost (coded 14) and placebo (coded 1), with the carboprost arm specifically labelled as being inconsistent by residual deviance

[9] Posterior mean residual deviance compared to 236 data points
[10] Deviance information criteria (DIC) – lower values preferred

- This trial reports small numbers of events on each arm (12 events in 200 participants)

- Maged 2020
  - Compares carbetocin (coded 2) and ergometrine plus oxytocin (coded 8), with the carbetocin arm specifically labelled as being inconsistent by residual deviance

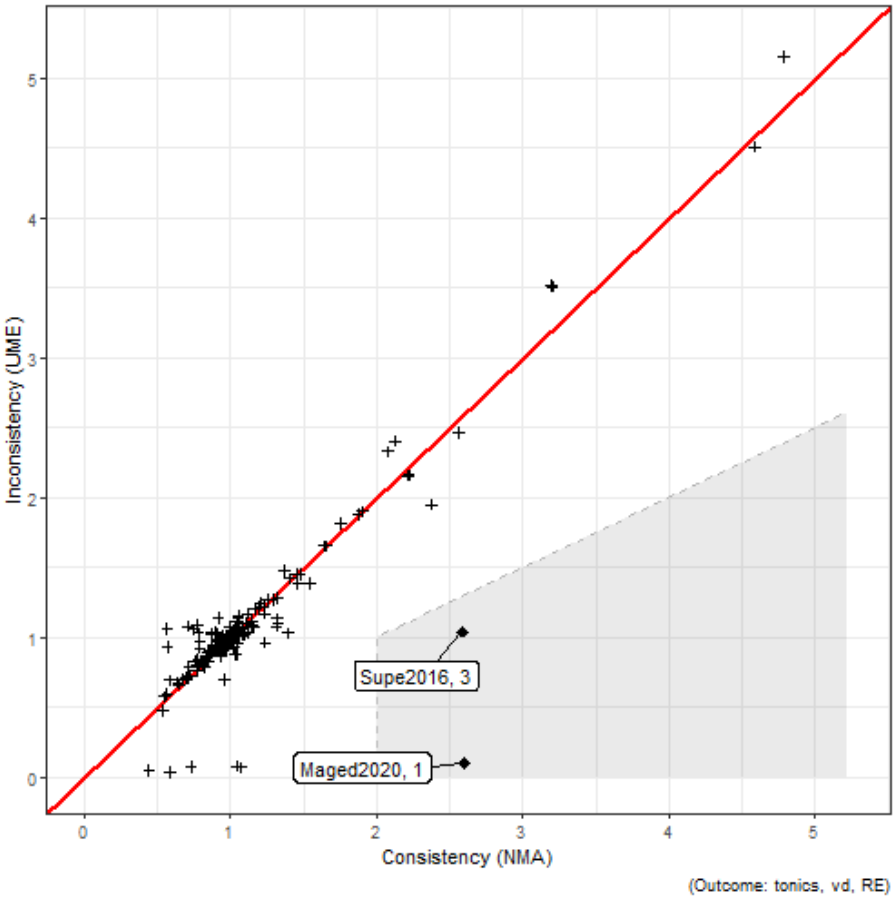

Figure 55. Dev-dev plot of each study arm's residual deviance under the consistency (NMA) and inconsistency models with RE structure for additional uterotonics, vaginal birth subgroup. Labels indicate study arms with high deviance in the NMA model, relative to their deviance in the UME model. The dotted line and grey shaded area outline a region where study arms fit poorly in the NMA model but well in the UME model, suggesting that they are predicted poorly when the model enforces consistency in treatment differences.

Checking inconsistency within individual treatment comparisons (Node-splitting)

Node-splitting procedures indicate that direct and indirect evidence on most treatment comparisons agree. Applying a Bonferroni correction suggests that there are no comparisons where direct and indirect evidence is inconsistent, given 36 comparisons (Table 57). We note some small p-values, e.g. for the comparison between misoprostol (>6000mcg and <8000mcg) and carbetocin and between oxytocin (<10) and ergometrine with oxytocin. We present the forest plot for these comparisons (Figure 56) but the inconsistency is likely to be the result of weak evidence meaning that effect estimates are imprecisely estimated for these comparisons (as can be seen in the credible intervals).

Table 57. Model fit statistics for node-split model (additional uterotonics, vaginal birth subgroup). No comparisons had p<0.0014 (Bonferroni correction of p <0.05 given 36 tests) when testing consistency between direct and indirect evidence.

Comparison	Total Residual Deviance	p-value
Carb vs Mis_a600b800	252.1	0.003
Plac vs Erg	254.8	0.157
Plac vs CarbProst	253.1	0.263
Plac vs Oxy_a1b5	252.4	0.667
Plac vs Oxy_a5b10	253.5	0.745
Plac vs Erg_Oxy	254.4	0.235
Plac vs Mis_b600	252.9	0.353
Plac vs Mis_a600b800	253.0	0.988
Mis_Oxy vs Oxy_a5b10	252.8	0.110
Mis_Oxy vs Oxy_a10	253.4	0.140
Mis_Oxy vs Erg_Oxy	253.6	0.707
Mis_Oxy vs Mis_b600	253.0	0.644
Erg vs CarbProst	249.2	0.046
Erg vs Oxy_a1b5	253.1	0.069
Erg vs Oxy_a5b10	248.6	0.673
Erg vs Mis_b600	249.0	0.553
Erg vs Mis_a600b800	253.2	0.996
CarbProst vs Oxy_a1b5	251.0	0.472
CarbProst vs Oxy_a5b10	252.0	0.211

CarbProst vs Erg_Oxy	254.5	0.819
CarbProst vs Mis_b600	249.5	0.219
CarbProst vs Mis_a600b800	253.6	0.041
Carb vs Oxy_a1b5	254.0	0.714
Carb vs Oxy_a5b10	252.9	0.270
Carb vs Oxy_a10	253.5	0.036
Carb vs Erg_Oxy	251.9	0.774
Carb vs Mis_b600	253.5	0.588
Oxy_a1b5 vs Mis_b600	252.6	0.698
Oxy_a1b5 vs Mis_a600b800	254.2	0.738
Oxy_a5b10 vs Erg_Oxy	250.5	0.217
Oxy_a5b10 vs Mis_b600	247.3	0.788
Oxy_a5b10 vs Mis_a600b800	254.2	0.306
Oxy_a10 vs Erg_Oxy	253.1	0.018
Oxy_a10 vs Mis_b600	254.2	0.483
Erg_Oxy vs Mis_b600	252.7	0.588
Mis_b600 vs Mis_a600b800	251.2	0.648
NMA (no nodes split)	**253.6**	**-**

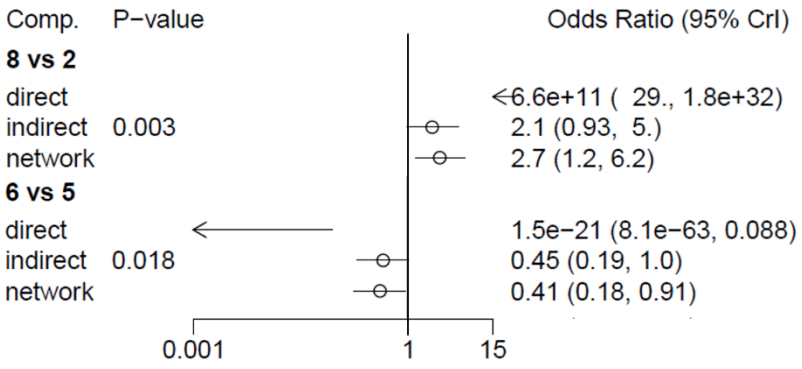

Figure 56. Treatment effect estimates separated by direct and indirect evidence for two comparisons in the vaginal birth subgroup: Misoprostol (>600mcg and < 800mcg) (8) vs Carbetocin (2) and Oxytocin (<10) (5) vs Ergometrine plus Oxytocin (6).

Caesarean Section birth subgroup

Global inconsistency check

Analysis of the dataset for the CS birth subgroup for the outcome additional uterotonics included 51 studies (107 arms) of 12 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Fitting of both fixed (FE) and random-effect (RE) network meta-analysis (NMA) models indicated strong support for the random-effect model on the basis of large reductions in DIC and residual deviance (Table 57). There was no reduction in DIC when the RE UME model was fitted, relative to the RE NMA, suggesting that direct and indirect evidence is consistent.

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 57), showed no study arms to have high deviance in the NMA model, relative to their deviance in the UME model. Taken together, the model fit and dev-dev plots suggest there is no evidence of inconsistency, and so node-splitting models were not required.

Table 58. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome additional uterotonics, CS birth subgroup.

Outcome	Pop.	Model	Posterior total residual deviance[11]	Between-study SD Mean, 95% credible interval	pD	DIC[12]
Uterotonics	CS	FE NMA	315.7	-	60.9	788.3
Uterotonics	CS	RE NMA	111.5	1.03 (0.76, 1.39)	94.7	617.9
Uterotonics	CS	FE UME	305.8	-	70.9	788.3
Uterotonics	CS	RE UME	110.8	1.20 (0.85, 1.68)	98.0	620.6

[11] Posterior mean residual deviance compared to 107 data points
[12] Deviance information criteria (DIC) – lower values preferred

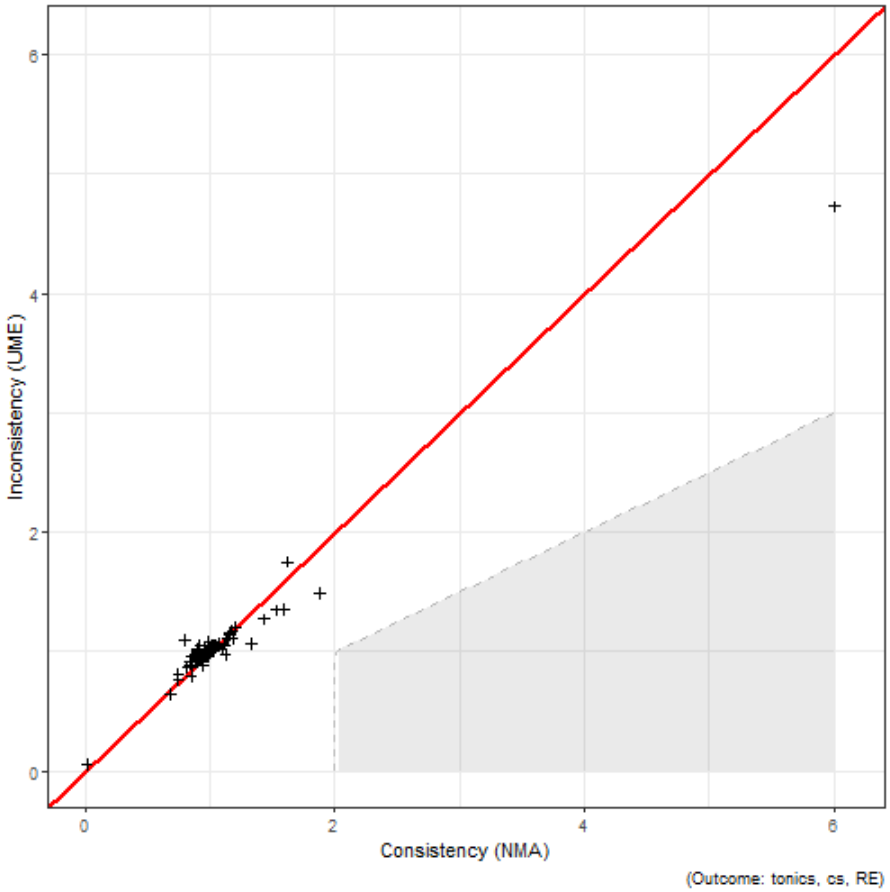

Figure 57. Dev-dev plot of each study arm's residual deviance under the consistency (NMA) and inconsistency models with RE structure for additional uterotonics, CS birth subgroup. No study arms were identified as inconsistent (i.e. there were no points in the shaded region).

Outcome: Blood transfusion

Summary

We identified strong heterogeneity in studies of this outcome that was adequately captured by the random-effects network meta-analysis. There was little evidence of inconsistency between direct and indirect evidence in the full population or either of the mode-of-delivery subgroups. One study in the full dataset (Modi et al. 2014) showed moderate inconsistency on the carboprost arm with indirect evidence from the network. Node-splitting of the full dataset suggests that there may be the potential for inconsistency on the oxytocin (10IU)-misoprostol (>600mcg and <800mcg)-placebo loop. However, this is likely to be the result of weak direct evidence: transfusion being a rare event in this population. Global inconsistency checks support that node-splitting models were not required for the vaginal birth and CS birth subgroups.

Full dataset

Global inconsistency check

Analysis of the full dataset for the outcome Transfusion included 113 studies (242 arms) of 13 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Fitting of both fixed and random-effect network meta-analysis (NMA) models indicated strong support for the random-effect model on the basis of large reductions in DIC and residual deviance (Table 59**Error! Reference source not found.**). Between-study SD was estimated to be 0.74 (95% credible interval [CrI] 0.51, 1.02), which is large on the odds ratio scale. Modelling treatment differences with a random effects structure results in good model fit, with the total residual deviance equivalent to the number of study arms. Total residual deviance was slightly lower in the inconsistency UME model than in the NMA model, however DIC was lower for the NMA model and the estimate of between-study SD was similarly large in both NMA and UME models. This suggests that there is evidence of substantial heterogeneity between study estimates, but no evidence of inconsistency.

Table 59. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome Transfusion, full dataset.

Outcome	Pop.	Model	Posterior total residual deviance[13]	Between-study SD Mean, 95% credible interval	pD	DIC[14]
Transfusion	Full	FE NMA	381.5	-	120.0	1142.9
Transfusion	Full	RE NMA	270.1	0.74 (0.51, 1.02)	163.1	1074.6
Transfusion	Full	FE UME	344.7	-	138.8	1124.9
Transfusion	Full	RE UME	268.1	0.75 (0.45, 1.11)	172.5	1082.0

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 58), shows that one study showed inconsistency with the rest of the dataset: Modi 2014. Modi 2014 compares oxytocin [>5 IU and ≤ 10 IU] (coded 4), misoprostol ≤600mcg (coded 8), ergometrine (coded 12) and carboprost (coded 13). In this four-armed trial events were rare with only two events observed, both on the carboprost arm, which likely explains the high deviance contribution for this study under the NMA model.

[13] Posterior mean residual deviance compared to 242 total data points
[14] Deviance information criteria (DIC) – lower values preferred

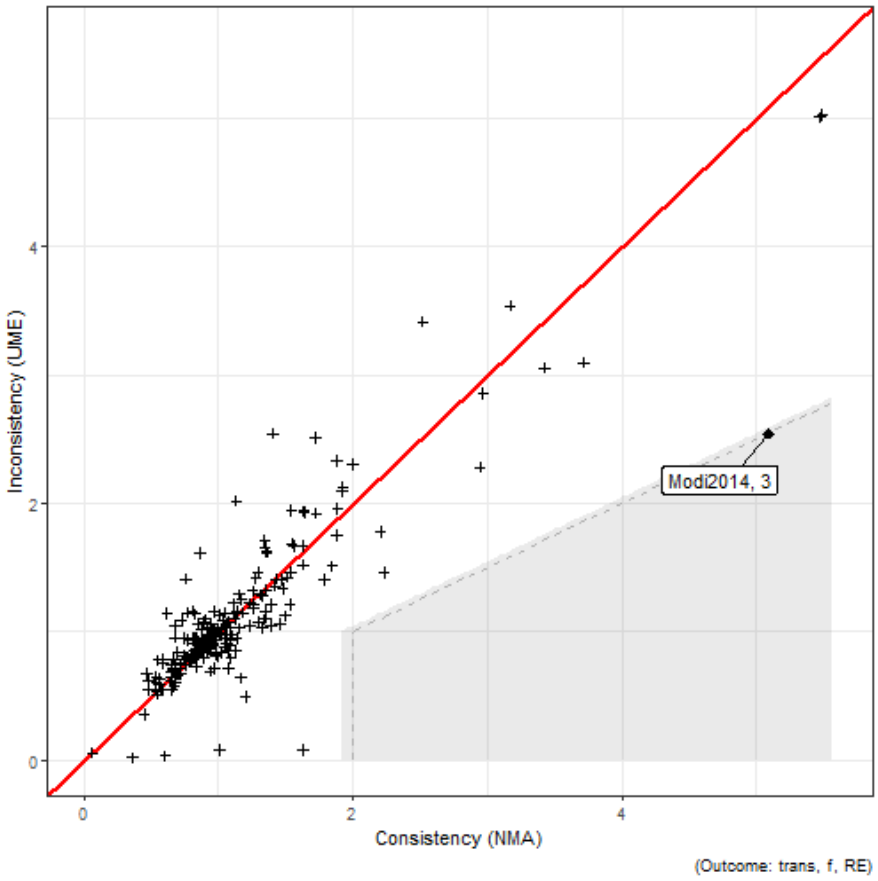

Figure 58. Dev-dev plot of each study arm's residual deviance under the standard and inconsistency models (RE model structure) for Transfusion, full dataset. Labels indicate study arms with high deviance in the NMA model, relative to their deviance in the UME model. The dotted line and grey shaded area denotes where study arms fit poorly in the NMA model but well in the UME model, suggesting that they are predicted poorly when the model enforces consistency in treatment differences.

Checking inconsistency within individual treatment comparisons (Node-splitting)

Node-splitting procedures indicate that direct and indirect evidence on most treatment comparisons agree. Applying a Bonferroni correction suggests that there are no comparisons where direct and indirect evidence is inconsistent, given 42 comparisons (Table 60). However, we note small p-values arising from comparisons of direct and indirect evidence for the treatment effect estimates between misoprostol (>6000mcg and <8000mcg) and placebo, misoprostol (>6000mcg and <8000mcg) and oxytocin (<10IU) and ergometrine and oxytocin (>1IU and <5IU). These are the result of very imprecise estimates from the direct evidence: for example, although misoprostol (>6000mcg and <8000mcg) was used in seven studies, there were either zero or only one person transfused in six of these.

Table 60. Model fit statistics for node-split model (Transfusion, full dataset). No comparisons where were indicated to show inconsistency between direct and indirect estimates (p-values <0.0014 [p<0.05 following Bonferroni correction for 35 comparisons]).

Comparison	Total Residual Deviance	p-value
Erg vs Oxy_a1b5	266.5	0.003
Oxy_a10 vs Mis_a600b800	267.8	0.008
Plac vs Mis_a600b800	267.7	0.018
Plac vs Erg	270.3	0.430
Plac vs Oxy_a1b5	269.0	0.390
Plac vs Oxy_a5b10	269.9	0.671
Plac vs Erg_Oxy	270.1	0.620
Plac vs Mis_b600	268.3	0.520
Mis_Oxy vs Carb	270.6	0.245
Mis_Oxy vs Oxy_a1b5	269.3	0.716
Mis_Oxy vs Oxy_a5b10	273.2	0.042
Mis_Oxy vs Oxy_a10	275.3	0.062
Mis_Oxy vs Erg_Oxy	270.2	0.648
Mis_Oxy vs Mis_b600	268.7	0.552
Erg vs CarbProst	263.1	0.245
Erg vs Oxy_a5b10	266.4	0.468
Erg vs Mis_b600	265.5	0.283
Erg vs Mis_a600b800	268.7	0.743
CarbProst vs Oxy_a5b10	266.0	0.304
CarbProst vs Erg_Oxy	270.2	0.986
CarbProst vs Mis_b600	264.8	0.302
Carb vs Oxy_a1b5	269.2	0.559
Carb vs Oxy_a5b10	265.9	0.627
Carb vs Oxy_a10	271.3	0.508
Carb vs Erg_Oxy	266.7	0.109
Carb vs Mis_b600	269.1	0.838

Oxy_a1b5 vs Mis_b600	262.0	0.511
Oxy_a1b5 vs Mis_a600b800	270.8	0.252
Oxy_a5b10 vs Erg_Oxy	265.4	0.282
Oxy_a5b10 vs Mis_b600	264.3	0.110
Oxy_a5b10 vs Mis_a600b800	271.0	0.235
Oxy_a10 vs Erg_Oxy	270.4	0.546
Oxy_a10 vs Mis_b600	269.7	0.700
Erg_Oxy vs Mis_b600	266.7	0.787
Mis_b600 vs Mis_a600b800	267.5	0.246
NMA (no nodes split)	**270.4**	**-**

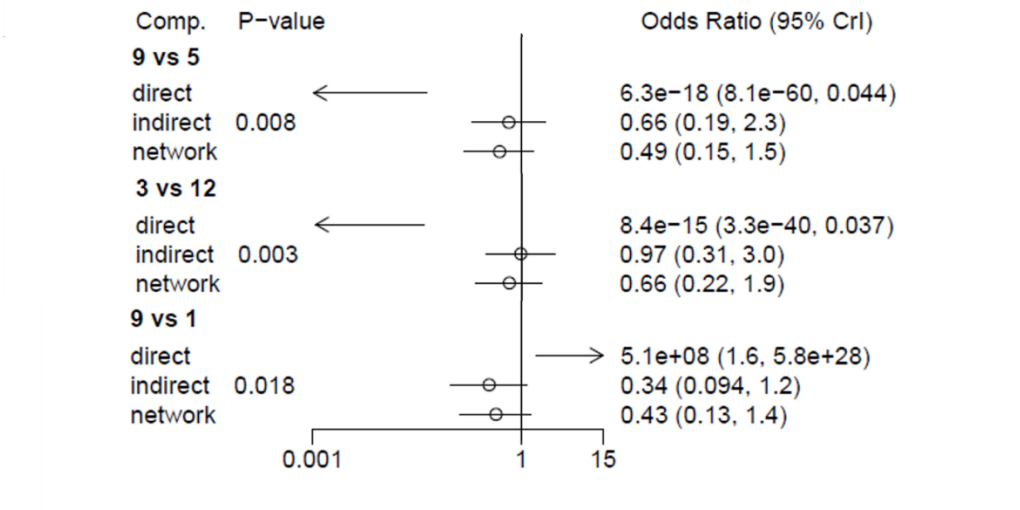

Figure 59. Treatment effect estimates separated by direct and indirect evidence for three comparisons: misoprostol (>600mcg and <800mcg) (9) vs oxytocin (5); oxytocin (>1IU and <5IU) (3) vs ergometrine (12) and misoprostol (>600mcg and <800mcg) (9) vs placebo (1)

Vaginal birth subgroup

Global inconsistency check

Analysis of the dataset for the vaginal birth subgroup for the outcome transfusion included 80 studies (175 arms) of 12 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Fitting of both fixed and random-effect network meta-analysis (NMA) models indicated strong support for the random-effect model on the basis of large decreases in DIC and residual deviance (Table 61). Between-study SD was estimated to be large at 0.53 (95% CrI 0.25, 0.84), suggesting that there is heterogeneity in studies' estimates of treatment effect for the same treatment comparison. There was no reduction in DIC when the RE UME model was fitted, relative to the RE NMA, suggesting no evidence of inconsistency.

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 60), showed no study arms to have high deviance in the NMA model, relative to their deviance in the UME model. Taken together, the model fit and dev-dev plots suggest there was little evidence of inconsistency so node-splitting models were not required.

Table 61. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome Transfusion, vaginal birth subgroup.

Outcome	Pop.	Model	Posterior total residual deviance[15]	Between-study SD Mean, 95% credible interval	pD	DIC[16]
Transfusion	VD	FE NMA	243.9	-	86.9	803.0
Transfusion	VD	RE NMA	200.4	0.53 (0.25, 0.84)	110.7	782.7
Transfusion	VD	FE UME	228	-	102.8	803.0
Transfusion	VD	RE UME	196.5	0.54 (0.21, 0.93)	121.1	789.7

[15] Posterior mean residual deviance compared to 175 data points
[16] Deviance information criteria (DIC) – lower values preferred

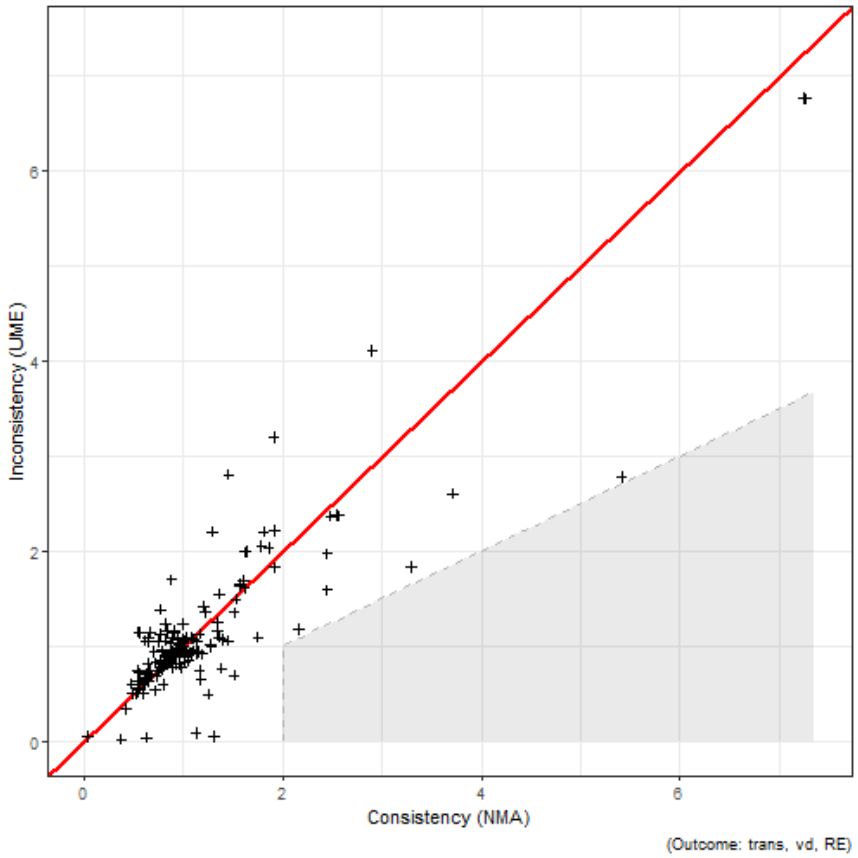

Figure 60. Dev-dev plot of each study arm's residual deviance under the consistency (NMA) and inconsistency models with RE structure for Transfusion, vaginal birth subgroup. No study arms had high deviance in the NMA model, relative to their deviance in the UME model.

Caesarean Section birth subgroup

Global inconsistency check

Analysis of the dataset for the CS birth subgroup for the outcome transfusion included 32 studies (65 arms) of 9 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Fitting of both fixed (FE) and random-effect (RE) network meta-analysis (NMA) models indicated strong support for the random-effects model on the basis of a large reduction in residual deviance and a moderate reduction in DIC (Table 62). There was no reduction in DIC when the RE UME model was fitted, relative to the RE NMA, suggesting that direct and indirect evidence is consistent.

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 61), showed no study arms to have high deviance in the NMA model, relative to their deviance in the UME model. Taken together, the model fit and dev-dev plots suggest there was little evidence of inconsistency so node-splitting models were not required.

Table 62. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome Transfusion, CS birth subgroup.

Outcome	Pop.	Model	Posterior total residual deviance[17]	Between-study SD Mean, 95% credible interval	pD	DIC[18]
Transfusion	CS	FE NMA	94.73	-	37.9	299.0
Transfusion	CS	RE NMA	67.95	1.11 (0.45, 1.99)	49.6	283.9
Transfusion	CS	FE UME	90.01	-	42.4	298.8
Transfusion	CS	RE UME	67.59	1.50 (0.48, 3.09)	52.8	286.8

[17] Posterior mean residual deviance compared to 65 data points
[18] Deviance information criteria (DIC) – lower values preferred

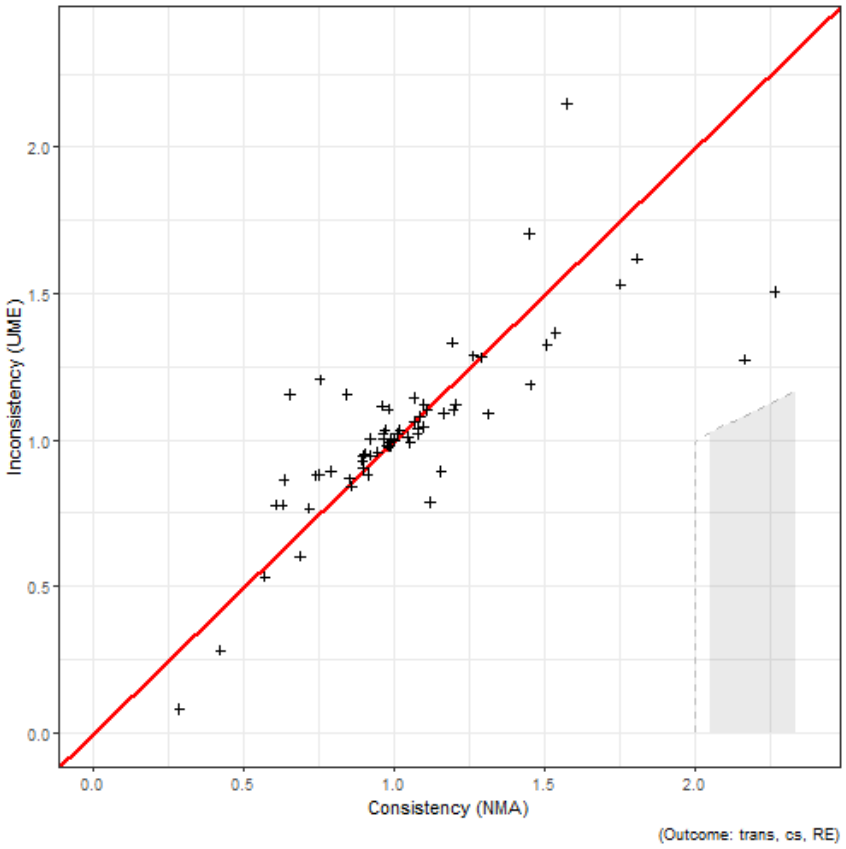

Figure 61. Dev-dev plot of each study arm's residual deviance under the consistency (NMA) and inconsistency models with RE structure for Transfusion, CS birth subgroup. No study arms were identified as inconsistent (i.e. there were no points in the shaded region).

Outcome: ICU admission

Summary

ICU admission was a rare event in these datasets and network meta-analysis (NMA) was possible for only the full and vaginal birth subgroups. Only one treatment comparison was informed by more than one study, providing insufficient evidence to inform a random-effects model structure.

There was only one loop of evidence within the full dataset and vaginal birth subgroup networks, and no evidence of inconsistency was identified within these datasets.

Full dataset

Global inconsistency check

Analysis of the full dataset for the outcome ICU admission included 9 studies (18 arms) of 8 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Fitting both fixed (FE) and random-effect (RE) NMA models indicated that the FE model structure was sufficient for the full dataset, with residual deviance of 17.2 (Table 63), approximately equivalent to the number of study arms (18).

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the fixed effects UME and NMA models (Figure 62), showed no study arms to have high deviance in the NMA model, relative to their deviance in the UME model. Taken together, the model fit, small number of studies on the loop of evidence, and dev-dev plots suggest there was little evidence of inconsistency; therefore, node-splitting models were not required.

Table 63. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome ICU admission, full dataset.

Outcome	Pop.	Model	Posterior total residual deviance[19]	Between-study SD Mean, 95% credible interval	pD	DIC[20]
ICU admission	Full	FE NMA	17.2	-	12.3	72.9
ICU admission	Full	RE NMA	16.3	1.87 (0.06, 4.75)	13.7	73.4
ICU admission	Full	FE UME	14.8	-	12.5	70.6
ICU admission	Full	RE UME	15.1	1.62 (0.04, 4.66)	13.2	71.6

[19] Posterior mean residual deviance compared to 18 total data points
[20] Deviance information criteria (DIC) – lower values preferred

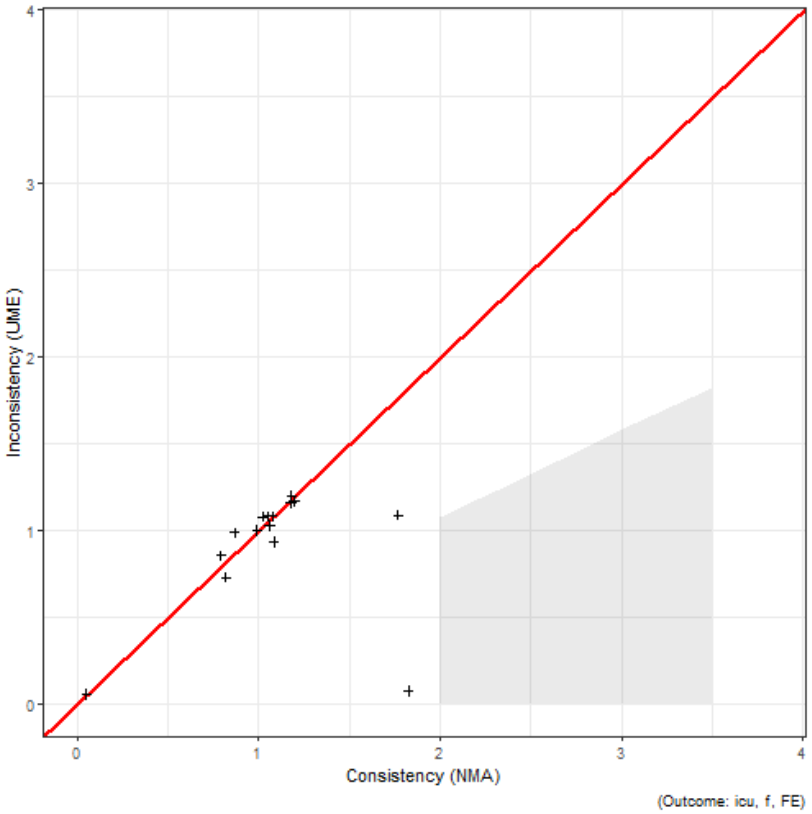

Figure 62. Dev-dev plot of each study arm's residual deviance under the standard and inconsistency models (FE model structure) for ICU admission, full dataset. No study arms had high deviance in the NMA model, relative to their deviance in the UME model.

Vaginal birth subgroup

Global inconsistency check

Analysis of the dataset for the vaginal birth subgroup for the outcome ICU admission included 8 studies (16 arms) of 7 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Fitting both fixed (FE) and random-effect (RE) NMA models indicated that the FE model structure was sufficient for the full dataset, with residual deviance of 16.0 (Table 64), equivalent to the 16 study arms.

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the fixed effects UME and NMA models (Figure 63), showed no study arms to have high deviance in the NMA model, relative to their deviance in the UME model. Taken together, the model fit, small number of studies on the loop of evidence, and dev-dev plots suggest there was little evidence of inconsistency; therefore, node-splitting models were not required.

Table 64. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome ICU admission, vaginal birth subgroup.

Outcome	Pop.	Model	Posterior total residual deviance[21]	Between-study SD Mean, 95% credible interval	pD	DIC[22]
ICU admission	VD	FE NMA	16.0	-	11.4	68.7
ICU admission	VD	RE NMA	15.0	1.83 (0.06, 4.72)	12.7	69.0
ICU admission	VD	FE UME	13.5	-	11.6	66.4
ICU admission	VD	RE UME	13.9	1.64 (0.04, 4.67)	12.3	67.5

[21] Posterior mean residual deviance compared to 16 data points
[22] Deviance information criteria (DIC) – lower values preferred

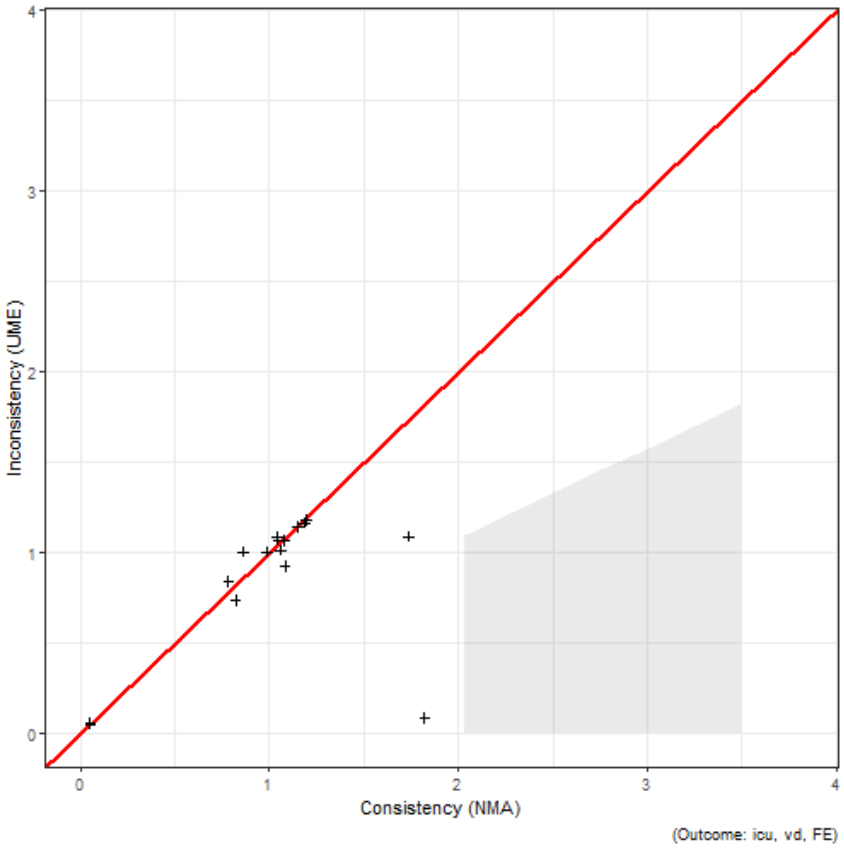

Figure 63. Dev-dev plot of each study arm's residual deviance under the consistency (NMA) and inconsistency models with FE structure for ICU admission, vaginal birth subgroup. No study arms had high deviance in the NMA model, relative to their deviance in the UME model.

Outcome: Mean blood loss

Summary

We identified moderate heterogeneity in both full and mode-of-delivery subgroup datasets for this outcome, but little evidence of inconsistency. Mean blood loss was analysed with treatment effects estimated on the log scale, with the effect of treatment assumed to be proportional rather than additive.

The only indicated inconsistency was connected to the estimate for the treatment effect of ergometrine (coded 13) relative to Oxytocin [>5 IU and ≤ 10 IU] (coded 5) from the study Modi 2014. Arm 3 from Modi 2014, which included carboprost, also showed relatively high residual deviance within the dataset. However, residual deviance for this arm was more similar between NMA and UME models, suggesting heterogeneity between study estimates for this treatment comparison rather than inconsistency.

Node-splitting models indicated potential inconsistency between direct and indirect evidence in the estimation of treatment differences between misoprostol plus oxytocin and oxytocin (>10IU) in the full dataset, and misoprostol (≤600mcg) and oxytocin (>10IU) in the vaginal delivery subgroup. While seven studies in the full dataset inform the comparison between oxytocin (>10IU) and misoprostol (≤600mcg) and nine inform the comparison between oxytocin (>10IU) and misoprostol plus oxytocin, only one study (Caliskan et al. 2003) informs

the comparison between misoprostol plus oxytocin and misoprostol (≤600mcg). This suggests that this loop of evidence (misoprostol (≤600mcg) – oxytocin (>10IU) – misoprostol plus oxytocin) contains inconsistency and we would suggest that Caliskan et al. 2003 is examined to ensure that there are no sources of potential inconsistency.

Full dataset

Global inconsistency check
Analysis of the full dataset for the outcome mean blood loss included 156 studies (332 arms) of 14 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Comparing fixed (FE) and random-effect (RE) network meta-analysis (NMA) models indicated support for the random-effect model on the basis of large decreases in DIC and residual deviance (Table 65).

Total residual deviance was lower in the inconsistency UME model than in the NMA model; however, DIC was lower for the NMA model and the estimate of between-study SD was similar in the NMA and UME models (Table 65). This suggests that there is little evidence of inconsistency but moderate heterogeneity between study estimates.

Table 65. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome Blood loss, full dataset.

Outcome	Pop.	Model	Posterior total residual deviance[23]	Between-study SD Mean, 95% credible interval	pD	DIC[24]
PPH	Full	FE NMA	5125.0	-	168.8	7526.2
PPH	Full	RE NMA	336.1	0.24 (0.23, 0.27)	314.4	2883.0
PPH	Full	FE UME	3533.0	-	199.4	5965.4
PPH	Full	RE UME	334.2	0.23 (0.20, 0.26)	317.4	2884.0

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 64), shows that one study arm showed inconsistency with the rest of the dataset. The point on the border of the shaded area is the third arm from the same study:

- Modi, 2014

[23] Posterior mean residual deviance compared to 332 total data points
[24] Deviance information criteria (DIC) – lower values preferred

- Compares Oxytocin [>5 IU and ≤ 10 IU] (coded 5), Misoprostol ≤600mcg (coded 9), Ergometrine (coded 13) and Carboprost (coded 14)

However, residual deviance is relatively low even for this study arm. Taken together, the model fit and dev-dev plots suggest there was little evidence of inconsistency in these data. Node-splitting models for the loop of evidence informed by Modi et al. 2014 were run in WinBUGS.

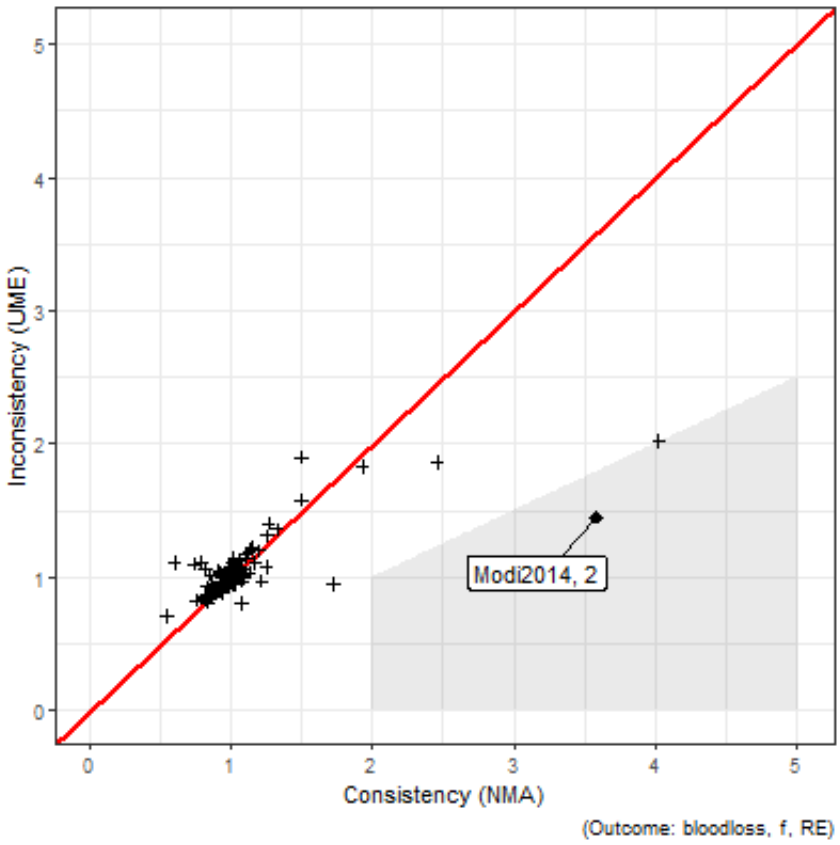

Figure 64. Dev-dev plot of each study arm's residual deviance under the standard and inconsistency models (RE model structure) for Blood loss, full dataset. Labels indicate study arms with high deviance in the NMA model, relative to their deviance in the UME model. The dotted line and grey shaded area denotes where study arms fit poorly in the NMA model but well in the UME model, suggesting that they are predicted poorly when the model enforces consistency in treatment differences.

Checking inconsistency within individual treatment comparisons (Node-splitting)

Node-splitting procedures indicated no evidence of a difference between direct and indirect evidence on most treatment comparisons. Evidence conflicted on a single comparison, for oxytocin (> 10IU) vs misoprostol with oxytocin (Table 66). A forest plot is presented for this comparison (Figure 65).

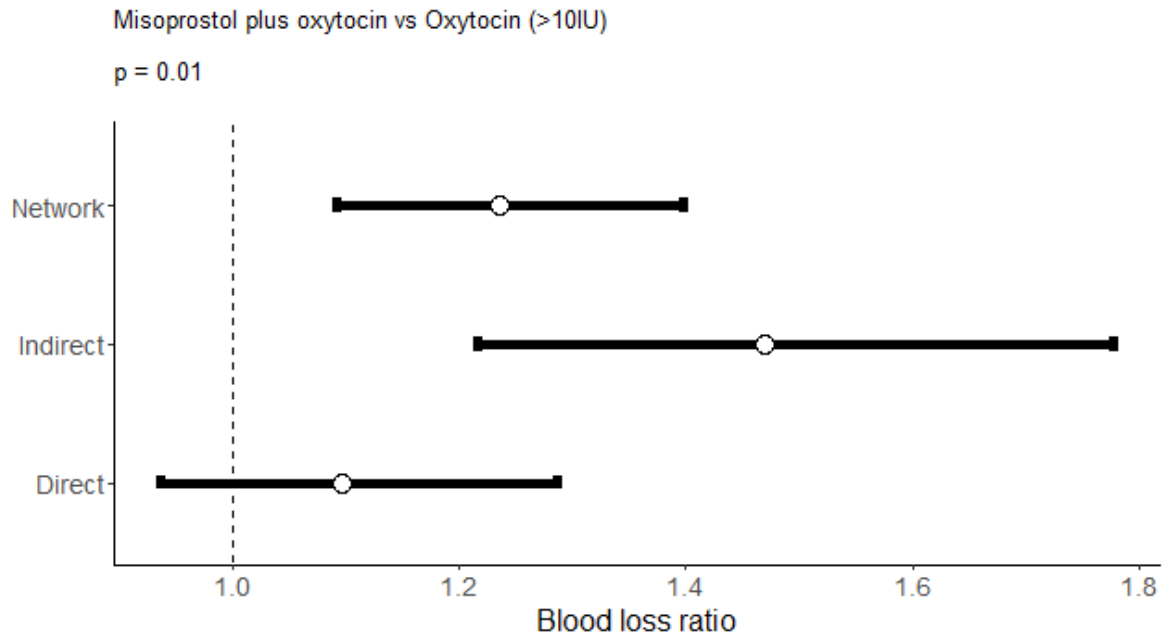

Figure 65. Treatment difference of misoprostol plus oxytocin vs oxytocin on outcome mean blood loss, full dataset, as estimated from the full network, indirect evidence only and direct evidence only. Ratios greater than 1 indicate that blood loss was greater in the misoprostol plus oxytocin group.

Table 66. Estimates of treatment effect from direct and indirect evidence from node-splitting models, full dataset. 'Comparison' indicates the pair of nodes for which evidence was split into direct and indirect evidence. Direct and indirect estimates are log blood loss ratios, where zero indicates no difference in blood loss between treatment groups.

Comparison	Total residual deviance	pD	DIC	Direct	Indirect	p value	Between-study SD
Oxy_a10 vs Mis_Oxy	**343.1**	**317.0**	**2893**	**0.09 (-0.06, 0.25)**	**0.38 (0.20, 0.58)**	**0.01**	**0.23 (0.20, 0.26)**
Carb vs Placebo	486.5	295.8	3015	-0.48 (-1.27, 0.20)	-0.39 (-0.54, -0.23)	0.42	0.26 (0.21, 0.27)
Oxy_b1 vs Placebo	341.8	317.1	2891	0.01 (-0.46, 0.47)	-0.21 (-0.86, 0.39)	0.70	0.24 (0.21, 0.27)
Oxy_a1b5 vs Placebo	377.8	345.8	2956	-0.19 (-0.41, 0.01)	-0.17 (-0.35, 0.02)	0.43	0.24 (0.21, 0.27)
Oxy_a5b10 vs Placebo	341.1	316.1	2890	-0.25 (-0.58, 0.09)	-0.18 (-0.32, -0.05)	0.37	0.24 (0.21, 0.27)
Erg_Oxy vs Placebo	342.3	315.5	2890	-0.11 (-0.45, 0.23)	-0.29 (-0.44, -0.14)	0.82	0.24 (0.21, 0.27)
Mis_b600 vs Placebo	347.0	318.7	2898	-0.19 (-0.35, -0.02)	-0.21 (-0.37, -0.06)	0.58	0.24 (0.21, 0.27)
Mis_a600b800 vs Placebo	531.0	430.0	3193	-0.31 (-0.79, 0.18)	-0.19 (-0.40, 0.02)	0.33	0.25 (0.21, 0.27)
Erg vs Placebo	1074	605.5	3912	-0.28 (-0.63, 0.07)	-0.12 (-0.28, 0.03)	0.21	0.24 (0.22, 0.28)
CarbProst vs Placebo	432.5	348.0	3013	-0.21 (-0.56, 0.14)	-0.40 (-0.59, -0.21)	0.83	0.24 (0.21, 0.27)
Oxy_a1b5 vs Carb	337.1	314.5	2884	0.13 (-0.07, 0.34)	0.23 (0.06, 0.40)	0.23	0.24 (0.21, 0.27)
Oxy_a5b10 vs Carb	339.8	317.7	2890	0.16 (0.01, 0.32)	0.20 (0.06, 0.34)	0.35	0.24 (0.21, 0.27)
Oxy_a10 vs Carb	537.2	416.8	3186	0.25 (0.05, 0.45)	0.21 (0.05, 0.37)	0.62	0.24 (0.21, 0.27)
Erg_Oxy vs Carb	358.9	321.1	2912	0.12 (-0.07, 0.32)	0.12 (-0.03, 0.26)	0.52	0.24 (0.21, 0.27)
Mis_b600 vs Carb	343.5	318.8	2895	0.38 (-0.18,	0.18 (0.07, 0.30)	0.75	0.24 (0.21, 0.27)

				0.96)			
Oxy_a1b5 vs Oxy_b1	537.9	140.0	2910	-0.13 (-0.71, 0.43)	-0.12 (-0.58, 0.34)	0.49	0.30 (0.21, 0.45)
Mis_b600 vs Oxy_b1	644.7	488.5	3366	-0.24 (-0.87, 0.40)	-0.07 (-0.43, 0.28)	0.31	0.24 (0.21, 0.27)
Erg_Oxy vs Oxy_a1b5	341.1	317.3	2891	-0.18 (-0.53, 0.18)	-0.05 (-0.20, 0.10)	0.25	0.24 (0.21, 0.27)
Mis_b600 vs Oxy_a1b5	2615.0	2371.0	7219	0.02 (-0.22, 0.25)	0.01 (-0.14, 0.16)	0.52	0.26 (0.21, 0.27)
Oxy_a10 vs Oxy_a5b10	557.2	430.5	3220	0.04 (-0.43, 0.51)	0.04 (-0.08, 0.16)	0.51	0.24 (0.21, 0.27)
Erg_Oxy vs Oxy_a5b10	866.3	-7.8	3091	0.02 (-0.31, 0.35)	-0.04 (-0.23, 0.22)	0.66	0.39 (0.22, 0.53)
Mis_b600 vs Oxy_a5b10	358.6	323.6	2915	0.03 (-0.06, 0.13)	-0.02 (-0.14, 0.09)	0.77	0.24 (0.21, 0.27)
Erg_Oxy vs Oxy_a10	374.6	330.7	2938	-0.05 (-0.35, 0.15)	-0.10 (-0.25, 0.05)	0.52	0.24 (0.21, 0.27)
Mis_b600 vs Oxy_a10	344.0	316.9	2893	-0.15 (-0.33, 0.03)	0.03 (-0.11, 0.17)	0.06	0.23 (0.21, 0.26)
Mis_b600 vs Erg_Oxy	343.7	320.7	2897	0.12 (-0.05, 0.28)	0.02 (-0.10, 0.14)	0.81	0.23 (0.20, 0.26)
Carb vs Mis_a600b800	336.5	314.5	2883	-0.34 (-0.80, 0.12)	-0.11 (-0.30, 0.07)	0.19	0.23 (0.21, 0.27)
Oxy_a1b5 vs Mis_a600b800	339.6	317.3	2889	-0.19 (-0.72, 0.35)	0.08 (-0.12, 0.28)	0.18	0.24 (0.21, 0.27)
Oxy_a5b10 vs Mis_a600b800	343.9	317.9	2894	0.05 (-0.18, 0.29)	0.04 (-0.17, 0.25)	0.53	0.24 (0.21, 0.27)
Oxy_a10 vs Mis_a600b800	344.1	317.8	2894	0.16 (-0.32, 0.64)	0.07 (-0.12, 0.27)	0.64	0.24 (0.21, 0.27)
Mis_b600 vs Mis_a600b800	387.5	337.3	2957	0.09 (-0.38, 0.56)	0.05 (-0.12, 0.21)	0.56	0.24 (0.21, 0.27)
Mis_a800b1000 vs Mis_a600b800	343.7	319.1	2895	-0.02 (-0.49, 0.44)	0.23 (-0.30, 0.75)	0.24	0.24 (0.21, 0.27)
Erg vs Mis_a600b800	410.0	339.4	2982	0.30 (-0.13,	0.17 (-0.07,	0.68	0.26 (0.21, 0.27)

				0.47)	0.27)		
CarbProst vs Mis_a600b800	362.3	336.3	2931	0.21 (-0.21, 0.62)	-0.16 (-0.37, 0.04)	0.94	0.23 (0.21, 0.27)
Oxy_a5b10 vs Mis_a800b1000	342.8	319.0	2894	-0.17 (-0.67, 0.34)	0.10 (-0.28, 0.49)	0.20	0.24 (0.21, 0.27)
Mis_b600 vs Mis_a800b1000	749.6	450.1	3432	0.11 (-0.37, 0.59)	-0.09 (-0.54, 0.37)	0.72	0.26 (0.21, 0.27)
Erg vs Mis_a800b1000	343.7	316.4	2893	0.15 (-0.25, 0.56)	0.02 (-0.33, 0.37)	0.69	0.24 (0.21, 0.27)
Oxy_a1b5 vs Mis_Oxy	342.2	317.8	2892	0.45 (-0.01, 0.92)	0.14 (-0.03, 0.31)	0.89	0.23 (0.21, 0.27)
Oxy_a5b10 vs Mis_Oxy	342.0	317.3	2892	0.26 (0.10, 0.41)	0.05 (-0.14, 0.25)	0.95	0.23 (0.21, 0.26)
Erg_Oxy vs Mis_Oxy	392.3	340.6	2965	0.06 (-0.42, 0.53)	0.12 (-0.04, 0.26)	0.42	0.24 (0.21, 0.27)
Mis_b600 vs Mis_Oxy	403.3	326.9	2963	0.16 (-0.25, 0.57)	0.18 (0.04, 0.31)	0.46	0.24 (0.21, 0.27)
Oxy_b1 vs Erg	341.9	316.4	2891	-0.17 (-0.81, 0.44)	0.14 (-0.22, 0.49)	0.18	0.23 (0.21, 0.27)
Oxy_a1b5 vs Erg	410.5	348.3	2991	0.00 (-0.29, 0.30)	-0.05 (-0.19, 0.11)	0.61	0.24 (0.21, 0.26)
Oxy_a5b10 vs Erg	350.1	318.0	2900	0.02 (-0.15, 0.19)	-0.07 (-0.20, 0.05)	0.82	0.24 (0.21, 0.27)
Erg_Oxy vs Erg	343.4	315.8	2892	-0.24 (-0.73, 0.26)	-0.09 (-0.22, 0.04)	0.29	0.24 (0.21, 0.27)
Mis_b600 vs Erg	347.6	317.6	2898	-0.04 (-0.16, 0.09)	0.03 (-0.11, 0.17)	0.25	0.24 (0.21, 0.27)
CarbProst vs Erg	361.9	332.6	2927	-0.11 (-0.28, 0.06)	-0.36 (-0.6, -0.11)	0.95	0.24 (0.21, 0.27)
Oxy_a1b5 vs CarbProst	1187.0	-426.7	2993	0.11 (-0.82, 1.14)	0.18 (-0.14, 0.51)	0.42	0.39 (0.21, 0.70)
Oxy_a5b10 vs CarbProst	348.9	322.7	2904	0.12 (-0.17, 0.41)	0.23 (0.06, 0.39)	0.26	0.24 (0.20, 0.26)
Erg_Oxy vs CarbProst	345.0	318.0	2895	0.11 (-0.29,	0.10 (-0.08,	0.53	0.24 (0.21, 0.27)

				0.51)	0.27)		
Mis_b600 vs CarbProst	372.1	335.5	2940	-0.16 (-0.54, 0.22)	0.17 (0.02, 0.33)	0.06	0.24 (0.21, 0.27)

Vaginal birth subgroup

Global inconsistency check

Analysis of the dataset for the vaginal delivery subgroup for the outcome blood loss included 109 studies (235 arms) of 13 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Fitting of both fixed and random-effect network meta-analysis (NMA) models indicated support for the random-effect model on the basis of a small decrease in DIC and a sizeable decrease in residual deviance (Table 67).

Total residual deviance and DIC were lower in the inconsistency UME model than in the NMA model and the estimate of between-study SD was the similar in the NMA and UME models (Table 67). This suggests no evidence of inconsistency, but that there is moderate heterogeneity between study estimates.

Table 67. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome Blood loss, vaginal delivery subgroup.

Outcome	Pop.	Model	Posterior total residual deviance[25]	Between-study SD Mean, 95% credible interval	pD	DIC[26]
PPH	VD	FE NMA	2961.0	-	120.9	4553.8
PPH	VD	RE NMA	239.6	0.25 (0.21, 0.29)	224.6	1936.4
PPH	VD	FE UME	1870.0	-	146.9	3489.5
PPH	VD	RE UME	238.1	0.24 (0.20, 0.28)	227.2	1937.6

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 66), shows that one study arm showed inconsistency with the rest of the dataset:

- Modi, 2014
    - Compares Oxytocin [>5 IU and ≤ 10 IU] (coded 5), Misoprostol ≤600mcg (coded 8), Ergometrine (coded 12) and Carboprost (coded 13)

[25] Posterior mean residual deviance compared to 235 data points
[26] Deviance information criteria (DIC) – lower values preferred

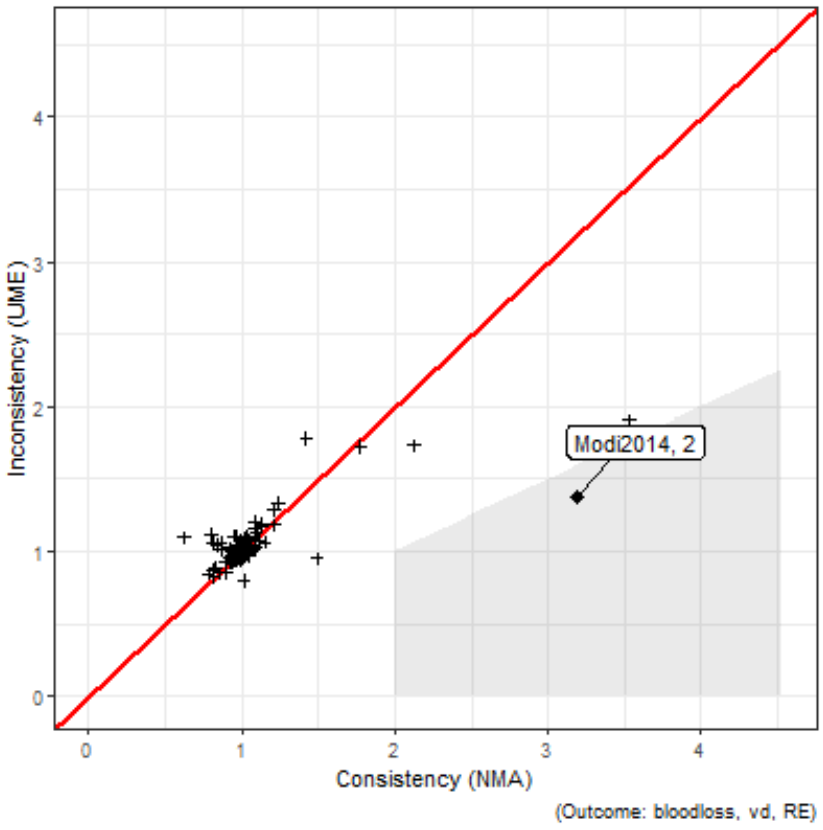

Figure 66. Dev-dev plot of each study arm's residual deviance under the consistency (NMA) and inconsistency models with RE structure for Blood loss, vaginal delivery subgroup. Labels indicate study arms with high deviance in the NMA model, relative to their deviance in the UME model. The dotted line and grey shaded area outline a region where study arms fit poorly in the NMA model but well in the UME model, suggesting that they are predicted poorly when the model enforces consistency in treatment differences.

Checking inconsistency within individual treatment comparisons (Node-splitting)

Node-splitting procedures indicated no evidence of a difference between direct and indirect evidence on most treatment comparisons. Evidence conflicted on a single comparison, for oxytocin (> 10IU) vs misoprostol (<600mcg) (Table 68). A forest plot is presented for this comparison (Figure 67).

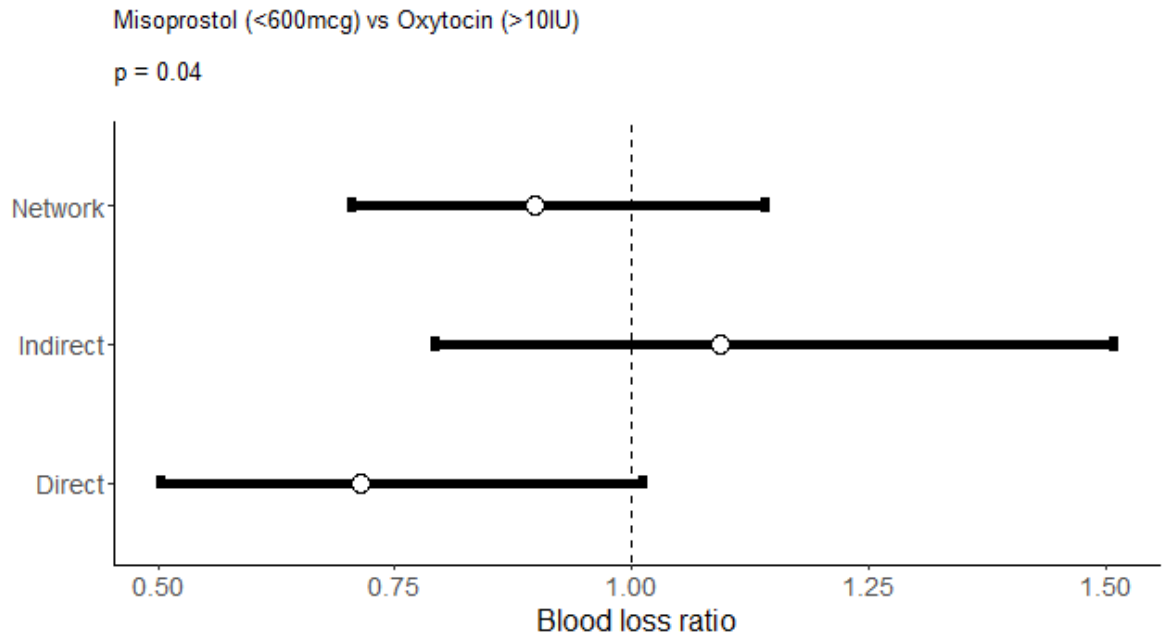

Figure 67. Treatment difference of misoprostol vs oxytocin on outcome mean blood loss, vaginal delivery subgroup, as estimated from the full network, indirect evidence only and direct evidence only. Ratios greater than 1 indicate that blood loss was greater in the misoprostol group.

Table 68. Estimates of treatment effect from direct and indirect evidence from node-splitting models, vaginal delivery subgroup. 'Comparison' indicates the pair of nodes for which evidence was split into direct and indirect evidence. Direct and indirect estimates are log blood loss ratios, where zero indicates no difference in blood loss between treatment groups.

Comparison	Total residual Deviance	pD	DIC	Direct	Indirect	P value	Between-study SD
Mis_b600 vs Oxy_a10	**249.5**	**229.4**	**1951**	**-0.34 (-0.69, 0.01)**	**0.09 (-0.23, 0.41)**	**0.04**	**0.25 (0.21, 0.29)**
Oxy_a1b5 vs Placebo	892.7	197.1	2562	-0.26 (-0.59, 0.07)	-0.02 (-0.34, 0.42)	0.17	0.32 (0.22, 0.49)
Oxy_a5b10 vs Placebo	1044.0	-455.7	2060	-0.25 (-1.12, 0.63)	-0.34 (-0.92, -0.03)	0.52	0.51 (0.22, 0.95)
Erg_Oxy vs Placebo	417.2	235.6	2125	-0.12 (-0.49, 0.25)	-0.27 (-0.45, -0.07)	0.74	0.29 (0.22, 0.29)
Mis_b600 vs Placebo	284.4	259.4	2016	-0.14 (-0.33, 0.06)	-0.23 (-0.41, -0.06)	0.77	0.25 (0.22, 0.29)
Mis_a600b800 vs Placebo	244.6	226.0	1943	-0.31 (-0.81, 0.20)	-0.19 (-0.42, 0.04)	0.34	0.25 (0.21, 0.29)
Erg vs Placebo	256.1	231.1	1959	-0.28 (-0.64, 0.08)	-0.12 (-0.28, 0.05)	0.21	0.25 (0.21, 0.29)
CarbProst vs Placebo	243.1	226.5	1942	-0.21 (-0.58, 0.16)	-0.40 (-0.61, -0.20)	0.82	0.25 (0.21, 0.29)
Oxy_a1b5 vs Carb	246.4	225.9	1944	0.19 (-0.17, 0.55)	0.20 (-0.03, 0.43)	0.49	0.25 (0.22, 0.29)
Oxy_a5b10 vs Carb	254.3	231.6	1958	0.10 (-0.13, 0.34)	0.22 (0.02, 0.42)	0.24	0.25 (0.22, 0.29)
Erg_Oxy vs Carb	278.3	255.1	2006	0.14 (-0.09, 0.37)	0.16 (-0.06, 0.38)	0.46	0.25 (0.22, 0.29)

Mis_b600 vs Carb	246.9	226.8	1946	0.39 (-0.20, 0.98)	0.19 (0.02, 0.36)	0.73	0.25 (0.22, 0.29)
Erg_Oxy vs Oxy_a1b5	244.7	227.4	1944	-0.30 (-0.81, 0.21)	-0.01 (-0.20, 0.18)	0.14	0.25 (0.21, 0.29)
Mis_b600 vs Oxy_a1b5	282.9	259.4	2015	0.01 (-0.22, 0.25)	0.01 (-0.17, 0.19)	0.50	0.25 (0.21, 0.29)
Erg_Oxy vs Oxy_a5b10	247.1	228.1	1947	0.08 (-0.13, 0.29)	-0.04 (-0.2, 0.12)	0.82	0.26 (0.22, 0.30)
Mis_b600 vs Oxy_a5b10	247.2	231.1	1950	0.04 (-0.07, 0.15)	0.02 (-0.12, 0.17)	0.57	0.26 (0.22, 0.30)
Erg_Oxy vs Oxy_a10	246.9	228.7	1948	-0.04 (-0.54, 0.47)	-0.20 (-0.49, 0.10)	0.71	0.25 (0.22, 0.29)
Mis_b600 vs Erg_Oxy	246.0	228.2	1946	0.11 (-0.06, 0.29)	-0.02 (-0.17, 0.12)	0.88	0.24 (0.21, 0.28)
Carb vs Mis_a600b800	239.0	224.0	1935	-0.34 (-0.83, 0.15)	-0.11 (-0.35, 0.13)	0.21	0.25 (0.22, 0.29)
Oxy_a1b5 vs Mis_a600b800	248.3	229.1	1950	-0.19 (-0.75, 0.36)	0.09 (-0.15, 0.33)	0.18	0.25 (0.21, 0.29)
Oxy_a5b10 vs Mis_a600b800	243.4	227.1	1943	0.05 (-0.20, 0.31)	0.01 (-0.24, 0.25)	0.60	0.25 (0.22, 0.29)
Mis_b600 vs Mis_a600b800	368.4	246.9	2087	0.08 (-0.42, 0.59)	0.05 (-0.15, 0.24)	0.56	0.27 (0.22, 0.30)
Mis_a800b1000 vs Mis_a600b800	56420.0	-25440	32450	1.32 (-0.52, 4.45)	0.50 (-0.60, 2.18)	0.58	0.52 (0.22, 0.91)
Erg vs Mis_a600b800	304.5	267.6	2044	0.15 (-0.18, 0.48)	0.09 (-0.11, 0.28)	0.64	0.25 (0.22, 0.29)
CarbProst vs Mis_a600b800	344.4	196.1	2013	0.21 (-0.26, 0.65)	-0.16 (-0.41, 0.06)	0.92	0.27 (0.21, 0.38)
Oxy_a5b10 vs Mis_a800b1000	251.4	226.4	1950	-0.17 (-0.70, 0.37)	0.09 (-0.32, 0.50)	0.23	0.25 (0.21, 0.29)
Mis_b600 vs Mis_a800b1000	285.8	234.2	1992	0.11 (-0.39, 0.62)	-0.13 (-0.52, 0.41)	0.70	0.27 (0.22, 0.29)
Erg vs Mis_a800b1000	961.0	-332.2	2101	0.15 (-0.67, 0.98)	0.02 (-0.67, 0.71)	0.63	0.42 (0.22, 0.65)

Oxy_a5b10 vs Mis_Oxy	249.8	228.9	1951	0.10 (-0.10, 0.30)	-0.24 (-0.71, 0.22)	0.91	0.25 (0.21, 0.29)
Oxy_a10 vs Mis_Oxy	244.9	226.4	1943	0.01 (-0.35, 0.36)	0.35 (-0.01, 0.70)	0.09	0.25 (0.21, 0.29)
Erg_Oxy vs Mis_Oxy	248.7	228.6	1949	0.05 (-0.45, 0.56)	0.03 (-0.20, 0.25)	0.54	0.25 (0.22, 0.29)
Mis_b600 vs Mis_Oxy	2469.0	-1981.0	1960	0.15 (-1.06, 1.35)	0.11 (-0.43, 0.70)	0.58	0.56 (0.22, 1.00)
Oxy_a1b5 vs Erg	244.0	227.5	1944	0.01 (-0.30, 0.31)	-0.03 (-0.22, 0.15)	0.59	0.25 (0.21, 0.29)
Oxy_a5b10 vs Erg	247.8	228.7	1949	0.03 (-0.16, 0.22)	-0.09 (-0.23, 0.04)	0.85	0.25 (0.21, 0.29)
Erg_Oxy vs Erg	250.2	229.9	1952	-0.24 (-0.76, 0.28)	-0.07 (-0.22, 0.08)	0.27	0.25 (0.22, 0.29)
Mis_b600 vs Erg	250.1	227.6	1950	-0.04 (-0.17, 0.10)	0.06 (-0.09, 0.22)	0.17	0.26 (0.22, 0.30)
CarbProst vs Erg	817.5	-190.3	2099	-0.09 (-0.42, 0.25)	-0.49 (-1.07, -0.06)	0.94	0.42 (0.22, 0.66)
Oxy_a1b5 vs CarbProst	753.1	-153.8	2071	0.11 (-0.94, 1.19)	0.14 (-0.31, 0.49)	0.46	0.43 (0.22, 0.69)
Oxy_a5b10 vs CarbProst	250.4	229.9	1952	0.12 (-0.18, 0.42)	0.22 (0.04, 0.40)	0.28	0.24 (0.21, 0.28)
Erg_Oxy vs CarbProst	252.5	237.2	1962	0.22 (-0.45, 0.88)	0.12 (-0.07, 0.31)	0.62	0.25 (0.22, 0.29)
Mis_b600 vs CarbProst	1219.0	-558.2	2133	-0.17 (-1.14, 0.79)	0.07 (-0.49, 0.40)	0.24	0.54 (0.22, 0.93)

Caesarean birth subgroup

Global inconsistency check

Analysis of the dataset for the CS delivery subgroup for the outcome blood loss included 46 studies (95 arms) of 12 treatments.

Results were based on 80,000 iterations following a burn-in of 60,000 iterations, which was sufficient to achieve convergence using a standard, uninformative prior for between-study standard deviation (SD).

Fitting both fixed (FE) and random-effect (RE) network meta-analysis (NMA) models gave similar values for DIC. However, residual deviance was lower by 5.3 for the RE NMA (Table 69) suggesting support for the RE model for these data.

Total residual deviance and DIC were lower in the inconsistency UME model than in the NMA model and the estimate of between-study SD was the similar in the NMA and UME models (Table 69). This suggests that there is no evidence of inconsistency, but moderate heterogeneity between study estimates.

The dev-dev plot, which shows the contribution of each study datapoint to the residual deviance under the random effects UME and NMA models (Figure 68), showed no study arms to have high deviance in the NMA model, relative to their deviance in the UME model. Taken together, the model fit and dev-dev plots suggest there was little evidence of inconsistency in these data. Therefore, node-splitting models were not required.

Table 69. Model fit statistics for fixed- and random-effect NMA and UME models of the outcome Blood loss, CS delivery subgroup.

Outcome	Pop.	Model	Posterior total residual deviance[a]	Between-study SD Mean, 95% credible interval	pD	DIC[b]
PPH	CS	FE NMA	1706.0	-	56.9	2506.8
PPH	CS	RE NMA	93.9	0.21 (0.16, 0.27)	88.9	926.5
PPH	CS	FE UME	717.0	-	65.0	1525.7
PPH	CS	RE UME	94.4	0.19 (0.14, 0.25)	89.2	927.3

[a] Posterior mean residual deviance compared to 95 data points
[b] Deviance information criteria (DIC) – lower values preferred

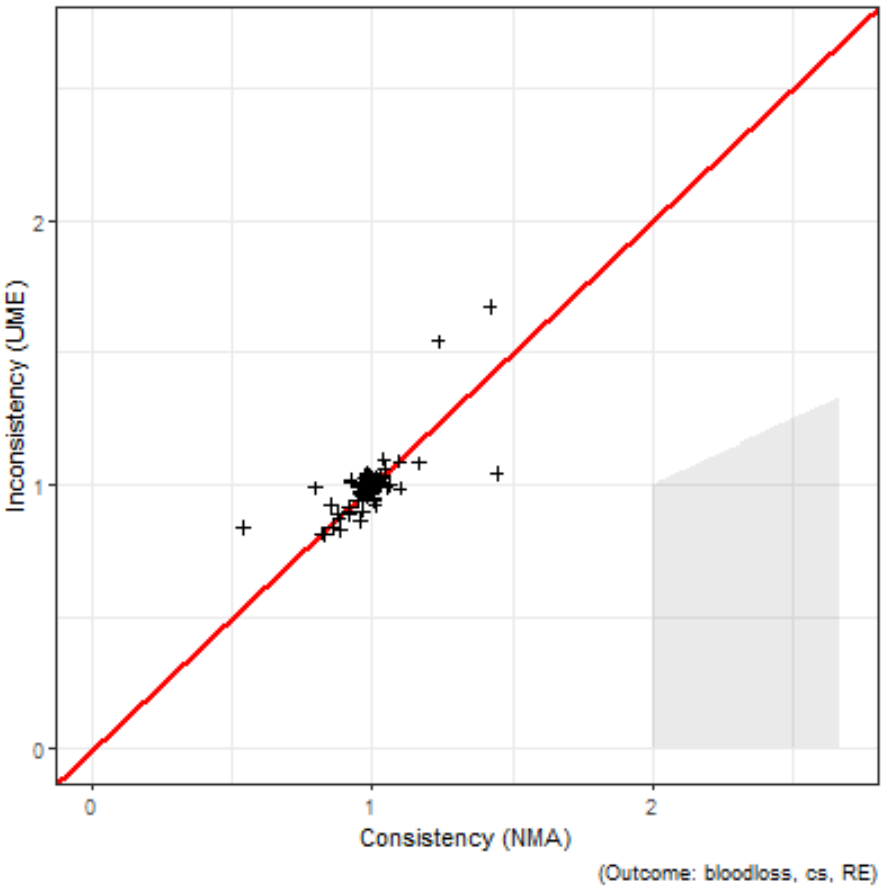

Figure 68. Dev-dev plot of each study arm's residual deviance under the consistency (NMA) and inconsistency models with RE structure for Blood loss, CS delivery subgroup. No study arms were identified as inconsistent (i.e. points in the shaded region).

NMA code

The code below was originally based on information within the TSU evidence synthesis technical support documents (Dias 2011, Dias 2014).

WinBUGS code for fixed effect model – binary outcomes

```
# Binomial likelihood, logit link
# Fixed effects model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)      # vague priors for all trial baselines
    for (k in 1:na[i])  {       # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
# model for linear predictor
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
        rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
```

```
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
             +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
      }
# summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
     }
totresdev <- sum(resdev[])      # Total Residual Deviance
d[1]<-0    # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.001) }

# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
 rk[k] <- rank(d[],k) # assumes events are "bad"
 best[k] <- equals(rk[k],1) #calculate probability that treat k is best
 for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability
that treat k is h-th best
 }

}                                                    # *** PROGRAM ENDS
```

WinBUGS code for random effect model – binary outcomes

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         # LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
    for (k in 1:na[i]) {             # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
        logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
            +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))         }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])           # Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){
      d[k] ~ dnorm(0,.001)
      }
```

```
sd ~ dunif(0,5)      # vague prior for between-trial SD
tau <- pow(sd,-2)    # between-trial precision = (1/between-trial variance)

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
 for (k in (c+1):nt) {
      or[c,k] <- exp(d[k] - d[c])
      lor[c,k] <- (d[k]-d[c])
      }
 }

# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
 rk[k] <- rank(d[],k) # assumes events are "bad"
 best[k] <- equals(rk[k],1) #calculate probability that treat k is best
 for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability
that treat k is h-th best
 }


}                                    # *** PROGRAM ENDS
```

WinBUGS code for fixed effect model – continuous outcomes

```
# Normal likelihood, log link
# Fixed effects model
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         #   LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
    for (k in 1:na[i]) {                #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)      # calculate variances
        prec[i,k] <- 1/var[i,k]         # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood
# model for linear predictor
        log(theta[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
  }
totresdev <- sum(resdev[])              #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm

# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

for (k in 1:nt) {
            blossRatio[k] <- exp(d[k])
      }

}                                       # *** PROGRAM ENDS
```

WinBUGS code for random effect model – continuous outcomes

```
# Normal likelihood, log link
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         #   LOOP THROUGH STUDIES
```

```
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
    for (k in 1:na[i]) {             #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)   # calculate variances
        prec[i,k] <- 1/var[i,k]      # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
        log(theta[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA

for (k in 1:nt) {
            blossRatio[k] <- exp(d[k])
      }

}                                    # *** PROGRAM ENDS
```

Acknowledgments

We would like to acknowledge Beatrice Downing and Nicky Welton from the Guidelines Technical Support Unit, at University of Bristol, for providing advice, models, inconsistency checking and quality assurance for the network meta-analyses included in this review.