WHO recommendations

Uterotonics for the prevention of postpartum haemorrhage

Web annex 2: Carbetocin versus placebo or no treatment

EVIDENCE TO DECISION FRAMEWORK

World Health Organization

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1. Background

- Carbetocin is a long-acting synthetic analogue of oxytocin with agonist properties. After intravenous injection, it produces sustained uterine contractions within 2 minutes, lasting for approximately 6 minutes and followed by rhythmic contractions for 60 minutes.
- When carbetocin is administered intramuscularly, the sustained uterine contractions last for approximately 11 minutes and the rhythmic contractions for 120 minutes.
- A heat-stable formulation of carbetocin is available that does not require cold chain storage and transport; it has been shown to maintain stability over a period of 36 months at 30 °C and 75% relative humidity. The heat-stable formulation of carbetocin differs from the existing non-heat-stable formulation of carbetocin only in its excipients[1] *(1)*.

2. Question

Following is the question of interest in PICO (population, intervention, comparator, outcome) format.

In women in the third stage of labour (P), does the use of carbetocin for prevention of postpartum haemorrhage (I) compared with placebo or no treatment (C), improve maternal and perinatal outcomes?

- If so, what route of administration and dosing regimen should be used?

Problem: Preventing the onset of postpartum haemorrhage (PPH)

Perspective: Clinical practice recommendation – population perspective

Population (P): All women in the third stage of labour

Intervention (I): Carbetocin

Comparator (C): Placebo or no treatment

Setting: Hospital or community setting

Subgroups: Women undergoing vaginal birth; women undergoing caesarean section

Priority outcomes (O):[2]

- Maternal death
- PPH ≥ 1000 ml
- Blood transfusion
- Severe maternal morbidity: intensive care unit (ICU) admissions
- Severe maternal morbidity: shock
- PPH ≥ 500 ml
- Use of additional uterotonics
- Blood loss (ml)
- Postpartum anaemia

[1] An "excipient" is an inactive substance that serves as the vehicle or medium for the active ingredients.

[2] These outcomes reflect the prioritized outcomes used in the development of this recommendation, in the *WHO recommendations for prevention and treatment of postpartum haemorrhage* (2012) *(1)*. The outcomes "shock", "maternal well-being" and "maternal satisfaction" have been added as part of this update.

- Breastfeeding
- Side-effects[1]
- Maternal well-being
- Maternal satisfaction

3. Assessment

3.1 Effects of interventions

What is the effect of carbetocin for PPH prevention on the priority outcomes?

Research evidence

Summary of evidence

Source and characteristics of studies

Evidence on the efficacy and safety of carbetocin for prevention of postpartum haemorrhage (PPH) was derived from an updated Cochrane systematic review with a network meta-analysis of all uterotonic agents for PPH prevention *(3)*. The network meta-analysis included 196 trials (135 559 women) that were conducted across 53 countries (including high-, middle- and low-income countries). Most trials (187/196, 95.4%) were performed in a hospital setting, seven in a community setting (3.6%), one in a mixed setting (0.5%) and in one trial the setting was unclear.

The majority of the trials included women undergoing a vaginal birth (140/196, 71.5%), while 53 trials (27.0%) involved women undergoing caesarean section, two trials (1.0%) included women undergoing either a vaginal birth or caesarean section, and one trial (0.5%) did not specify the mode of birth. A total of 124 trials (63.3%) included women with a singleton pregnancy, 36 trials (18.4%) included women with either singleton or multiple pregnancies, one trial (0.5%) included women with twin pregnancies only and the remaining 35 trials (17.9%) did not specify. A total of 108 trials (55.1%) included both nulliparous and multiparous women, six trials (3.1%) included only nulliparous or primigravida women, one trial included only multiparous women (0.5%), and 81 trials (41.3%) did not specify parity.

Across all 196 trials (412 trial arms) in the network meta-analysis, the following agents were used either as intervention or comparator:

- 137 trial arms (33.3%) used oxytocin
- 96 trial arms (23.3%) used misoprostol
- 39 trial arms (9.5%) used ergometrine
- 35 trial arms (8.5%) used oxytocin plus ergometrine
- **33 trial arms (8%) used carbetocin**
- 29 trial arms (7%) used placebo or no treatment
- 26 trial arms (6.3%) used misoprostol plus oxytocin
- 17 trial arms (4.1%) used injectable prostaglandins.

Two small randomized trials (169 women) in the network meta-analysis directly compared carbetocin with placebo or no treatment. Both these trials were conducted in hospital settings. The trials were carried out in Norway and the United States

[1] This includes nausea, vomiting, headache, abdominal pain, hypertension, shivering, fever and diarrhoea.

of America (USA). The parity was unspecified and only women at high risk of PPH undergoing caesarean section were included. The intervention was 100 μg of carbetocin administered by an intravenous bolus in both studies. The USA trial compared carbetocin versus placebo; while the Norwegian trial was a three-arm trial which compared carbetocin versus oxytocin versus placebo.

Effects of carbetocin compared with placebo or no treatment

The results below report the findings of the network meta-analysis for the priority outcomes (which generated effect estimates from both direct and indirect evidence).

Maternal death: It is unclear whether carbetocin reduces the risk of maternal death when compared with placebo or no treatment, because the certainty of the evidence is very low.

PPH ≥ 1000 ml: When compared with placebo or no treatment, moderate-certainty evidence suggests that carbetocin probably reduces PPH ≥ 1000 ml (risk ratio [RR] 0.52, 95% confidence interval [CI] 0.38–0.72).

Blood transfusion: Moderate-certainty evidence suggests that carbetocin probably reduces the use of blood transfusion when compared with placebo or no treatment (RR 0.48, 95% CI 0.26–0.89).

Severe maternal morbidity – ICU admissions: It is uncertain whether carbetocin reduces maternal ICU admission as the events were very few. There were no data for the outcome "shock" reported in the included trials.

PPH ≥ 500 ml: When compared with placebo or no treatment, moderate-certainty evidence suggests that carbetocin probably reduces PPH ≥ 500 ml when compared with placebo or no treatment (RR 0.42, 95% CI 0.31–0.57).

Use of additional uterotonics: Low-certainty evidence suggests that the use of carbetocin may reduce the use of additional uterotonics when compared with placebo or no treatment (RR 0.19, 95% CI 0.13–0.27).

Mean blood loss: Moderate-certainty evidence suggests that the use of prophylactic carbetocin probably reduces average blood loss compared with women receiving placebo or no treatment (mean difference [MD] 138.37 ml lower, 95% CI 193.24–83.50 ml lower).

Postpartum anaemia: This outcome was not directly reported in the review. However, there is moderate-certainty evidence suggesting that prophylactic carbetocin compared with placebo or no treatment probably reduces the **mean change in haemoglobin levels** measured before versus after birth (MD 4.33 g/L lower, 95% CI 6.42–2.23 g/L lower).

Breastfeeding: Low-certainty evidence suggests that the use of prophylactic carbetocin during the third stage of labour may make little or no difference to whether women are breastfeeding at discharge from the hospital (RR 0.96, 95% CI 0.87–1.06).

Any side-effect: Low-certainty evidence suggests that the use of prophylactic carbetocin may make little or no difference to women's risk of experiencing **nausea** (RR 0.88, CI 95% 0.48–1.61), **headache** (RR 1.35, 95% CI 0.65–2.82) or **abdominal pain** (RR 1.14, CI 95% 0.75–1.73). Moderate-certainty evidence suggests that prophylactic carbetocin probably makes little or no difference to the risk of **shivering** (RR 0.54, 95% CI 0.26–1.11) or **fever** (RR 1.14, 95% CI 0.36–3.59) when compared with placebo or no treatment. It is uncertain whether the use of carbetocin makes any difference to the incidence of **vomiting** or **hypertension** during the third stage of labour. Other important side-effects related to uterotonics, such as **diarrhoea**, were not reported in the studies included in the review.

Maternal well-being: No trials reported on this outcome.

Maternal satisfaction: No trials reported on this outcome.

Additional considerations

Subgroup analyses did not reveal a substantial difference in the effects of prophylactic carbetocin when compared with placebo or no treatment by mode of birth (vaginal versus caesarean section) or by setting (community versus hospital). A separate Cochrane review published in 2012 on carbetocin for preventing postpartum haemorrhage focused on the effects of prophylactic carbetocin versus placebo and other uterotonics, and identified only one trial comparing carbetocin to placebo *(4)*. Results were consistent with the above findings.

Desirable effects

How substantial are the desirable anticipated effects of carbetocin versus placebo or no treatment?

Judgement

—	—	—	—	✓	—
Don't know	Varies	Trivial	Small	Moderate	Large

Undesirable effects

How substantial are the undesirable anticipated effects of carbetocin versus placebo or no treatment?

Judgement

—	—	—	—	—	✓
Don't know	Varies	Large	Moderate	Small	Trivial

Certainty of the evidence

What is the overall certainty of the evidence of effects of carbetocin versus placebo or no treatment?

—	—	—	✓	—
No included studies	Very low	Low	Moderate	High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with carbetocin for PPH prevention?

Research evidence

In a review of qualitative studies looking at "what women want" from intrapartum care, findings indicate that most women want a normal birth (with good outcomes for mother and baby), but acknowledge that medical intervention may sometimes be necessary (*high confidence*) *(5)*. Most women, especially those giving birth for the first time, are apprehensive about labour and birth (*high confidence*) and of medical interventions, although in certain contexts and/or situations women welcome interventions to address recognized complications (*low confidence*). Where interventions are introduced, women would like to receive relevant information from technically competent health care providers who are sensitive to their needs (*high confidence*).

Findings from another qualitative systematic review exploring perceptions of PPH prevention and treatment by women and providers suggest that in some low- and middle-income countries (LMICs) women do not recognize the clinical definitions of blood loss or what might be considered "normal" blood loss (*moderate confidence*) *(6)*. Furthermore, in some LMICs, women place a greater value on the expulsion of so-called "dirty blood", which they perceive as a normal cleansing process and something that should not be prevented (*moderate confidence*).

The same review also highlights women's need for information about PPH, ideally given during antenatal care (*moderate confidence*), and the importance of kind, clinically competent staff with a willingness to engage in shared decision-making around PPH management (*moderate/low confidence*). In addition, women are concerned about feelings of exhaustion and anxiety (at being separated from their baby) following a PPH, as well as the long-term psychological effects of the event and the negative impact that all of these issues may have on their ability to breastfeed (*moderate/low confidence*).

Additional considerations

None.

Judgement

— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ Probably no important uncertainty or variability	— No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour carbetocin or placebo/no treatment?

Judgement

— Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	— Probably favours carbetocin	✓ Favours carbetocin

3.3 Resources

How large are the resource requirements (costs) of carbetocin for PPH prevention?

Research evidence

A systematic review of the literature found no direct evidence on the costs and cost–effectiveness of carbetocin compared with no uterotonic for PPH prevention *(7)*. However, the review found a cost–effectiveness analysis from the United Kingdom of Great Britain and Northern Ireland (United Kingdom) that compared carbetocin with other uterotonic agents *(8)*. This analysis concluded that carbetocin might be the most cost-effective uterotonic agent for vaginal and caesarean birth in high-income country (HIC) settings when the relatively high costs of managing PPH and side-effects associated with other options are considered. No cost–effectiveness analysis from LMICs was identified.

In the same review *(7)*, six other studies that evaluated economic outcomes related to carbetocin use following caesarean section were identified: five were cost–effectiveness analyses *(9–13)* and one was a service evaluation study *(14)*; three were from an HIC (the United Kingdom) and three were from middle-income countries (Ecuador, Malaysia and Peru). All six studies compared carbetocin (100 μg) with oxytocin (5 international units [IU] or 10 IU, if dose was reported). Findings were somewhat inconsistent across the cost–effectiveness studies with several suggesting that carbetocin might be cost-effective following caesarean section compared with oxytocin, and others indicating that uncertainty around the supply cost and other resource data made it difficult to determine whether it might be cost-effective or not *(11,13)*. In addition, the United Kingdom service evaluation study *(14)* reported a significant increase in the cost of care during the period from birth of baby to transfer to the postnatal ward of low-risk women undergoing elective caesarean birth (from approximately US$ 104.27 before the introduction of carbetocin, to US$ 128.35 following this; $P < 0.01$), but economic modelling was not performed in this study. In general, the certainty of the evidence overall was undermined by methodological limitations and uncertainty in the underlying data of the studies.

Findings from one prospective study *(12)* included in the review suggested that the cost–effectiveness of carbetocin might be greater following emergency caesarean section than for elective caesarean section, due to a larger reduction observed in the use of additional uterotonics with emergency caesarean section, which could be investigated further.

Additional considerations

In 2013, the World Health Organization (WHO) was approached by Merck for Mothers (a philanthropic initiative of Merck, known outside the USA as Merck Sharpe & Dohme [MSD]) and Ferring Pharmaceuticals to explore the potential value of heat-stable carbetocin for reducing the incidence of maternal death. WHO convened an international panel of stakeholders who identified the need for demonstration of non-inferiority of heat-stable carbetocin before a change in guidance and practice could be considered. If non-inferior to oxytocin, the heat-stable formulation of carbetocin would be made available in public-sector health care facilities in high-burden countries at an affordable and sustainable price (comparable to the United Nations Population Fund [UNFPA] price of oxytocin), according to a memorandum of understanding (MoU) signed by representatives of WHO, Ferring Pharmaceuticals and Merck *(1)*.

In the published literature, the cost of carbetocin varies from US$ 13.10 to US$ 25.60 per 100 μg dose *(8–10,12)*. The price listed in the *British National Formulary* is equivalent to US$ 23.11 *(15)*.

Main resource requirements

Resource	Description
Staff	Carbetocin requires parenteral administration by trained maternity staff.
Training	The introduction of carbetocin would require additional training, both in settings where uterotonics have not previously been available and in settings where other uterotonics are already part of standard practice which extends beyond PPH prevention, e.g. induction of labour.
Supplies	Carbetocin indicative costs: ■ Cost per 100 µg: US$ 13.10 –25.60 *(8–10,12)*. Other costs: ■ Needle and syringe cost: approximately US$ 0.07 *(16)*.
Equipment and infrastructure	Minimal requirements.
Time	IM administration takes 2 minutes (same as for oxytocin) *(17)*.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

— Don't know	— Varies	✓ Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings

Certainty of evidence on required resources

What is the certainty of the evidence on costs?

Judgement

— No included studies	— Very low	✓ Low	— Moderate	— High

Cost-effectiveness

Judgement

— Don't know	✓ Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	— Probably favours carbetocin	— Favours carbetocin

3.4 Equity

What would be the impact of carbetocin for PPH prevention on health equity?

Research evidence

There is no direct evidence on the impact of introducing carbetocin for PPH prevention on health equity.

Additional considerations

The 2015 WHO *State of inequality* report indicates that women who are poor, least educated, and who reside in rural areas have lower coverage of health interventions and worse health outcomes than more advantaged women *(18)*. Therefore, reducing maternal morbidity due to PPH could have a positive impact on health equity and improve outcomes among disadvantaged women. Reducing the need for additional interventions to treat PPH (such as additional uterotonics and blood transfusion) would probably reduce inequities, especially in contexts where health services are covered through out-of-pocket means.

Conversely, the price of carbetocin may make it unaffordable for health services where resources are limited, and/or where women are required to pay for health services out of pocket. On the other hand, its heat stability potential reduces the need for cold chain storage and transport and reduces wastage that could be associated with temperature-unstable uterotonics.

Judgement

— Don't know	✓ Varies	— Reduced	— Probably reduced	— Probably no impact	— Probably increased	— Increased

3.5 Acceptability

Is carbetocin for PPH prevention acceptable to key stakeholders?

Research evidence

Findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment by women and health care providers suggest that providers would use a uterotonic (such as carbetocin) to prevent PPH if it was shown to be effective (*moderate confidence*) *(6)*. Findings also revealed that in a small number of LMIC settings, traditional birth attendants (TBAs) prefer to use herbal medicines with uterotonic properties to prevent PPH (*moderate confidence*), while in several HICs, experienced midwives adopted expectant management techniques and made selective use of guideline recommendations (ignoring uterotonics), especially if the birth was perceived to be normal (*moderate confidence*).

There were no findings from studies of women's perceptions relating to the acceptability of this particular intervention.

Additional considerations

None.

Judgement

— Don't know	✓ Varies	— No	— Probably No	— Probably Yes	— Yes

3.6 Feasibility

Is carbetocin for PPH prevention feasible to implement?

Research evidence

Findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment among women and health care providers indicate that resource constraints may influence the use of uterotonics (such as carbetocin) for PPH prevention, particularly in LMICs (*high confidence*) *(6)*. In a wide variety of settings, health care providers felt they did not have sufficient staff with experience of using uterotonics (*high confidence*) and needed more training in PPH management (*high confidence*).

Similar to oxytocin, it is possible that carbetocin could be made available in an easy-to-use, single-dose device such as Uniject, which might incur additional costs but might increase coverage through its use by lay health workers.

There were no findings from the studies on women's perceptions relating to the feasibility of introducing carbetocin into clinical care.

Additional considerations

The qualitative systematic review found that oxytocin storage in areas with limited/inconsistent electricity may hinder utilization (*high confidence*) *(6)*. The heat-stable formulation of carbetocin does not require cold chain transport or refrigerated storage.

Judgement

—	—	—	—	✓	—
Don't know	Varies	No	Probably No	Probably Yes	Yes

4. Summary of judgements table

Desirable effects	— Don't know	— Varies		— Trivial	— Small	✓ Moderate	— Large
Undesirable effects	Don't know	— Varies		— Large	— Moderate	— Small	✓ Trivial
Certainty of the evidence	— No included studies			— Very low	— Low	✓ Moderate	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ Probably no important uncertainty or variability	— No important uncertainty or variability
Balance of effects	— Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	— Probably favours carbetocin	✓ Favours carbetocin
Resources required	— Don't know	— Varies	✓ Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings
Certainty of the evidence on required resources	— No included studies			— Very low	✓ Low	— Moderate	— High
Cost-effectiveness	— Don't know	✓ Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	— Probably favours carbetocin	— Favours carbetocin
Equity	— Don't know	✓ Varies	— Reduced	— Probably reduced	— Probably no impact	— Probably increased	— Increased
Acceptability	— Don't know	✓ Varies		— No	— Probably No	— Probably Yes	— Yes
Feasibility	— Don't know	— Varies		— No	— Probably No	✓ Probably Yes	— Yes

Judgement

We recommend against the intervention	We recommend considering the intervention only	We recommend the intervention
☐	☑ in specific contexts ☐ with targeted monitoring and evaluation ☐ in the context of rigorous research	☐

5. Summary of Findings table

Patient or population: Women in the third stage of labour
Setting: Hospital or community setting
Intervention: Carbetocin
Comparator: Placebo or no treatment
Source: Gallos ID, Papadopoulou I, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev. 2018:CD011689 *(3)*.

Outcome	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with placebo or no treatment	Risk with carbetocin	Risk difference with carbetocin
Maternal death	Not reported	—	3.20 (0.13–77.79)	⊕⊖⊖⊖ VERY LOW	3.20 (0.13–77.79)	⊕⊖⊖⊖ VERY LOW	1 per 1000	2 per 1000	1 more per 1000 (1 fewer to 77 more)
							1 per 1000 (for vaginal birth)	2 per 1000 (for vaginal birth)	1 more per 1000 (1 fewer to 77 more) (for vaginal birth)
							See comment[a] (for caesarean birth)	See comment[b] (for caesarean birth)	See comment[c] (for caesarean birth)
PPH ≥1000 ml	Not estimable	⊕⊕⊖⊖ LOW	0.52 (0.37–0.73)	⊕⊕⊖⊖ LOW	0.52 (0.37–0.73)	⊕⊕⊕⊖ MODERATE	27 per 1000	14 per 1000	13 fewer per 1000 (17 fewer to 7 fewer)
							27 per 1000 (for vaginal birth)	14 per 1000 (for vaginal birth)	13 fewer per 1000 (17 fewer to 7 fewer) (for vaginal birth)
							See comment[a] (for caesarean birth)	See comment[b] (for caesarean birth)	See comment[c] (for caesarean birth)
Blood transfusions	Not reported	—	0.48 (0.26–0.89[d]	⊕⊕⊖⊖ LOW	0.48 (0.26–0.89)	⊕⊕⊕⊖ MODERATE	27 per 1000	13 per 1000	14 fewer per 1000 (20 fewer to 3 fewer)
							27 per 1000 (for vaginal birth)	13 per 1000 (for vaginal birth)	14 fewer per 1000 (20 fewer to 3 fewer) (for vaginal birth)
							See comment[a] (for caesarean birth)	See comment[b] (for caesarean birth)	See comment[c] (for caesarean birth)

Outcome	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with placebo or no treatment	Risk with carbetocin	Risk difference with carbetocin
Intensive care unit (ICU) admissions	Not reported	—	1.00 (0.11–8.74)[d]	⊕⊖⊖⊖ VERY LOW	1.00 (0.11–8.74)	⊕⊖⊖⊖ VERY LOW	2 per 1000	2 per 1000	0 fewer per 1000 (2 fewer to 15 more)
							2 per 1000 (for vaginal birth)	2 per 1000 (for vaginal birth)	0 fewer per 1000 (2 fewer to 15 more) (for vaginal birth)
							See comment[a] (for caesarean birth)	See comment[b] (for caesarean birth)	See comment[c] (for caesarean birth)
Maternal shock	Not reported	—	—	—	—	—	—	—	—
PPH ≥ 500 ml	0.75 (0.30–1.85)	⊕⊕⊖⊖ LOW	0.40 (0.29–0.55)	⊕⊕⊕⊖ MODERATE	0.42 (0.31–0.57)	⊕⊕⊕⊖ MODERATE	255 per 1000	107 per 1000	148 fewer per 1000 (176 fewer to 110 fewer)
							255 per 1000 (for vaginal birth)	107 per 1000 (for vaginal birth)	148 fewer per 1000 (176 fewer to 110 fewer) (for vaginal birth)
							320 per 1000 (for caesarean birth)	134 per 1000 (for caesarean birth)	186 fewer per 1000 (221 fewer to 138 fewer) (for caesarean birth)
Use of additional uterotonics	0.19 (0.12–0.32)	⊕⊖⊖⊖ VERY LOW	0.19 (0.13–0.29)	⊕⊕⊖⊖ LOW	0.19 (0.13–0.27)	⊕⊕⊖⊖ LOW	211 per 1000	40 per 1000	171 fewer per 1000 (184 fewer to 154 fewer)
							193 per 1000 (for vaginal birth)	37 per 1000 (for vaginal birth)	156 fewer per 1000 (168 fewer to 141 fewer) (for vaginal birth)
							746 per 1000 (for caesarean birth)	142 per 1000 (for caesarean birth)	604 fewer per 1000 (649 fewer to 545 fewer) for caesarean birth)

Outcome	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with placebo or no treatment	Risk with carbetocin	Risk difference with carbetocin
Mean blood loss (ml)	MD 274 lower (591.60 lower to 43.60 higher)	⊕⊕⊖⊖ LOW	MD 135.26 lower (190.82 lower to 79.71 lower)	⊕⊕⊖⊖ LOW	MD 138.37 lower (193.24 lower to 83.50 lower)	⊕⊕⊕⊖ MODERATE	The mean blood loss was 295 ml (range: 167.4–853 ml)	The mean blood loss with carbetocin in vaginal birth 138.37 lower (range: 193.24 ml lower to 83.50 ml lower)	
							The mean blood loss for vaginal birth was 294 ml (range: 167.4–680 ml)	The mean blood loss with carbetocin was on average 138.37 ml lower (range: 193.24 ml lower to 83.50 ml lower)	
							The mean blood loss for caesarean birth 815 ml (range: 800–853 ml)	The mean blood loss with carbetocin in caesarean birth 138.37 ml lower (range: 193.24 ml lower to 83.5 ml lower)	
Change in haemoglobin (Hb) (g/L)	MD 3.40 lower (7.23 lower to 0.43 higher)	⊕⊕⊖⊖ LOW	MD 4.47 lower (6.71 lower to 2.23 lower)	⊕⊖⊖⊖ VERY LOW	MD 4.33 lower (6.42 lower to 2.23 lower)	⊕⊕⊕⊖ MODERATE	The mean change in Hb was 8.1 g/L (range: 6.0–13.5 g/L)	The mean change in Hb in the intervention group was 4.33 lower (range: 6.42 g/L lower to 2.23 g/L lower)	
							The mean change in Hb for vaginal birth was 8.1 g/L (range: 6.0–13.5 g/L)	The mean change in haemoglobin with carbetocin in vaginal birth was on average 4.33 g/L lower (range: 6.42 g/L lower to 2.23 g/L lower)	
							The mean change in Hb for caesarean birth was 8.4 g/L	The mean change in haemoglobin with carbetocin in caesarean birth was on average 4.33 g/L lower (range: 6.42 g/L lower to 2.23 g/L lower)	
Breastfeeding	Not reported	—	0.96 (0.87–1.06)[d]	⊕⊖⊖⊖ VERY LOW	0.96 (0.87–1.06)	⊕⊕⊖⊖ LOW	746 per 1000	716 per 1000	30 fewer per 1000 (97 fewer to 45 more)
							746 per 1000 (for vaginal birth)	716 per 1000 (for vaginal birth)	30 fewer per 1000 (97 fewer to 45 more) (for vaginal birth)
							See comment[a] (for caesarean birth)	See comment[b] (for caesarean birth)	See comment[c] (for caesarean birth)
Nausea	Not reported	—	0.88 (0.48–1.61)[d]	⊕⊕⊖⊖ LOW	0.88 (0.48–1.61)	⊕⊕⊖⊖ LOW	37 per 1000	33 per 1000	4 fewer per 1000 (19 fewer to 23 more)
							37 per 1000 (for vaginal birth)	33 per 1000 (for vaginal birth)	4 fewer per 1000 (19 fewer to 23 more)
							67 per 1000 (for caesarean birth)	59 per 1000 (for caesarean birth)	8 fewer per 1000 (35 fewer to 41 more)

Outcome	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with placebo or no treatment	Risk with carbetocin	Risk difference with carbetocin
Vomiting	Not reported	—	0.91 (0.49–1.68)[d]	⊕⊖⊖⊖ VERY LOW	0.91 (0.49–1.68)	⊕⊖⊖⊖ VERY LOW	34 per 1000	31 per 1000	3 fewer per 1000 (17 fewer to 23 more)
							34 per 1000 (for vaginal birth)	31 per 1000 (for vaginal birth)	3 fewer per 1000 (17 fewer to 23 more) (for vaginal birth)
							See comment[a] (for caesarean birth)	See comment[b] (for caesarean birth)	See comment[c] (for caesarean birth)
Headache	5.00 (0.25–99.16)	⊕⊕⊖⊖ LOW	1.32 (0.62–2.82)	⊕⊕⊖⊖ LOW	1.35 (0.65–2.82)	⊕⊕⊖⊖ LOW	12 per 1000	16 per 1000	4 more per 1000 (4 fewer to 22 more)
							12 per 1000 (for vaginal birth)	16 per 1000 (for vaginal birth)	4 more per 1000 (4 fewer to 22 more) (for vaginal birth)
							See comment[a] (for caesarean birth)	See comment[b] (for caesarean birth)	See comment[c]
Abdominal pain	Not reported	—	1.14 (0.75–1.73)[d]	⊕⊕⊖⊖ LOW	1.14 (0.75–1.73)	⊕⊕⊖⊖ LOW	339 per 1000	383 per 1000	47 more per 1000 (85 fewer to 247 more)
							339 per 1000 (for vaginal birth)	383 per 1000 (for vaginal birth)	47 more per 1000 (85 fewer to 247 more) (for vaginal birth)
							See comment[a] (for caesarean birth)	See comment[b] (for caesarean birth)	See comment[c] (for caesarean birth)
Hypertension	Not reported	—	1.04 (0.08–13.13)[d]	⊕⊖⊖⊖ VERY LOW[e]	1.04 (0.08–13.13)	⊕⊖⊖⊖ VERY LOW	7 per 1000	7 per 1000	0 fewer per 1000 (6 fewer to 84 more)
							7 per 1000 (for vaginal birth)	7 per 1000 (for vaginal birth)	0 fewer per 1000 (6 fewer to 84 more) (for vaginal birth)
							See comment[a] (for caesarean birth)	See comment[b] (for caesarean birth)	See comment[c] (for caesarean birth)

Outcome	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with placebo or no treatment	Risk with carbetocin	Risk difference with carbetocin
Shivering	Not reported	—	0.54 (0.26–1.11)[d]	⊕⊕⊕⊖ MODERATE	0.54 (0.26–1.11)	⊕⊕⊕⊖ MODERATE	148 per 1000	80 per 1000	68 fewer per 1000 (110 fewer to 16 more)
							148 per 1000 (for vaginal birth)	80 per 1000 (for vaginal birth)	68 fewer per 1000 (110 fewer to 16 more) (for vaginal birth)
							See comment[a] (for caesarean birth)	See comment[b] (for caesarean birth)	See comment[c] (for caesarean birth)
Fever	Not reported	—	1.14 (0.36–3.59)[d]	⊕⊕⊕⊖ MODERATE	1.14 (0.36–3.59)	⊕⊕⊕⊖ MODERATE	29 per 1000	33 per 1000	4 more per 1000 (19 fewer to 75 more)
							29 per 1000 (for vaginal birth)	33 per 1000 (for vaginal birth)	4 more per 1000 (19 fewer to 75 more) (for vaginal birth)
							See comment[a] (for caesarean birth)	See comment[b] (for caesarean birth)	See comment[c] (for caesarean birth)
Diarrhoea	Not reported	—	—	—	—	—	—	—	—

Note: The assumed risks in the placebo or no treatment group are based on weighted means of baseline risks from the studies with placebo or no treatment groups in the network meta-analysis. The corresponding risks in the carbetocin group (and their 95% confidence interval) are based on the assumed risks in the placebo or no treatment group and the relative effects of carbetocin (and its 95% CI) derived from the network meta-analysis.

[a] There were no included studies or there were no events in the included studies to estimate the baseline risk.
[b] Absolute risk with carbetocin cannot be estimated in the absence of absolute risk with placebo or no treatment.
[c] Risk difference cannot be estimated in the absence of absolute risks with placebo or no treatment and carbetocin.
[d] The included studies did not provide any direct evidence for this outcome, therefore the effect estimate from the indirect evidence is identical to the network effect estimate.
[e] There was no first-order loop in the indirect evidence for this outcome. The lowest-order available loop was therefore used (based on comparison with three additional uterotonics) to rate the certainty of this indirect evidence.

CI: confidence interval; Hb: haemoglobin; MD: mean difference RR: risk ratio

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence[1]

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Further information available at: http://www.gradeworkinggroup.org/

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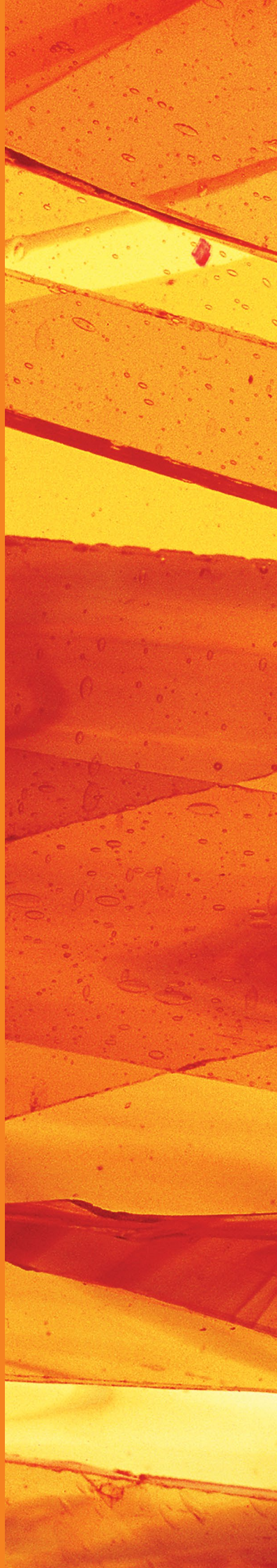

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