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[Intervention Review]

Carbetocin for preventing postpartum haemorrhage

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ABSTRACT

Background

Postpartum haemorrhage (PPH) is one of the major contributors to maternal mortality and morbidity worldwide. Active management of the third stage of labour has been proven to be effective in the prevention of PPH. Syntometrine is more effective than oxytocin but is associated with more side effects. Carbetocin, a long-acting oxytocin agonist, appears to be a promising agent for the prevention of PPH.

Objectives

To determine if the use of oxytocin agonist is as effective as conventional uterotonic agents for the prevention of PPH, and assess the best routes of administration and optimal doses of oxytocin agonist.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (1 March 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1 of 4), MEDLINE (1966 to 1 March 2011) and EMBASE (1974 to 1 March 2011). We checked references of articles and communicated with authors and pharmaceutical industry contacts.

Selection criteria

Randomised controlled trials which compared oxytocin agonist (carbetocin) with other uterotonic agents or with placebo or no treatment for the prevention of PPH.

Data collection and analysis

Two review authors independently assessed trials for inclusion, assessed risk of bias and extracted data.

Main results

We included 11 studies (2635 women) in the review. Six trials compared carbetocin with oxytocin; four of these were conducted for women undergoing caesarean deliveries, one was for women following vaginal deliveries and one did not state the mode of delivery clearly. The carbetocin was administered as 100 µg intravenous dosage across the trials, while oxytocin was administered intravenously but at varied dosages. Four trials compared intramuscular carbetocin and intramuscular syntometrine for women undergoing vaginal deliveries. Three of the trials were on women with no risk factor for PPH, while one trial was on women with risk factors for PPH. One trial compared the use of intravenous carbetocin with placebo. Use of carbetocin resulted in a statistically significant reduction

in the need for therapeutic uterotonics (risk ratio (RR) 0.62; 95% confidence interval (CI) 0.44 to 0.88; four trials, 1173 women) compared to oxytocin for those who underwent caesarean section, but not for vaginal delivery. Compared to oxytocin, carbetocin was associated with a reduced need for uterine massage following both caesarean delivery (RR 0.54; 95% CI 0.37 to 0.79; two trials, 739 women) and vaginal delivery (RR 0.70; 95% CI 0.51 to 0.94; one trial, 160 women). There were no statistically significant differences between carbetocin and oxytocin in terms of risk of any PPH (blood loss greater than 500 ml) or in risk of severe PPH (blood loss greater than 1000 ml). Comparison between carbetocin and syntometrine showed a lower mean blood loss in women who received carbetocin compared to syntometrine (mean difference (MD) -48.84 ml; 95% CI -94.82 to -2.85; four trials, 1030 women). There was no statistically significant difference in terms of the need for therapeutic uterotonic agents, but the risk of adverse effects such as nausea and vomiting were significantly lower in the carbetocin group: nausea (RR 0.24; 95% CI 0.15 to 0.40; four trials, 1030 women); vomiting (RR 0.21; 95% CI 0.11 to 0.39; four trials, 1030 women). The incidence of postpartum hypertension was also significantly lower in women who received carbetocin compared to those who received syntometrine. Cost-effectiveness of carbetocin was investigated by one study published as an abstract, with limited data.

Authors' conclusions

For women who undergo caesarean section, carbetocin resulted in a statistically significant reduction in the need for therapeutic uterotonics compared to oxytocin, but there is no difference in the incidence of postpartum haemorrhage. Carbetocin is associated with less blood loss compared to syntometrine in the prevention of PPH for women who have vaginal deliveries and is associated with significantly fewer adverse effects. Further research is needed to analyse the cost-effectiveness of carbetocin as a uterotonic agent.

PLAIN LANGUAGE SUMMARY

Carbetocin for preventing postpartum haemorrhage

In low- and middle-income countries, postpartum haemorrhage is a major cause of maternal deaths and ill health. In high-income countries, the problems are much less but there is still a small risk of major bleeding problems for women after giving birth. Active management of the third stage of labour, which is generally used to reduce blood loss at birth, consists of giving the mother a drug that helps the uterus to contract, early cord clamping and controlled cord traction to deliver the placenta. Different drugs have been tried and generally either intramuscular oxytocin or intramuscular syntometrine is given. Carbetocin is an oxytocin agonist. Oxytocin agonists are a group of drugs that mimic the oxytocin action, oxytocin being the natural hormone that helps to reduce blood loss at birth. This review includes 11 randomised controlled trials involving 2635 women. The trials compared carbetocin against either oxytocin or syntometrine given after delivery, vaginally or by caesarean section. The comparison between intramuscular carbetocin and oxytocin showed that there was no difference in the risk of heavy bleeding, but that women who received carbetocin were less likely to require other medications to produce uterine contractions following caesarean sections. Comparisons between carbetocin and syntometrine showed that women who received carbetocin had less blood loss compared to women who received syntometrine after vaginal delivery, and were much less likely to experience side effects such as nausea and vomiting. The incidence of hypertension at 30 and 60 minutes post delivery was also significantly lower in women who received carbetocin compared to those who received syntometrine. Five of the 11 studies were known to be supported by a pharmaceutical company.

BACKGROUND

Postpartum haemorrhage (PPH) or excessive bleeding at or after childbirth is a potentially life-threatening complication and is one of the major contributors to maternal mortality and morbidity worldwide (Lewis 2004). Maternal death often occurs within a short period of time due to irreversible shock (Kane 1992). The effects on maternal morbidity include anaemia, fatigue and depression (McCormick 2002). Although there has been a marked improvement in management in recent years, it is known to contribute to almost one-quarter of all maternal deaths worldwide (Carroli 2008). Etuk et al reported a postpartum haemorrhage case fatality rate of 2.2% in a teaching hospital in Nigeria (Etuk 1997). Maternal mortality rates are much lower among developed countries, but haemorrhage remains one of the top causes of maternal deaths over the years (Cantwell 2011). Uterine atony ac-

counts for a significant majority of PPH. Prevention of PPH is therefore of great importance in the pursuit of improved health care for women. This is particularly important in the current context of increasing caesarean delivery rate (Villar 2006), with operative delivery being a recognised risk factor for PPH.

PPH is defined as blood loss of 500 ml or more and severe PPH as 1000 ml or more in the third stage of labour. Active management of the third stage of labour has been proven to be effective in the prevention of PPH (Begley 2010). Active management of the third stage of labour has three components - use of an uterotonic agent, early cord clamping and controlled cord traction. The pharmacologic agents currently used are mainly syntometrine (a combination of oxytocin and ergometrine) and oxytocin. The Cochrane review by McDonald 2004 concluded that syntometrine is associated with a statistically significant reduction in the risk of PPH for blood loss exceeding 500 ml but not exceeding 1000 ml when compared to oxytocin alone. However, the unpleasant side effects of nausea, vomiting and elevated blood pressure in previously normotensive women have been well documented as being considerably higher in women receiving syntometrine (McDonald 1993). The incidence of these side effects in the western studies was as high as 20% to 30%. These side effects are mainly due to the ergometrine component. The Cochrane review on the prophylactic use of ergot alkaloids in the third stage of labour concluded that ergot alkaloids are effective in reducing blood loss and PPH, but adverse effects include vomiting, elevation of blood pressure and pain after birth requiring analgesia, particularly with the intravenous route of administration (Liabsuetrakul 2007). Some authors also reported a higher incidence of retained placenta associated with the use of syntometrine compared with oxytocin (Yuen 1995). More importantly, syntometrine has also been associated with severe complications such as coronary artery spasm (Carey 1993) and intracerebral haemorrhage (Dumoulin 1981). In addition, syntometrine cannot be used in 10% to 20% of the obstetric population as a result of co-existing medical conditions such as pre-eclampsia and cardiac conditions. These women are then given oxytocin which, because of its short duration of action, is less effective in preventing PPH.

Over the past two decades, several other alternatives have been explored, including the use of prostaglandins such as misoprostol and carboprost. Promising results have been published recently with the use of misoprostol for the prevention of postpartum haemorrhage compared to placebo (Chong 2006; Gulmezoglu 2011; Mobeen 2011). The recent Cochrane review by Gulmezoglu et al concluded that oral or sublingual misoprostol shows promising results when compared to placebo in reducing blood loss postpartum. However, oral misoprostol is associated with higher risk of severe postpartum haemorrhage and use of additional uterotonics compared to the conventional injectable uterotonics (Gulmezoglu 2011). Among the other agents or interventions that have been studied for prevention of postpartum haemorrhage, oxytocin agonist (carbetocin) appears to be a promising agent for this indication (Chong 2003).

Carbetocin is a long-acting synthetic octapeptide analogue of oxytocin with agonist properties. The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin. Like oxytocin, carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus, resulting in rhythmic contractions of the uterus, increased frequency of existing contractions and increased uterine tone. In pharmacokinetic studies, intravenous injections of carbetocin produced tetanic uterine contractions within two minutes, lasting six minutes, followed by rhythmic contractions for a further hour. Intramuscular injection produced tetanic contractions in less than two minutes, lasting about 11 minutes, and followed by rhythmic contractions for an additional two hours. The prolonged duration of activity after intramuscular compared with the intravenous carbetocin was significant (Hunter 1992). In comparison to oxytocin, carbetocin induces a prolonged uterine response when administered postpartum, in terms of both amplitude and frequency of contractions.

The potential advantage of intramuscular carbetocin over intramuscular oxytocin is its longer duration of action. Its relative lack of gastrointestinal and cardiovascular side effects should also prove advantageous compared to syntometrine and other ergot alkaloids. Carbetocin is currently indicated for prevention of uterine atony after delivery by caesarean section in spinal or epidural anaesthesia in 23 countries. However, it is not approved by the FDA for use following vaginal births. We conducted a systematic review of the literature for studies on this subject and performed a meta-analysis in order to assess the effectiveness and safety of carbetocin, an oxytocin agonist, in the prevention of PPH.

OBJECTIVES

Primary objective

To determine whether carbetocin is as effective as conventional uterotonic agents for the prevention of postpartum haemorrhage (PPH).

Secondary objective

To determine the best route of administration and the optimal dose of carbetocin for the prevention of PPH.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised controlled trials (RCTs) and quasi-RCTs. We also planned to include cross-over trials and cluster randomised trials if available.

Types of participants

Women who undergo caesarean or vaginal births.

Types of interventions

1. Carbetocin versus other uterotonic agents at any route or doses.
2. Carbetocin versus placebo or no treatment.

Types of outcome measures

Primary outcomes

1. Severe postpartum haemorrhage (PPH) (measured or clinically estimated blood loss 1000 ml or more, or as defined by trial authors), irrespective of the mode of delivery.
2. Maternal death or severe morbidity (e.g. major surgery, organ failure, intensive care unit admission, hyperpyrexia or as defined by trial authors).

Secondary outcomes

Maternal

1. Any PPH (measured or clinically estimated blood loss of at least 500 ml, or as defined by trialists), irrespective of the mode of delivery.
2. Manual removal of the placenta.
3. Blood transfusion.
4. Use of therapeutic uterotonics.
5. Additional treatment for PPH (uterine tamponade, X-ray embolisation).
6. Side effects reported either individually or as a composite where appropriate (elevation of blood pressure, vomiting, nausea, shivering, hyperpyrexia, headache, chest pain, shortness of breath, diarrhoea).
7. Postnatal anaemia (defined by trialists, absolute or relative drop in Hb).
8. Thromboembolic events.
9. Cost.

Neonatal

1. Admission to neonatal intensive care unit.
2. Respiratory distress.
3. Jaundice requiring phototherapy.
4. Not breastfed at discharge.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Groups Trials Register by contacting the Trials Search Co-ordinator (1 March 2011).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we searched:

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1) using the search strategy given in Appendix 1
2. MEDLINE (OVID platform) (1966 to 1 March 2011) using the search strategy in Appendix 2
3. EMBASE (Dialog Datastar) (1974 to 1 March 2011) using the search strategy in Appendix 3.

Searching other resources

References from published studies

We checked references of articles for any unknown trials which were not indexed in the databases.

Unpublished literature

We attempted to obtain unpublished trials from the pharmaceutical industry. We also consulted authors of included studies to find out if they knew of any published or unpublished randomised controlled trials for the use of carbetocin in the prevention of postpartum haemorrhage.

Language restrictions

We did not apply any language restrictions

Data collection and analysis

To avoid duplication of data, in September 2010, the Pregnancy and Childbirth Group developed a hierarchy of reviews on prevention of PPH for women giving birth vaginally.

Each review includes comparisons between one of the methods (from two to 11) with only those methods above it on the list. Thus, this review of ergometrine + oxytocin (4) will include only comparisons with ergometrine (3), oxytocin (2) or placebo (1). If we identify methods in the future, we will add them to the end of the list. The current list is as follows.

1. Placebo/no treatment;
2. oxytocin (Cotter 2001);
3. ergometrine (Liabsuetrakul 2007);
4. ergometrine + oxytocin (McDonald 2004);
5. prostaglandins (Gulmezoglu 2011);
6. carbetocin;
7. uterine massage (before or after placental delivery) (Hofmeyr 2008);
8. breast stimulation for reducing blood loss.

The authors of the reviews that were published before the introduction of this plan will update their reviews according to the above hierarchy when they next update their reviews. Due to the limited number of studies involving carbetocin at the moment, we have covered prevention strategies to reduce the risk of PPH after both vaginal and caesarean deliveries in this review. With more studies in this topic, separate reviews following vaginal and caesarean deliveries will be generated in the future.

For the methods used when assessing the trials identified in the previous version of this review, *see* Appendix 4. For this update we used the following methods when assessing the trial identified by the new search.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion and where necessary, consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved any discrepancy through discussion and through consultation with the third author. We entered data into Review Manager software (RevMan 2011) and checked accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any discrepancy through discussion and through consultation with the third reviewer.

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

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk of bias.

If we identify cluster randomised trials, we planned to explain recruitment bias, baseline imbalance, loss of clusters, incorrect analysis and comparability with individually randomised trials.

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

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

We assessed the methods as:

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

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

We describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We consider studies to be at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

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

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

We describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

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

We describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or was supplied by the trial authors, we re-included missing data in the analyses which we undertook.
We assessed methods as:

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

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.
We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

We described for each included study any important concerns we have about other possible sources of bias.
We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio (RR) with 95% confidence intervals (CI).

Continuous data

For continuous data, we used the mean difference (MD) if outcomes were measured in the same way between trials. We used the standardised mean difference (SMD) to combine trials that measured the same outcome, but used different methods.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis; i.e. we attempted to include all participants randomised to each group in the analyses, and analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if I^2 was greater than 30% and either T^2 was greater than zero or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates of this review, If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and we judged the trials' populations and methods sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if we detected substantial statistical heterogeneity, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. We treated the random-effects summary as the average range of possible treatment effects and discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we have not combined trials.

For random-effects analyses, we have presented the results as the average treatment effect with its 95% CI, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We performed the following subgroup analyses.

High-risk versus low-risk pregnancy for PPH - for studies that compared the use of carbetocin and syntometrine. We undertook subgroup analyses for women with and without risk factors for PPH (Data analysis 3). Overall summary for all the women who received either carbetocin or syntometrine following vaginal delivery was also provided (Data analysis 2).

We pooled studies that were similar in design and that showed homogeneous results using a fixed-effect model. If the results were shown to be heterogeneous between trials while using the fixed-effects model, we chose a random-effects model to estimate summary effect.

Sensitivity analysis

As we identified very few studies for inclusion in this review, and as the results showed similar trends across studies, we have not performed a sensitivity analysis in this review.

However, in the next update of this review, if more trials are identified and if allocation concealment is a significant factor for heterogeneity a sensitivity analyses, we will do so.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of ongoing studies.

Results of the search

We identified a total of eleven randomised controlled trials (RCTs), involving 2635 women, from our searches. Two review authors (Lin Lin Su and Miny Samuel) scanned the abstracts, found 11 studies which met our inclusion criteria, and independently examined independently papers Two of the RCTs were published as abstracts and not in full text, which limited the amount of information which could be obtained from the trials (Barton 1996; Del Angel-Garcia 2006). For details of the included studies, *see* the Characteristics of included studies table. Two additional trials are ongoing (Gomez 2011; Kalahroudi 2010), for further details, see Characteristics of ongoing studies. There are no excluded studies.

Included studies

Six trials compared the use of carbetocin with oxytocin; four were conducted for women undergoing caesarean deliveries (Attilakos 2010; Borruto 2009; Boucher 1998; Dansereau 1999) and one was for women who had vaginal deliveries (Boucher 2004). The mode of delivery is not clear in one trial (Del Angel-Garcia 2006). A standard dose of 100 µg carbetocin as an intravenous bolus is administered across all trials, but the dose of the comparator drug, oxytocin, varies across the trials. Out of the four trials that compared carbetocin with oxytocin, two trials (Boucher 1998; Dansereau 1999) were conducted on women who underwent elective caesarean deliveries. Two trials (Attilakos 2010; Borruto 2009) included participants undergoing both elective and emergency caesarean sections. Two trials (Attilakos 2010; Dansereau 1999) recruited women with or without risk factors for postpartum haemorrhage (PPH) while the study by Borruto 2009 enrolled women

with at least one risk factor for PPH. In Dansereau 1999, differences in baseline characteristics were noted between the groups receiving oxytocin and carbetocin, such as the number of women with history of PPH and gestational diabetes. We performed a post-hoc analysis following correction for the imbalance in distribution of some (such as history of gestational diabetes) but not all of these characteristics (such as past history of PPH). Subgroup analysis was performed by the authors for women with risk factors for PPH in Attilakos 2010. One trial (Boucher 2004) comparing carbetocin and oxytocin was conducted on women with at least one risk factor for PPH who underwent vaginal deliveries.

Four trials compared the use of carbetocin and syntometrine for women undergoing vaginal deliveries (Askar 2011; Leung 2006; Nirmala 2009; Su 2009). Three of the trials (Askar 2011; Leung 2006; Su 2009) were conducted on women with no risk factor for PPH while one trial (Nirmala 2009) was conducted on women with risk factors for PPH.

One trial compared the use of carbetocin with placebo following caesarean deliveries (Barton 1996).

In the trial conducted by Attilakos 2010, participants included women undergoing both elective and emergency caesarean section, as well as women with or without risk factors for PPH. However, subgroup analysis was performed for the risk of PPH and it was concluded that the use of additional oxytocics was reduced in the carbetocin group, irrespective of the presence of risk factors for PPH.

Prior to the full publication, two of the above studies were presented at more than one conference, followed by the publication of abstracts in conference proceedings. We have listed references for these abstracts with the main publication in the Included studies section, but we only extracted the data for pooling from the full publications. However, Barton 1996 was not published in full; we therefore had to extract the data from the abstract.

The study by Del Angel-Garcia 2006 compared the use of carbetocin and syntocinon in women with risk factors for PPH. The main objective of this study, which was only published in an abstract, was economic evaluation of carbetocin for the prevention of uterine atony in patients with risk factors for PPH. In this study, patients who received carbetocin were compared against patients who received syntocinon. However, the mode of delivery was not clear from the abstract and there was a lack of raw data in the abstract. The results of the study in terms of efficacy were therefore not used for analyses.

Risk of bias in included studies

Overall, reporting of methodological quality in the selected trials was fair.

(1) Random sequence generation and allocation concealment (selection bias)

The randomisation process in general and concealment of allocation in particular are considered the most important and sensitive indicators that bias has been minimised in a clinical trial (Schulz 1995). All the studies were randomised.

For studies comparing carbetocin and oxytocin, method of randomisation was by computer-generated numbers for three studies (Attilakos 2010; Boucher 2004; Dansereau 1999), but it was not clear in the other three studies (Borruto 2009; Boucher 1998; Del Angel-Garcia 2006). Three studies did a block randomisation (Attilakos 2010; Boucher 2004; Dansereau 1999) with a block size of two, four and 10 respectively. However, adequate concealment allocation was only described in two out of the six trials (Attilakos 2010; Boucher 2004). The use of a randomisation block size of two (Dansereau 1999) made allocation concealment less effective, as every second participant's allocation could be correctly predicted.

For trials comparing carbetocin and syntometrine, computer generated randomisation and adequate concealment allocation were performed for all the four trials (Askar 2011; Leung 2006; Nirmala 2009; Su 2009).

For the trial comparing carbetocin and placebo (Barton 1996), method of randomisation and allocation concealment were not described.

(2) Blinding (performance and detection bias)

For Askar 2011, Attilakos 2010, Boucher 1998, Boucher 2004, Dansereau 1999, Leung 2006, Nirmala 2009 and Su 2009, participants and medical personnel were blinded to the intervention, with low risk of performance and detection bias.

In Borruto 2009, the authors mentioned that the participants were divided in two groups with blinding to the study medication, but it was not clearly mentioned whether the assessors were blinded to the study medications. In Barton 1996, the abstract states that it is a double-blind study, but there was no further information. Blinding was not described in the abstract by Del Angel-Garcia 2006.

(3) Attrition bias and selective reporting bias

For Boucher 1998, three women were excluded from the study because they did not receive the study medication. This is unlikely to affect the results, although not all the analyses were performed on all of the 57 women who received the medications. There was therefore no intention-to-treat analysis, resulting in unclear risk of reporting bias.

For Dansereau 1999, 35 women were withdrawn from the study before the study drug was received. Twenty-four women were subsequently not included in the primary efficacy analysis due to major protocol violations. However, post-hoc analyses were carried out, including the 24 women who had protocol violations, and when the 24 women were considered as treatment success (i.e. no need for further oxytocic therapy), the same result was obtained. Intention-to-treat analysis was performed for analyses of

the adverse symptoms or signs. However, it was not performed for the analyses looking at the efficacy of the interventions, as the 24 women who had protocol violations were not included in these analyses.
For Boucher 2004, only four women were excluded postrandomisation, the small number of which is unlikely to influence the result. Certain data were not available, resulting in a lower number of participants being assessed for certain outcomes. For example, the outcome of mean blood loss and the percentage of women with estimated blood loss greater than 500 ml was only assessed in 64/83 (77.1%) in the carbetocin group and 67/77 (87.0%) in the oxytocin group. The availability of these data may influence the results. Intention-to-treat analysis was not strictly followed. Some of the data were not accounted for in the analysis.

For Barton 1996 and Del Angel-Garcia 2006, there was unclear risk of attrition bias and selective reporting bias, as there was inadequate information in the abstract.
For Attilakos 2010, three out of 380 prepared ampoules were not used (one was opened by mistake, one shattered during opening and one had possible contamination). This is unlikely to affect the analyses. Analyses were performed for all the 377 participants who completed study.
For Leung 2006, a total of 329 women received the randomised medications. However, 15 out of the 165 women who received carbetocin and 14 out of the 164 women who received syntometrine were excluded from analyses as they did not have paired haemoglobin test after 48 hours of delivery. Inclusion of these women for analyses of other outcome measures, such as use of therapeutic outcomes, could add further information.
For Su 2009, 50 women were withdrawn from the study after informed consent, but before randomisation. This is unlikely to influence the results of the data analyses. Analyses were performed for all the participants randomised and completed the study.
For Nirmala 2009, Borruto 2009 and Askar 2011, analyses were performed on all the 120, 104 and 240 participants recruited in the studies respectively.

(4) Other potential sources of bias

For Attilakos 2010, the authors have received travel expenses from Ferring for presentation. For Boucher 1998, Boucher 2004, Dansereau 1999 and Leung 2006, the project benefited from a grant by the pharmaceutical company. For Su 2009, the carbetocin was purchased from Ferring Inc at a discounted price.

Effects of interventions

We analysed a total of 11 trials in this review. Analyses were performed for the three comparisons: (1) carbetocin versus oxytocin; (2) carbetocin versus syntometrine and (3) carbetocin versus placebo. Oxytocin can be used following both vaginal and caesarean deliveries. The types of participants for vaginal and caesarean deliveries were different and the mode of delivery is an important factor which could influence the treatment outcomes. We therefore carried out separate analyses for caesarean and vaginal deliveries in studies which compared the use of carbetocin versus oxytocin. For studies which compared the use of carbetocin and syntometrine, we carried out subgroup analyses for women with and without risk factors for PPH, as these two groups of women are at very different risks of PPH. The exact number of trials and participants varied for each outcome, with some comparisons only having one trial available, which limits the conclusions that can be drawn for some comparisons. For our secondary objective, no study has been conducted to determine the best route of administration and the optimal dose of oxytocin agonist for the prevention of PPH.

PPH

Carbetocin versus oxytocin

Severe PPH (blood loss greater than 1000 ml) was reported in two studies (Attilakos 2010; Boucher 1998) and there was no significant difference in the number of women with severe PPH undergoing caesarean delivery (risk ratio (RR) 0.91; 95% confidence interval (CI) 0.39 to 2.15; two trials; 432 women), *see* Analysis 1.1. PPH was defined as greater than 500 ml blood loss in one trial (Borruto 2009) and not defined in one trial (Dansereau 1999). We pooled data from all four studies (Attilakos 2010; Borruto 2009; Boucher 1998; Dansereau 1999) to determine the overall treatment effect in reducing any PPH in women who underwent caesarean deliveries. The results showed that the risk of any PPH was similar in both the group receiving carbetocin and the group receiving oxytocin (RR 0.66; 95% (CI) 0.42 to 1.06; four trials; 1195 women). For women who underwent vaginal delivery, again the risk of having PPH was similar in both the oxytocin and carbetocin groups (RR 0.95, 95% CI 0.43 to 2.09; one trial, 131 women) - *see* Analysis 1.2.

Carbetocin versus syntometrine

We analysed the outcome of PPH (greater than 500 ml) in all the four studies comparing the use of carbetocin and syntometrine following vaginal deliveries. Pooled data showed no statistically significant difference between the two interventions (RR 1.00; 95% CI 0.48 to 2.07; four trials, 1030 women; Analysis 2.2). Three studies (Askar 2011; Leung 2006; Su 2009) reported the outcome of severe PPH (greater than 1000 ml) which showed no difference between the two interventions (RR 0.50; 95% CI 0.09 to 2.72; three trials, 910 women; Analysis 2.1).

Carbetocin versus placebo

PPH was not stated as an outcome measure in the study by Barton 1996, which compared the use of carbetocin and placebo following caesarean deliveries.

Use of therapeutic uterotonics

Carbetocin versus oxytocin

Four trials, with a total of 1173 women, compared the use of carbetocin and oxytocin as uterotonic agents following caesarean deliveries. The use of carbetocin compared with the use of oxytocin, was associated with a reduced need for subsequent use of therapeutic uterotonics for women in this group (RR 0.62; 95% CI 0.44 to 0.88; Analysis 1.3). The dose of carbetocin used was 100 µg across the trials. However, the dosage of oxytocin varied in the trials - a total of 32.5 units over 16 hours in the trial by Boucher 1998; five units oxytocin intravenous bolus followed by 20 units oxytocin over eight hours in Dansereau 1999; 10 units oxytocin infusion over two hours in Borruto 2009 and five units oxytocin as intravenous bolus in Attilakos 2010. There was no significant result heterogeneity between the trials (I^2 = 17%, P = 0.31).
There was no statistically significant difference for this comparison in the vaginal delivery group (RR 0.93; 95% CI 0.44 to 1.94; one trial, 160 women; Analysis 1.3).
In Del Angel-Garcia 2006, uterine atony was reported in 19% in the oxytocin group compared to 8% in the carbetocin group (P < 0.0001). This is not used in statistical analyses due to the uncertainty regarding the mode of delivery as well as the lack of raw data for analyses.

Carbetocin versus syntometrine

The outcome of use of additional uterotonics was analysed in all the four trials, with a total of 1030 women, which compared the use of single dose of intramuscular carbetocin versus a single dose of intramuscular syntometrine following vaginal deliveries. Pooled data showed no statistically significant difference between the two interventions (RR 0.83; 95% CI 0.60 to 1.15; Analysis 2.3).

Carbetocin versus placebo

In the only trial comparing carbetocin and placebo, the percentage of women requiring additional oxytocic therapy was significantly lower in the carbetocin group compared with the placebo group (RR 0.18; 95% CI 0.09 to 0.35; one trial, 119 women; Analysis 4.1).

Need for blood transfusion

Carbetocin versus oxytocin

Only one study analysed this outcome for women undergoing caesarean delivery and there was no difference in the need for blood transfusion between the carbetocin and oxytocin groups (RR 0.80; 95% CI 0.22 to 2.95; one trial, 377 women; Analysis 1.4).

Carbetocin versus syntometrine

This outcome was analysed in three studies which compared the use of carbetocin and syntometrine. Pooled analyses showed no statistically significant difference between the two groups for this outcome (RR 1.75; 95% CI 0.52 to 5.93; three trials, 910 women; Analysis 2.4).

Blood loss; change in haemoglobin (Hb) levels/haematocrit levels

Carbetocin versus oxytocin

The outcome of mean blood loss was not a specified outcome in the review, but we performed analyses as two studies reported mean blood loss. In women who underwent caesarean section, mean blood loss was observed to be greater in the oxytocin group compared to the carbetocin group, but the difference was not statistically significant (mean difference (MD) -29.00 ml; 95% CI -83.18 to 25.18; two trials, 161 women; Analysis 1.5). In the trial involving women undergoing vaginal delivery, no significant difference was observed between the carbetocin and oxytocin arms (MD 3.30 ml; 95% CI -57.40 to 64.00; one trial, 160 women; Analysis 1.5). Two studies reported on change of Hb levels and both showed a trend towards a greater drop in Hb levels in the oxytocin group compared to women in the carbetocin group; however, the difference was not statistically significant (MD 0.80 g/dL; 95% CI -0.76 to 2.36 in the caesarean delivery trial; MD 3.10 g/dL; 95% CI -0.38 to 6.58 in the vaginal delivery trial) in both the caesarean and vaginal delivery groups, *see* Analysis 1.6. In the study by Attilakos 2010, estimated blood loss was reported as median and range instead of mean blood loss, limiting the inclusion of the results into the meta analysis. No statistically significant difference was noted between the carbetocin and oxytocin arms in the blood loss in this study. Only one study (Boucher 2004) reported change in haematocrit levels, but there was no difference between the carbetocin and oxytocin groups (MD 0.01 g/L; 95% CI 0.00 to 0.02; one trial, 160 women; Analysis 1.7).

Carbetocin versus syntometrine

Mean blood loss was reported in all four studies which compared the use of carbetocin and syntometrine. Pooled analyses showed mean blood loss following delivery was lower in the women who received carbetocin compared to women who received syntometrine (MD -48.84 ml; 95% CI -94.82 to -2.85; four trials, 1030 women; Analysis 2.5). Separate analyses showed that the difference was statistically significant in women with risk factors for PPH (MD -99.00 ml; 95% CI -145.27 to -52.73; one trial, 120 women; Analysis 3.5), but not statistically significant in women without risk factors for PPH (MD -34.60 ml, 95% CI -83.76 to 14.57; three trials, 910 women). Significant heterogeneity was noted among the studies with two trials (Askar 2011; Nirmala 2009) showing significant differences between carbetocin and syntometrine but the other two trials (Leung 2006; Su 2009) showing no significant difference. It is noted that the method of blood loss estimation in the trials varied, which is a possible reason for the heterogeneity. In Askar 2011 and Nirmala 2009, measurement of blood loss was performed by the gravimetric method, whereas in Leung 2006 and Su 2009, the amount of blood loss was by visual estimation.

Need for uterine massage (outcome not prespecified at the protocol stage)

Carbetocin versus oxytocin

We did not prespecify this outcome at the protocol stage, but analysed it as it was an outcome identified by trialists. The need for uterine massage was evaluated in two trials in the caesarean delivery group (Borruto 2009; Dansereau 1999) and the only trial in the vaginal delivery group (Boucher 2004). All three trials showed that the administration of carbetocin is associated with a reduced need for uterine massage (RR 0.54; 95% CI 0.37 to 0.79; two trials, 739 women in the caesarean section group; RR 0.70; 95% CI 0.51 to 0.94; one trial, 160 women in the vaginal delivery group. *See* Analysis 1.8). In the trial comparing carbetocin and placebo (Barton 1996), uterine tone was significantly increased in carbetocin-treated women compared with placebo-treated women for 20 minutes following drug administration ($P < 0.05$), but there were no differences in fundal position or lochia between the groups. However, no actual figure for these outcomes was presented in the abstract.

Adverse effects

Carbetocin versus oxytocin

Information about the incidence of nausea and vomiting among women was available from all the trials, comparing the use of carbetocin and oxytocin. Pooled data did not reveal any statistically significant differences in terms of the adverse effects. For Attilakos 2010 and Borruto 2009, the adverse effects were described without a direct comparison of the adverse effects between the two groups of carbetocin and oxytocin, which limited the inclusion of the information into the meta-analysis. Meta-analyses were performed only for adverse effects where direct comparisons were made between the two groups. For women who underwent caesarean delivery, the risk of experiencing headache, chills, abdominal pain, dizziness, tremor, nausea, vomiting, back pain, pruritis/itching, feeling of warmth, metallic taste, flushing, sweating, shortness of breath and premature ventricular contractions were similar in women given oxytocin and carbetocin (*see* Analysis 1.9). Similar results were observed in women who underwent vaginal delivery (Analysis 1.10). For the women who underwent vaginal delivery, those who were given carbetocin had a lower risk of experiencing headache, nausea and vomiting but the difference was not statistically significant: headache (RR 0.51; 95% CI 0.20 to 1.30; one trial, 160 women; Analysis 1.11), nausea (RR 0.66; 95% CI 0.22 to 2.00; one trial, 160 women; Analysis 1.12), vomiting (RR 0.07; 95% CI 0.00 to 1.25; one trial, 160 women; Analysis 1.13).

Carbetocin versus syntometrine

Four studies (total of 1030 participants) compared the adverse effects experienced by the patients between carbetocin and syntometrine. Nausea and vomiting were analysed in all the four studies and pooled data showed that women who received carbetocin were much less likely to experience these symptoms compared to women who received syntometrine: nausea (RR 0.24; 95% CI 0.15 to 0.40; four trials, 1030 women; Analysis 2.7), vomiting (RR 0.21; 95% CI 0.11 to 0.39; four trials, 1030 women; Analysis 2.6). The other side effects which were statistically less likely to be experienced by women in the carbetocin group were tremor (two trials, 490 women; Analysis 2.8), sweating (one trial, 370 women; Analysis 2.11) and uterine/abdominal pain (two trials, 610 women; Analysis 2.12), although some of these outcomes were analysed by some but not all of the studies. Pooled data showed no significant difference for symptoms such as headache, flushing and shivering.

Two studies (Askar 2011; Leung 2006) looked at the incidence of post delivery hypertension, immediately as well as 30 and 60 minutes following delivery. The women who received carbetocin were much less likely to have hypertension of equal to or greater than 140/90 mmHg at 30 minutes after delivery (RR 0.07; 95% CI 0.01 to 0.49; two trials, 570 women) and at 60 minutes after delivery (RR 0.07; 95% CI 0.01 to 0.54; two trials, 540 women). *See* Analysis 2.16.

Carbetocin versus placebo

In the trial comparing carbetocin and placebo, it was reported that flushing, abdominal pain and pruritus were significantly more

common in the carbetocin-treated women than in the placebo-treated women. Carbetocin also produced transient tachycardia and a decrease in diastolic blood pressure compared with placebo. However, no actual figures were presented for these adverse events and statistical analysis is therefore not possible.

Cost effectiveness

Only one study (Del Angel-Garcia 2006) looked at the cost effectiveness of carbetocin as compared to another uterotonic agent. In the study, mean cost per patient treated with carbetocin was $3525 versus $4054 for oxytocin ($P < 0.0001$). The mean cost-effectiveness ratio for oxytocin was $4944, while for carbetocin it was $3874, showing that carbetocin was more cost-effective.

DISCUSSION

Current evidence shows that carbetocin significantly reduces the need for therapeutic uterotonics compared to placebo and oxytocin in women undergoing caesarean delivery. However, pooled data showed that the risk of any postpartum haemorrhage (PPH) or severe PPH (blood loss greater than 1000 ml) was similar in both the group receiving carbetocin and the group receiving oxytocin. Carbetocin results in a reduced need for uterine massage postdelivery in both caesarean and vaginal deliveries. In fact, one of the recommendations from The Society of Obstetricians and Gynaecologists of Canada for PPH prevention is that carbetocin, 100 µg given as an intravenous bolus over one minute, should be used instead of continuous oxytocin infusion in elective caesarean section for the prevention of PPH and to decrease the need for therapeutic uterotonics (Leduc 2009).

Following our previous review, four trials have been completed comparing the use of carbetocin and syntometrine for women who undergo vaginal deliveries, three studies for women with no risk factor for PPH and one for women with risk factors for PPH. The results showed no statistically significant difference in terms of the outcome of the need for therapeutic uterotonics and PPH. The finding that carbetocin is more effective in preventing PPH compared to oxytocin but not when compared to syntometrine is consistent with the prior knowledge that syntometrine is a more effective uterotonic agent than oxytocin. However, pooled analyses from the comparison between carbetocin and syntometrine showed a lower postpartum mean blood loss for women who received carbetocin compared to women who received syntometrine. Difficulty in accurate measurements of estimated blood loss is widely acknowledged, and fewer investigators are using estimated blood loss as a primary clinical outcome measure. However, comparison of this secondary outcome showed a statistically lower mean blood loss in women who received carbetocin.

For trials comparing carbetocin and oxytocin, adequate randomisation was conducted for three out of the six trials, while allocation concealment was adequate for two out of the six studies. As there were very few studies and as the results showed similar trends across studies, we did not perform a sensitivity analysis. However, in the next update of this review, if more trials are identified and if allocation concealment is a significant factor for heterogeneity, we will perform a sensitivity analysis. Intention-to-treat analyses were performed for two out of the six studies in the review. For trials comparing carbetocin and syntometrine, all the studies were of high methodological quality, with computer generated randomisation and adequate concealment allocation. Intention-to-treat analyses were performed for three of the four studies in the review. None of the studies did an intention-to-treat analysis when analysing the effectiveness of oxytocin and carbetocin. An intention-to-treat analysis was only performed for outcomes related to safety in the Dansereau 1999 study.

Although our initial objective was to look at several primary and secondary outcomes, the identified trials did not report certain outcomes mentioned in our initial protocol. These outcomes include incidence of retained placenta, major maternal morbidity, maternal deaths, thromboembolic events and additional treatment on PPH. There were also no data reported regarding the use of carbetocin and breastfeeding, and the neonatal outcomes such as jaundice, admission to intensive care unit and respiratory distress. Future trials should therefore consider the assessment of these outcomes in addition to the outcomes already reported, so that the systematic review can evaluate the evidence from an overall perspective.

Although there is a trend towards less nausea and vomiting with carbetocin in some studies, no statistically significant differences were found in women given carbetocin versus oxytocin for both types of deliveries. Adverse drug-related events are usually uncommon with uterotonic agents such as oxytocin and carbetocin. Therefore, trials with large sample sizes may be required to show any difference in the adverse effects of the two medications.

Syntometrine, a commonly used uterotonic agent, is known to be associated with more adverse effects than oxytocin (McDonald 2004). Pooled data comparing syntometrine and carbetocin showed that adverse effects such as nausea, vomiting, tremor and uterine pain were less likely to be experienced by women who received carbetocin compared to syntometrine. Minimising these adverse effects in the immediate postnatal period adds an additional benefit and enhances the delivery process for the women. Leung 2006 and Nirmala 2009 looked at the outcome of postnatal blood pressure and did not show any statistically significant difference between the two groups. Another significant finding in this review is that women who received carbetocin were statistically less likely to have hypertension at 30 and 60 minutes post delivery compared to syntometrine, which is an important outcome to study. This finding could be potentially beneficial for women

with known hypertension for whom the use of syntometrine is contraindicated. However, women with known hypertension were excluded from the studies in the review. While the data show favourable data for carbetocin from the aspect of hypertension, the safety of carbetocin use in women with hypertension or pre-eclampsia remains an important question and needs to be further evaluated. Neonatal outcomes were not evaluated in the trials in this review.

Another perceived benefit of carbetocin is the long-acting nature leading to prolonged uterine response. Although intravenous or intramuscular oxytocin bolus is used in many units, no trial has compared the use of carbetocin with intravenous or intramuscular bolus of oxytocin. Intravenous oxytocin infusion, instead of intravenous oxytocin bolus, was the route of administration for oxytocin in all three trials in this review.

Our secondary objective was to determine the best route of administration and the optimal dose of oxytocin agonist for the prevention of PPH. However, as carbetocin was given as an intravenous bolus of 100 µg across the three trials, no comparison of the route of administration and dosage of carbetocin could be performed.

Besides medical considerations, the choice of the most appropriate uterotonic agent will be dependent on factors such as cost, especially in countries with lower resource settings. The unit cost of carbetocin is known to be considerably higher than oxytocin. Del Angel-Garcia 2006 from Mexico performed the first study which compared the cost-effectiveness of prophylactic carbetocin and oxytocin following caesarean section, and the results showed that the mean cost per woman was significantly lower following carbetocin treatment compared with oxytocin treatment. The study is only published in the form of an abstract and there is a lack of raw data for analyses. There is a paucity of data regarding cost-effectiveness of carbetocin, and more research is therefore needed to address this important issue.

Convenience of carbetocin may be another factor to consider in choosing the uterotonic agent. Carbetocin is used as a standard 100 µg dose which comes in one ampoule; whereas oxytocin infusion often requires the use of multiple ampoules of medication, which is more time-consuming.

AUTHORS' CONCLUSIONS

Implications for practice

Caesarean delivery

Current evidence shows that carbetocin significantly reduces the need for therapeutic uterotonics and the need for uterine massage compared to placebo and oxytocin in women undergoing caesarean delivery. Pooled data showed no difference in risk of postpartum haemorrhage (PPH) in women who received carbetocin compared to oxytocin following caesarean deliveries.

Vaginal delivery

Carbetocin is similar to syntometrine in the prevention of postpartum haemorrhage for women who have vaginal deliveries, with limited evidence showing a lower postpartum mean blood loss for women who received carbetocin compared to syntometrine. What is statistically and clinically significant is the much lower adverse effects experienced by women who received carbetocin compared to syntometrine. Limited evidence shows significant reduction in the need for uterine massage if given carbetocin compared to oxytocin.

There is evidence to show the benefit of carbetocin over oxytocin for preventing PPH following caesarean deliveries. Carbetocin should also be considered as an option over syntometrine, due to the lower likelihood of adverse effects.

Implications for research

More trials comparing the use of carbetocin with either oxytocin or syntometrine will help to allow better assessment of the efficacy of carbetocin, particularly whether the medication allows reduction of the rates of PPH, besides the reduction in the use of therapeutic uterotonic agents. The safety profile of carbetocin in women with hypertension and cardiac diseases need to be further studied. Cost-effectiveness of carbetocin versus other uterotonic agents and the use of carbetocin as a therapeutic agent for PPH are other useful areas to investigate.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Askar 2011

Methods	Study design: prospective double-blind randomised controlled study Method of randomisation: computer-generated randomisation code Concealment of allocation: use of sealed, consecutively numbered, opaque envelope Blinding: the participants, nurses and doctors attending the delivery were blinded to the type of medication injected (glass ampoules were masked to make the medications look identical) Sample size calculation: not mentioned.
Participants	A total of 240 women completed the study. Inclusion criteria: normal singleton pregnancies achieving normal vaginal delivery at or beyond 37 weeks of gestation Exclusion criteria: (1) women younger than 18 years old and those with known or suspected coagulopathy; (2) contraindications or hypersensitivity to the use of syntometrine or carbetocin; (3) women with risk factors for PPH
Interventions	Patients were randomised to receive either a single intramuscular dose of carbetocin (100 μg) or a single intramuscular dose of syntometrine (5 units of oxytocin and 500 μg of ergometrine)
Outcomes	Primary outcome measure was the need for additional uterotonic therapy. Secondary outcome measures were the incidences of PPH, severe PPH and adverse effects profile
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomisation: computer-generated randomisation code
Allocation concealment (selection bias)	Low risk	Concealment of allocation: use of sealed, consecutively numbered, opaque envelope
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the 240 participants randomised completed the study.
Selective reporting (reporting bias)	Low risk	Data of all the 240 participants randomised were analysed.
Other bias	Low risk	No other bias noted.

Askar 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: the participants, nurses and doctors attending the delivery were blinded to the type of medication injected (glass ampoules were masked to make the medications look identical)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nurses and doctors attending the delivery were blinded to the type of medication injected

Attilakos 2010

Methods	Study design: double-blind randomised trial. Method of randomisation: the randomisation sequence (1:1 ratio - blocks of 10, no stratification) was generated by computer Concealment of allocation: the preparation of the 'blinded' ampoules was undertaken by external agency which provided 380 sequentially numbered and labelled boxes, each containing 1 ampoule of the study drug. The next consecutively numbered box was used following randomisation Blinding: all boxes and ampoules were identically labelled, with the study number (1-380) being the only differentiating feature between different drug packs. The participants and investigators were blinded to the random allocation sequence Sample size: based on a previous audit, additional oxytocics were used after 21% of caesarean sections. A sample size of 338 women (169 in each arm) was needed to detect a difference of 21% versus 10% for the use of additional oxytocics (power 80%, α = 0.05). A total of 380 women were recruited to allow for participant withdrawal, mistakes in randomisation, etc Intention-to-treat: the data were analysed by intention-to-treat principle
Participants	A total of 377 women were randomised and analysed. 3 of the 380 prepared ampoules were not used (one was opened by mistake, one shattered during opening and one had possible contamination). In all these cases, the next consecutive pack was opened Inclusion criteria: women at term undergoing elective or emergency caesarean section under regional anaesthesia Exclusion criteria: women with placenta praevia, multiple gestation and placental abruptio; women undergoing caesarean section under general anaesthesia; preterm gestation (less than 37 weeks); women having emergency caesarean section for fetal or maternal distress
Interventions	Women were randomised to receive either carbetocin 100 µg or oxytocin 5 IU intravenously after delivery of the baby
Outcomes	Primary outcome measure: proportion of women in each arm of the trial who needed additional oxytocic intervention Secondary outcome measures: estimated blood loss, difference in preoperative and postoperative haemoglobin, vital signs, uterine tone, incidence of blood transfusion and adverse effects

Attilakos 2010 (*Continued*)

Notes	The authors have received travel expenses from Ferring for presentation	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Method of randomisation: the randomisation sequence (1:1 ratio - blocks of 10, no stratification) was generated by computer
Allocation concealment (selection bias)	Low risk	Concealment of allocation: the preparation of the 'blinded' ampoules was undertaken by external agency which provided 380 sequentially numbered and labelled boxes each containing 1 ampoule of the study drug. The next consecutively numbered box was used following randomisation. 3 of the 380 prepared ampoules were not used (one was opened by mistake, one shattered during opening and one had possible contamination). In all these cases, the next consecutive pack was opened
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data of the 377 participants were randomised.
Selective reporting (reporting bias)	Low risk	Intention-to-treat: the data were analysed by the intention-to-treat principle
Other bias	Unclear risk	The authors have received travel expenses from Ferring for presentation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: all boxes and ampoules were identically labelled, with the study number (1-380) being the only differentiating feature between different drug packs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The participants and investigators were blinded to the random allocation sequence

Barton 1996

Methods	Study design: randomised controlled trial.
Participants	A total of 119 women undergoing elective caesarean section were recruited in the study (62 in carbetocin arm and 57 in the placebo arm)
Interventions	Participants were allocated to receive a single intravenous injection of either 100 micrograms of carbetocin or saline
Outcomes	Primary outcome: incidence of supplementary oxytocic therapy. Secondary outcomes: time to onset of uterine contraction and time to oxytocic intervention, uterine tone, fundal position, lochia, safety variables including vital signs, blood chemistry and haematology and adverse events
Notes	The publication was only in the form of an abstract.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not described.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The publication was only in the form of an abstract.
Selective reporting (reporting bias)	Unclear risk	The publication was only in the form of an abstract.
Other bias	Unclear risk	The publication was only in the form of an abstract.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding was not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding was not described.

Borruto 2009

Methods	Study design: prospective, randomised controlled clinical trial Method of randomisation: not described. Method of concealment: not described.
Participants	A total of 104 patients with at least 1 risk factor for PPH who underwent caesarean deliveries were recruited Inclusion criteria: term pregnancies (after 36 weeks) with singleton fetuses. Predictors for PPH were co-existing hypertension, chronic anaemia, low socio-economic background, past history of PPH, previous delivery by caesarean section, long birth interval (> 60 month); prolonged second stage of labour and non use of oxytocics Exclusion criteria: toxemia, eclampsia and epilepsy.
Interventions	Participants were randomised to a single 100 µg intravenous dose of carbetocin with that of a standard 2-hours 10 IU intravenous infusion of oxytocin
Outcomes	Primary outcome: proportion of patients requiring additional oxytocic intervention for uterine atony. Other outcome measures: need for uterine massage, blood loss, postpartum uterine involution (fundal height below the umbilicus), side effects of medications
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not described.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the 104 participants enrolled completed the study.
Selective reporting (reporting bias)	Low risk	The data of all the 104 participants enrolled were analysed.
Other bias	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding was not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding was not described.

Boucher 1998

Methods	Study design: double-blind, randomised, prospective study. Method of randomisation: not described. Method of allocation concealment: not described. Blinding: participants, outcome assessors and investigators were blinded to the treatment allocation. Intention-to-treat analysis: no.
Participants	Inclusion criteria: 60 participants were enrolled from a single hospital from Canada. Women 18 years or older, healthy and non-labouring with a singleton pregnancy and normal placental location, scheduled for an elective caesarean section under epidural anaesthesia Exclusion criteria: history of heart disease hypertension, cardiac arrhythmia, or evidence of liver, renal or endocrine disease, use of general anaesthesia for caesarean section
Interventions	Allocation to receiving either carbetocin (100 µg intravenous bolus followed by normal saline infusion) or oxytocin (2.5 units of oxytocin as intravenous bolus, 10 units of oxytocin as rapid infusion, followed by 20 units of oxytocin as intravenous infusion for a total of 16 hours)
Outcomes	Volume of blood lost from the time of drug administration to closure of the abdomen, number of women needing additional oxytocic treatment, treatment tone, position of the fundus, amount and type of lochia, and vital signs
Notes	The trial was supported by a grant from Ferring Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not described.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 women were excluded from the study because they did not receive the study medication. However, this is unlikely to affect the results
Selective reporting (reporting bias)	Unclear risk	Not all the analyses were performed on all the 57 women who received the medications. There was therefore no intention-to-treat analysis
Other bias	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	Blinding: participants were blinded to the treatment allocation

Boucher 1998 (*Continued*)

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors and investigators were blinded to the treatment allocation

Boucher 2004

Methods	Study design: double-blind randomised trial. Method of randomisation: separate randomisation lists using a block size of 4 were prepared for each study site by an independent statistical group using computer-generated codes. Concealment of allocation: adequate, randomisation codes were sealed in sequentially-numbered envelopes. Women were randomised when reaching 6 cm (multiparous) or full (primiparous) cervical dilatation. Blinding: clinical staff and the participants were blinded to the intervention. Sample size: sample size was determined using an estimate that 20% of high-risk pregnant women would require additional uterotonic medication (primary outcome measure) following vaginal delivery to prevent PPH. With a power of 80% to detect a 15% difference between study groups, 152 women were required. Intention-to-treat analysis was not strictly followed. Some of the data were not accounted in the analysis
Participants	Inclusion criteria: a total of 164 women with at least 1 risk factor for PPH were enrolled after informed consent. Risk factors for PPH included history of PPH or retained placenta, grand multiparity (> 5), uterine overdistension related to multiple gestation, fetal macrosomia or polyhydramnios, chorioamnionitis, antepartum haemorrhage, induction or augmentation of labour with oxytocin for at least 4 hours, prolonged labour or rapid excessive labour Exclusion criteria: women younger than 18 years of age, known or suspected coagulopathy, history of heart disease or cardiac arrhythmia, history or evidence of chronic liver, renal, or endocrine disease or hypersensitivity to study drugs
Interventions	Allocation to receiving either carbetocin (100 µg intramuscular injection) or oxytocin (10 units intravenous infusion) given over 2 hours
Outcomes	Need for additional uterotonic intervention, need for uterine massage, change in haemoglobin and haematocrit over the initial 24 hours postpartum, estimated blood loss from the time of drug administration to the end of delivery, uterine tone and amount and type of lochia. Clinical safety assessment was performed by recording vital signs and adverse events
Notes	The study benefited from a grant from Ferring Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Boucher 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	Method of randomisation: separate randomisation lists using a block size of 4 were prepared for each study site by an independent statistical group using computer-generated codes
Allocation concealment (selection bias)	Low risk	Concealment of allocation: adequate, randomisation codes were sealed in sequentially-numbered envelopes. Women were randomised when reaching 6 cm (multiparous) or full (primiparous) cervical dilatation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some of the data were not accounted in the analysis.
Selective reporting (reporting bias)	Unclear risk	Some of the data were not accounted in the analysis.
Other bias	Unclear risk	The study benefited from a grant from Ferring Inc.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: clinical staff and the participants were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical staff were blinded to the intervention.

Dansereau 1999

Methods	Study design: double-blind randomised controlled trial. Method of randomisation: computer-generated randomisation code, stratified by centre and with use of random blocks of 2. Concealment of allocation: not clear. Blinding: physicians, nurses, participants, investigators and sponsor representatives were blinded to the treatment codes at all time. Sample size calculation: the investigators used a variable sample size, sequential design and analysis. The type I and II errors rates were defined at 0.05. Intention-to-treat analysis: only for safety but not for efficacy of the intervention
Participants	Inclusions: 694 women were enrolled from 7 hospitals in Canada. Women were eligible if they were scheduled for an elective caesarean section through a lower segment transverse incision under regional anaesthesia Exclusions: current or previous history of significant disease including heart disease, chronic hypertension requiring treatment, liver, renal or endocrine disorders (other than gestational diabetes), or known coagulopathy, diagnosed placenta praevia or abruptio

Dansereau 1999 (*Continued*)

	placenta, use of general anaesthesia and classic uterine incision
Interventions	Allocation to receiving either carbetocin (100 µg of carbetocin as intravenous bolus, followed by normal saline infusion) or oxytocin (5 units of intravenous bolus, followed by 20 units of oxytocin as an intravenous infusion)
Outcomes	Primary outcomes: need for additional oxytocic intervention in the 48 hours after delivery to maintain the uterus well contracted. Secondary outcomes: position of the fundus and tone of the uterus, amount of lochia, vital signs, drop in haemoglobin level by postoperative day 2 (compared with preoperative value), side effects, delay between drug administration and adequate uterine contraction, delay before need for additional oxytocic, and difference in postoperative blood chemistry. Safety analysis performed
Notes	The trial was supported by a clinical research grant from Ferring Inc, Canada

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Method of randomisation: computer-generated randomisation code, stratified by centre and with use of random blocks of 2
Allocation concealment (selection bias)	High risk	C - Inadequate. The use of a randomisation block size of two made allocation concealment less effective, as every second participant's allocation could be correctly predicted
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis was only for safety but not for efficacy of the intervention
Selective reporting (reporting bias)	Unclear risk	Intention-to-treat analysis was only for safety but not for efficacy of the intervention
Other bias	Unclear risk	The trial was supported by a clinical research grant from Ferring Inc, Canada
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Physicians, nurses and participants were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators and sponsor representatives were blinded to the treatment codes at all time

Del Angel-Garcia 2006

Methods	Study design: randomised pragmatic clinical trial.
Participants	Inclusion: pregnant women with risk factors for PPH. A total of 152 women were included
Interventions	The participants received either carbetocin or syntocinon.
Outcomes	Main objective: cost-effectiveness. Other outcomes: uterine atony and postpartum bleeding
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described.
Allocation concealment (selection bias)	Unclear risk	Method of sequence allocation not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The publication was only in the form of an abstract.
Selective reporting (reporting bias)	Unclear risk	The publication was only in the form of an abstract.
Other bias	Unclear risk	The publication was only in the form of an abstract.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.

Leung 2006

Methods	Study design: prospective double-blind randomised controlled trial. Method of randomisation: computer-generated randomisation code. Concealment of allocation:use of a sealed, consecutively numbered, opaque envelope that contained the computer-generated code prepared before the recruitment. Blinding: clinical staff and the participants were blinded to the intervention. Sample size: with power of 90% to detect a difference of 0.5 g/dL in the haemoglobin concentration change with an alpha of 0.05 required a sample size of 150 in each arm Intention-to-treat analysis: statistical analysis was based on an intention-to-treat principle
Participants	Inclusion criteria: women with singleton pregnancy achieving vaginal delivery beyond 34 weeks' gestation A total of 300 participants were recruited, with 150 in the carbetocin arm and 150 in the syntometrine arm Exclusion criteria: presence of contraindications for the use of syntometrine or carbetocin; women with high risk factors for primary PPH
Interventions	Participants were randomised to receive either a single intramuscular dose of carbetocin (100 μg) or a single intramuscular dose of syntometrine (5 units of syntocinon and 0.5 mg ergometrine)
Outcomes	Primary outcome: drop in haemoglobin concentration (from on admission to 48 hours after delivery) Secondary outcomes: estimated blood loss; incidence of PPH; need for blood transfusion and adverse effects
Notes	The project was supported by Ferring Pharmaceuticals Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomisation: computer-generated randomisation code
Allocation concealment (selection bias)	Low risk	Concealment of allocation:use of a sealed, consecutively numbered, opaque envelope that contained the computer-generated code prepared before the recruitment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A total of 329 women received the randomised medications. However, 15 out of the 165 women who received carbetocin and 14 out of the 164 women who received syntometrine were excluded from analyses as they did not have paired haemoglobin test after 48 hours of delivery. Inclusion of these women for analyses of other outcome measures such as use of therapeutic outcomes could add further information

Leung 2006 (*Continued*)

Selective reporting (reporting bias)	Low risk	Analyses were performed for all the participants with completed data
Other bias	Unclear risk	The project was supported by Ferring Pharmaceuticals Ltd.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: clinical staff and the participants were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All staffs were blinded to the intervention.

Nirmala 2009

Methods	Study design: prospective randomised controlled study. Method of randomisation: computer-generated randomised codes Concealment of allocation: randomised codes sealed in sequentially numbered envelopes Blinding: the preparation and administration of the medication was carried out by midwives who were not involved in the management of the patient except for drug administration Sample size: method of sample size calculation not mentioned
Participants	A total of 120 pregnant women recruited. Inclusion criteria: pregnant women beyond 36 weeks' gestation with a viable fetus with at least 1 risk factor for PPH achieving vaginal delivery. The PPH risk factors included were history of blood transfusion or iron sucrose injection, history of retained placenta, grandmultiparity, twin pregnancy, fetal macrosomia, polyhydramnios, induction or augmentation of labour with oxytocin for at least 4 hours or prolonged labour Exclusion criteria: women younger than 18 years old, history of significant heart disease, hypertension, liver, renal, vascular or endocrine disease or hypersensitivity to oxytocin or carbetocin
Interventions	Participants were randomised to receive either a single intramuscular dose of carbetocin 100 μg or a single ampoule of intramuscular syntometrine (0.5 mg ergometrine and 5 IU oxytocin)
Outcomes	Outcome measures include changes in vital signs, amount of intrapartum blood loss, uterine fundal position, addition of another oxytocic agent, side effects of drugs, amount of lochia, haemoglobin drop after 24 hours postpartum, and incidence of PPH
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Nirmala 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	Method of randomisation: computer-generated randomised codes
Allocation concealment (selection bias)	Low risk	Concealment of allocation: randomised codes sealed in sequentially numbered envelopes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the 120 women randomised completed the study.
Selective reporting (reporting bias)	Low risk	The data of all the 120 women randomised in the study were analysed
Other bias	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: the preparation and administration of the medication was carried out by midwives who were not involved in the management of the patient except for drug administration
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was carried out by midwives who were not involved in the management of the patient except for drug administration

Su 2009

Methods	Study design: prospective double-blind randomised controlled trial. Method of randomisation: computer-generated randomisation list was prepared by a statistician from an independent biostatistics unit. Randomisation was blocked and stratified by parity. Concealment of allocation: the randomisation list was forwarded from the biostatistics unit to the hospital pharmacy, where the medications are kept. The medications were specially packed and coded by the pharmacy according to the randomisation and allocation lists provided by the biostatistics unit. The glass ampoules were masked to make the medications look identical. The corresponding opaque package containing the allocated drug was kept at the delivery suite and was administered by the midwife according to the master list. Blinding: clinical staff and the participants were blinded to the intervention. Sample size: based on the experience at the centre, the need for additional uterotonic agents was 10-15%. A value of 13% was chosen. To declare an equivalence of 10% with 80% power and a 2-sided test of 5%, 180 subjects were needed in each arm. An additional 10 subjects were recruited to account for possible attrition Intention-to-treat analysis: statistical analysis was based on an intention-to-treat principle

Su 2009 (*Continued*)

Participants	Inclusion criteria: women with no contraindication for vaginal delivery at or beyond 34 weeks of gestation A total of 370 subjects were recruited, 185 were randomised to receive syntometrine and 185 randomised to receive carbetocin Exclusion criteria: caesarean deliveries; women with risk factors for PPH; women with contraindication for the use of syntometrine such as hypertension and cardiac disease; history of hypersensitivity to syntometrine or carbetocin
Interventions	Patients were randomised to receive either a single intramuscular dose of carbetocin (100 μg) or a single intramuscular dose of syntometrine (5 units of oxytocin and 500 μg of ergometrine)
Outcomes	Primary outcome measure: need for additional uterotonic agent. Secondary outcome measures: PPH; severe PPH; adverse effects of interventions
Notes	The carbetocin was purchased from Ferring Inc at a discounted price

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Method of randomisation: computer-generated randomisation list was prepared by a statistician from an independent biostatistics unit. Randomisation was blocked and stratified by parity
Allocation concealment (selection bias)	Low risk	Concealment of allocation: the randomisation list was forwarded from the biostatistics unit to the hospital pharmacy, where the medications are kept. The medications were specially packed and coded by the pharmacy according to the randomisation and allocation lists provided by the biostatistics unit. The glass ampoules were masked to make the medications look identical. The corresponding opaque package containing the allocated drug was kept at the delivery suite and was administered by the midwife according to the master list
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the 370 participants randomised completed the study.
Selective reporting (reporting bias)	Low risk	Analyses were performed for all the 370 participants randomised in the study
Other bias	Low risk	

Su 2009 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: clinical staff and the participants were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The medication codes were only broken at the completion of the trial

PPH: postpartum haemorrhage

Characteristics of ongoing studies *[ordered by study ID]*

Gomez 2011

Trial name or title	Comparison of the effectiveness of carbetocin versus oxytocin in managing the third stage of labour in a group of women with risk factors for postpartum haemorrhage
Methods	Randomised controlled trial with the use of permuted block randomisation
Participants	Pregnant women over 34 weeks' gestation with risk factors for postpartum haemorrhage and who undergo vaginal delivery
Interventions	For the intervention group, participants will receive 100 µg of carbetocin diluted in 10 cc of saline administered as a single intravenous bolus dose. For the comparator group, the participants will receive 10 units of oxytocin in 10 cc of saline administered as a single intravenous bolus followed by an intravenous administration of 60 units of oxytocin diluted in 1000 cc of saline at a rate of 80 mL/hour over 12 hours during the third stage of labour
Outcomes	Primary outcome is the average volume of postpartum bleeding within 24 hours of delivery. Secondary outcomes are adverse drug effects and the need for uterotonic agents
Starting date	Anticipated 15/7/2010.
Contact information	Dr Milton cesar Gomez gomez Email: micegogo@hotmail.com
Notes	

Kalahroudi 2010

Trial name or title	Comparison effect of carbetocin and syntometrine in prevention of postpartum haemorrhage
Methods	Randomised double blind clinical trial.
Participants	200 pregnant women with vaginal delivery.

Kalahroudi 2010 (*Continued*)

Interventions	The participants were randomly assigned to receive either 1 ml of intramuscular syntometrine or 1 ml of intramuscular carbetocin following vaginal delivery
Outcomes	All patients were assessed 0.5 and 1 hour after delivery for uterine tonicity and blood pressure. Haemoglobin was checked 24 hours after delivery. The need for uterotonic agents and rate of adverse effects were compared
Starting date	21/1/2010.
Contact information	Dr Mansoureh Samimi Email: dr.samimi.2007@yahoo.com
Notes	

DATA AND ANALYSES

Comparison 1. Carbetocin versus oxytocin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe postpartum haemorrhage (> 1000 ml)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Caesarean delivery	2	432	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.39, 2.15]
1.2 Vaginal delivery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Postpartum haemorrhage (> 500 ml or as defined by trialist)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Caesarean delivery	4	1195	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.42, 1.06]
2.2 Vaginal delivery	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.43, 2.09]
3 Use of additional uterotonic therapy	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Caesarean delivery	4	1173	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.51, 0.81]
3.2 Vaginal delivery	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.44, 1.94]
4 Need for blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Caesarean delivery	1	377	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.22, 2.95]
4.2 Vaginal delivery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Mean blood loss (millilitres)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Caesarean delivery	2	161	Mean Difference (IV, Fixed, 95% CI)	-29.00 [-83.18, 25.18]
5.2 Vaginal delivery	1	160	Mean Difference (IV, Fixed, 95% CI)	3.30 [-57.40, 64.00]
6 Mean haemoglobin difference (g/dL)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Caesarean delivery	2	1012	Mean Difference (IV, Fixed, 95% CI)	0.80 [-0.76, 2.36]
6.2 Vaginal delivery	1	160	Mean Difference (IV, Fixed, 95% CI)	3.10 [-0.38, 6.58]
7 Mean haematocrit difference (g/L)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Caesarean delivery	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Vaginal delivery	1	160	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.00, 0.02]
8 Need for uterine massage (not prespecified)	3	899	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.49, 0.84]
8.1 Caesarean delivery	2	739	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.31, 0.96]
8.2 Vaginal delivery	1	160	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.51, 0.94]
9 Maternal adverse drug reactions for caesarean delivery	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Headache	3	820	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.59, 1.18]
9.2 Chills	1	57	Risk Ratio (M-H, Fixed, 95% CI)	2.9 [0.12, 68.33]
9.3 Abdominal pain/pain	2	716	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.85, 1.24]
9.4 Dizziness	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.06, 14.70]
9.5 Tremor	1	659	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.51, 1.13]
9.6 Nausea	2	716	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.16]
9.7 Vomiting	2	716	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.59, 1.49]
9.8 Back pain	1	659	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.40, 1.67]
9.9 Pruritis/itching	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.21, 4.39]
9.10 Feeling of warmth	1	659	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.84, 1.61]

9.11 Metallic taste	1	659	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.53, 1.73]
9.12 Flushing	1	659	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.87, 1.48]
9.13 Sweating	1	659	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.42, 2.38]
9.14 Shortness of breath	1	57	Risk Ratio (M-H, Fixed, 95% CI)	6.77 [0.37, 125.32]
9.15 Premature ventricular contractions	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.59]
10 Maternal adverse drug reactions for vaginal delivery	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Headache	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.20, 1.30]
10.2 Chills	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.40, 2.79]
10.3 Abdominal pain/pain	1	160	Risk Ratio (M-H, Fixed, 95% CI)	10.21 [0.57, 181.71]
10.4 Dizziness	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.38, 3.08]
10.5 Tremor	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.32, 4.16]
10.6 Nausea	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.22, 2.00]
10.7 Vomiting	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.25]
10.8 Pruritis/itching	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.89]
10.9 Nervous	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.55, 2.77]
10.10 Cardiovascular	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.29, 1.59]
10.11 Vasodilation	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.35, 3.50]
10.12 Hemic/lymphatic	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.36, 1.94]
10.13 Leukocytosis	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.25, 1.91]
10.14 Digestive	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.26, 1.62]
10.15 Urogenital	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.43, 3.92]
10.16 Skin/appendages	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.50]
11 Headache in caesarean/vaginal delivery	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Caesarean	3	820	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.41, 1.67]
11.2 Vaginal	1	160	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.20, 1.30]
12 Nausea for caesarean/vaginal delivery	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Caesarean	2	716	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.16]
12.2 Vaginal	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.22, 2.00]
13 Vomiting for caesarean/vaginal delivery	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Caesarean	2	716	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.59, 1.49]
13.2 Vaginal	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.25]
14 Tremor for caesarean/vaginal delivery	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Caesarean	1	659	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.51, 1.13]
14.2 Vaginal	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.32, 4.16]
15 Chills in caesarean/vaginal delivery	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Caesarean	1	57	Risk Ratio (M-H, Fixed, 95% CI)	2.9 [0.12, 68.33]
15.2 Vaginal	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.40, 2.79]
16 At least one adverse event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Caesarean delivery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Vaginal delivery	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.71, 1.27]

Comparison 2. Carbetocin versus syntometrine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe postpartum haemorrhage (> 1000 ml)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 All women	3	910	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.09, 2.72]
2 Postpartum haemorrhage (> 500 ml)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 All women	4	1030	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.48, 2.07]
3 Use of additional uterotonic therapy	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 All women	4	1030	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.60, 1.15]
4 Need for blood transfusion	3	910	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.52, 5.93]
5 Mean blood loss (millimetres)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 All women	4	1030	Mean Difference (IV, Random, 95% CI)	-48.84 [-94.82, -2.85]
6 Vomiting	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 All women	4	1030	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.11, 0.39]
7 Nausea	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 All women	4	1030	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.15, 0.40]
8 Tremor	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 All women	2	490	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.22, 0.83]
9 Retching	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 All women	1	370	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.03, 0.62]
10 Headache	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 All women	4	1030	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.46, 1.48]
11 Sweating	1	370	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.12, 0.90]
11.1 All women	1	370	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.12, 0.90]
12 Uterine or abdominal pain	2	610	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.35, 0.92]
12.1 All women	2	610	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.35, 0.92]
13 Facial flushing	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 All women	3	910	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.22, 1.09]
14 Shivering	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.63]
14.1 All women	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.63]
15 Mean haemoglobin difference (g/dL)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 All women	2	420	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.17, -0.03]
16 Hypertension (blood pressure greater than or equal to 140/90) immediately after delivery	2	540	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.15, 1.64]
17 Hypertension (blood pressure greater than or equal to 140/90) 30 minutes after delivery	2	540	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.44]
18 Hypertension (blood pressure greater than or equal to 140/90) 60 minutes after delivery	2	540	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.54]

Comparison 3. Carbetocin versus syntometrine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe postpartum haemorrhage (> 1000ml)	3	910	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.09, 2.72]
1.1 Women without risk factor for PPH	3	910	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.09, 2.72]
2 Postpartum haemorrhage (> 500 ml)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Women with risk factor for PPH	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.13, 1.91]
2.2 Women without risk factor for PPH	3	910	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.56, 3.39]
3 Use of additional uterotonic therapy	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Women with risk factor for PPH	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.09, 1.17]
3.2 Women without risk factor for PPH	3	910	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.26]
4 Need for blood transfusion	3	910	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.52, 5.93]
4.1 Women without risk factor for PPH	3	910	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.52, 5.93]
5 Mean blood loss (millimetres)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Women with risk factor for PPH	1	120	Mean Difference (IV, Random, 95% CI)	-99.0 [-145.27, -52.73]
5.2 Women without risk factor for PPH	3	910	Mean Difference (IV, Random, 95% CI)	-34.60 [-83.76, 14.57]
6 Vomiting	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Women with risk factor for PPH	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.08]
6.2 Women without risk factor for PPH	3	910	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.11, 0.40]
7 Nausea	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Women with risk factor for PPH	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.02]
7.2 Women without risk factor for PPH	3	910	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.15, 0.40]
8 Tremor	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Women with risk factor for PPH	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Women without risk factor for PPH	1	370	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.22, 0.83]
9 Retching	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Women without risk factor for PPH	1	370	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.03, 0.62]
10 Headache	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Women with risk factor for PPH	1	120	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.47]

10.2 Women without risk factor for PPH	3	910	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.42, 1.42]
11 Sweating	1	370	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.12, 0.90]
11.1 Women without risk factor for PPH	1	370	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.12, 0.90]
12 Uterine or abdominal pain	2	610	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.35, 0.92]
12.1 Women without risk factor for PPH	2	610	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.35, 0.92]
13 Facial flushing	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Women with risk factor for PPH	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Women without risk factor for PPH	3	910	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.22, 1.09]
14 Shivering	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.63]
14.1 Women without risk factor for PPH	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.63]
15 Mean haemoglobin difference (g/dL)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 Women with risk factor for PPH	1	120	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.17, -0.03]
15.2 Women without risk factor for PPH	1	300	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.37, 0.17]
16 Hypertension (blood pressure greater than or equal to 140/90 mmHg) immediately after delivery	2	540	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.15, 1.64]
16.1 Women without risk factor for PPH	2	540	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.15, 1.64]
17 Hypertension (blood pressure greater than or equal to 140/90) 30 minutes after delivery	2	540	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.44]
17.1 Women without risk factor for PPH	2	540	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.44]
18 Hypertension (blood pressure greater than or equal to 140/90) 60 minutes after delivery	2	540	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.54]
18.1 Women without risk factor for PPH	2	540	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.54]

Comparison 4. Carbetocin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of additional uterotonic therapy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Caesarean delivery	1	119	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.09, 0.35]

Analysis 1.1. Comparison 1 Carbetocin versus oxytocin, Outcome 1 Severe postpartum haemorrhage (> 1000 ml).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 1 Severe postpartum haemorrhage (> 1000 ml)

Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Caesarean delivery					
Attilakos 2010	9/186	9/189		85.4 %	1.02 [0.41, 2.50]
Boucher 1998	0/29	1/28		14.6 %	0.32 [0.01, 7.59]
Subtotal (95% CI)	**215**	**217**		**100.0 %**	**0.91 [0.39, 2.15]**
Total events: 9 (Carbetocin), 10 (Oxytocin)					
Heterogeneity: Chi^2 = 0.47, df = 1 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 0.20 (P = 0.84)					
2 Vaginal delivery					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Carbetocin), 0 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

Analysis 1.2. Comparison 1 Carbetocin versus oxytocin, Outcome 2 Postpartum haemorrhage (> 500 ml or as defined by trialist).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 2 Postpartum haemorrhage (> 500 ml or as defined by trialist)

Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Caesarean delivery					
Attilakos 2010	9/186	9/189		25.2 %	1.02 [0.41, 2.50]
Borruto 2009	12/52	23/52		64.9 %	0.52 [0.29, 0.93]
Boucher 1998	0/29	1/28		4.3 %	0.32 [0.01, 7.59]
Dansereau 1999	2/330	2/329		5.6 %	1.00 [0.14, 7.04]
Subtotal (95% CI)	**597**	**598**		**100.0 %**	**0.66 [0.42, 1.06]**
Total events: 23 (Carbetocin), 35 (Oxytocin)					
Heterogeneity: Chi^2 = 1.88, df = 3 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 1.72 (P = 0.086)					
2 Vaginal delivery					
Boucher 2004	10/64	11/67		100.0 %	0.95 [0.43, 2.09]
Subtotal (95% CI)	**64**	**67**		**100.0 %**	**0.95 [0.43, 2.09]**
Total events: 10 (Carbetocin), 11 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.90)					

Analysis 1.3. Comparison 1 Carbetocin versus oxytocin, Outcome 3 Use of additional uterotonic therapy.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 3 Use of additional uterotonic therapy

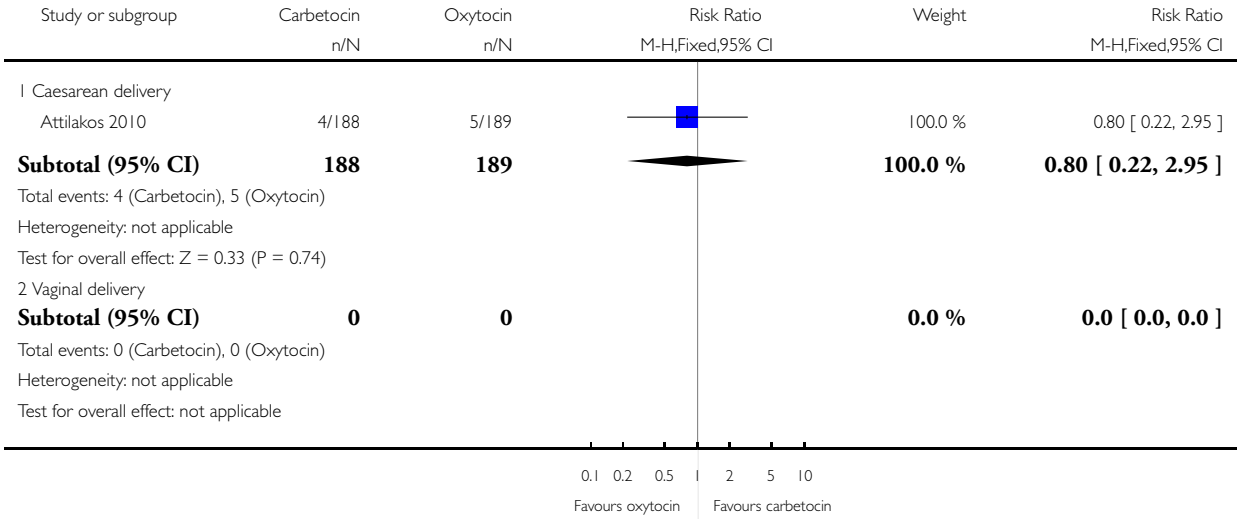
Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Caesarean delivery					
Attilakos 2010	63/188	86/189		67.9 %	0.74 [0.57, 0.95]
Borruto 2009	2/52	5/52		4.0 %	0.40 [0.08, 1.97]
Boucher 1998	0/29	3/28		2.8 %	0.14 [0.01, 2.56]
Dansereau 1999	15/317	32/318		25.3 %	0.47 [0.26, 0.85]
Subtotal (95% CI)	**586**	**587**		**100.0 %**	**0.64 [0.51, 0.81]**
Total events: 80 (Carbetocin), 126 (Oxytocin)					
Heterogeneity: Chi^2 = 3.61, df = 3 (P = 0.31); I^2 =17%					
Test for overall effect: Z = 3.74 (P = 0.00018)					
2 Vaginal delivery					
Boucher 2004	12/83	12/77		100.0 %	0.93 [0.44, 1.94]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**0.93 [0.44, 1.94]**
Total events: 12 (Carbetocin), 12 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					

Analysis 1.4. Comparison 1 Carbetocin versus oxytocin, Outcome 4 Need for blood transfusion.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 4 Need for blood transfusion

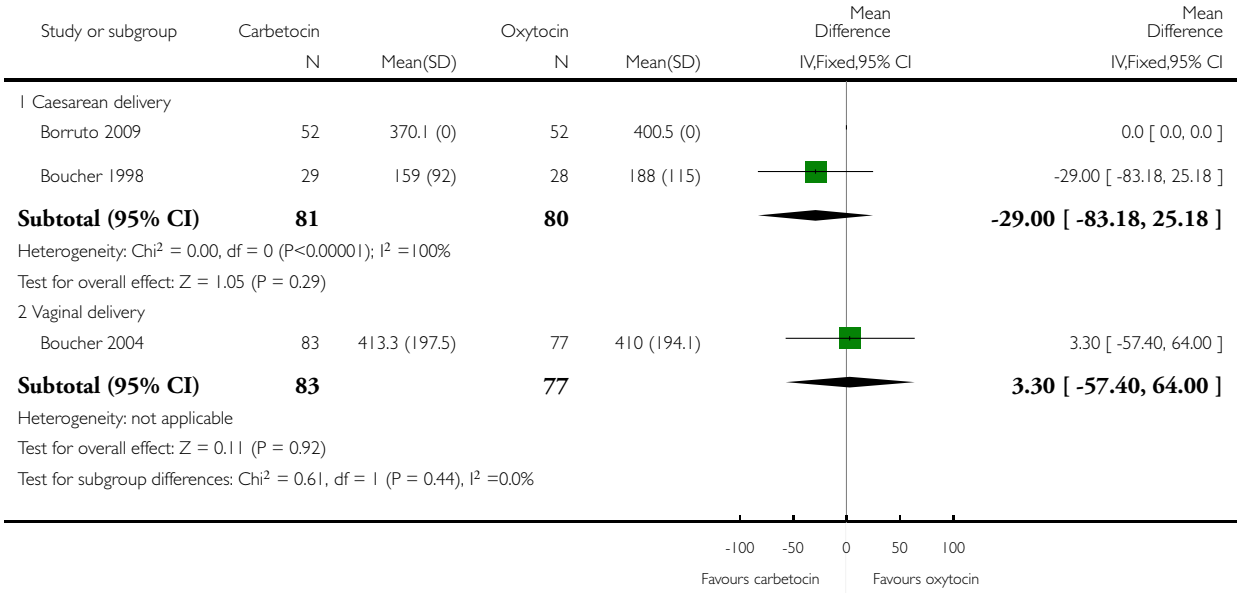


Analysis 1.5. Comparison 1 Carbetocin versus oxytocin, Outcome 5 Mean blood loss (millilitres).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 5 Mean blood loss (millilitres)

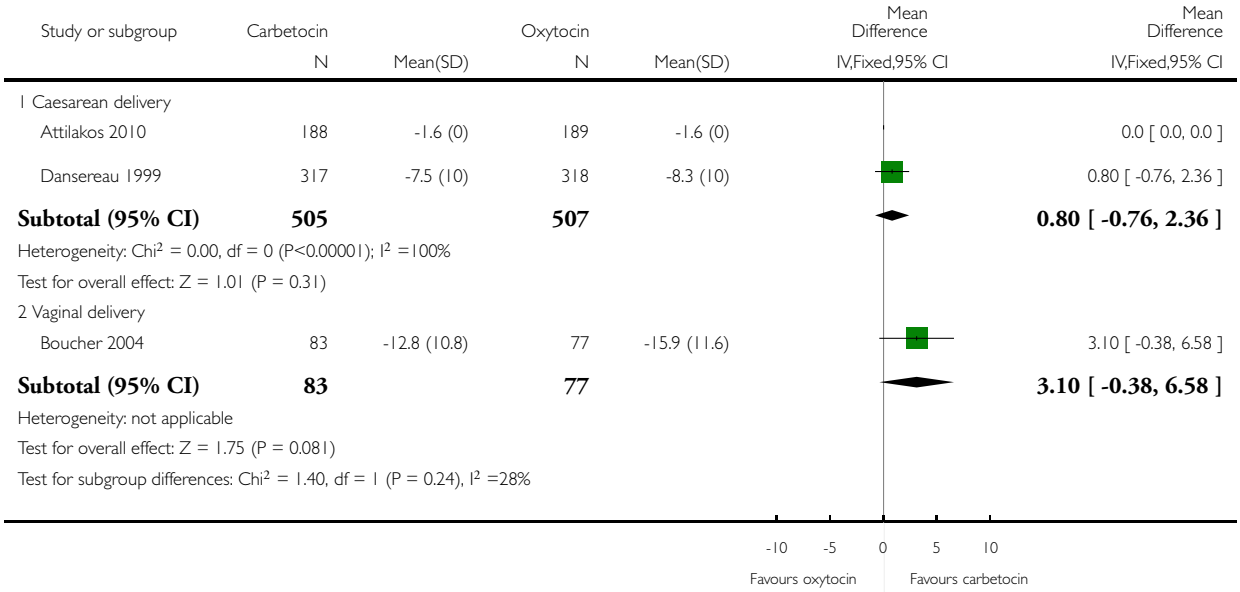


Analysis 1.6. Comparison 1 Carbetocin versus oxytocin, Outcome 6 Mean haemoglobin difference (g/dL).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 6 Mean haemoglobin difference (g/dL)



Analysis 1.7. Comparison 1 Carbetocin versus oxytocin, Outcome 7 Mean haematocrit difference (g/L).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 7 Mean haematocrit difference (g/L)

Study or subgroup	Carbetocin N	Mean(SD)	Oxytocin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Caesarean delivery							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Vaginal delivery							
Boucher 2004	83	-0.04 (0.03)	77	-0.05 (0.04)		100.0 %	0.01 [0.00, 0.02]
Subtotal (95% CI)	**83**		**77**			**100.0 %**	**0.01 [0.00, 0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.78 (P = 0.075)							
Test for subgroup differences: Not applicable							

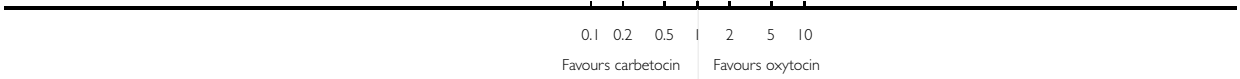
Analysis 1.8. Comparison 1 Carbetocin versus oxytocin, Outcome 8 Need for uterine massage (not prespecified).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 8 Need for uterine massage (not prespecified)

Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Caesarean delivery					
Borruto 2009	20/52	30/52		33.8 %	0.67 [0.44, 1.01]
Dansereau 1999	9/317	24/318		12.1 %	0.38 [0.18, 0.80]
Subtotal (95% CI)	**369**	**370**		**45.9 %**	**0.54 [0.31, 0.96]**
Total events: 29 (Carbetocin), 54 (Oxytocin)					
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 1.90$, df = 1 (P = 0.17); $I^2 = 47\%$					
Test for overall effect: Z = 2.11 (P = 0.035)					
2 Vaginal delivery					
Boucher 2004	36/83	48/77		54.1 %	0.70 [0.51, 0.94]
Subtotal (95% CI)	**83**	**77**		**54.1 %**	**0.70 [0.51, 0.94]**
Total events: 36 (Carbetocin), 48 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.36 (P = 0.018)					
Total (95% CI)	**452**	**447**		**100.0 %**	**0.64 [0.49, 0.84]**
Total events: 65 (Carbetocin), 102 (Oxytocin)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.46$, df = 2 (P = 0.29); $I^2 = 19\%$					
Test for overall effect: Z = 3.26 (P = 0.0011)					
Test for subgroup differences: $Chi^2 = 0.58$, df = 1 (P = 0.45), $I^2 = 0.0\%$					

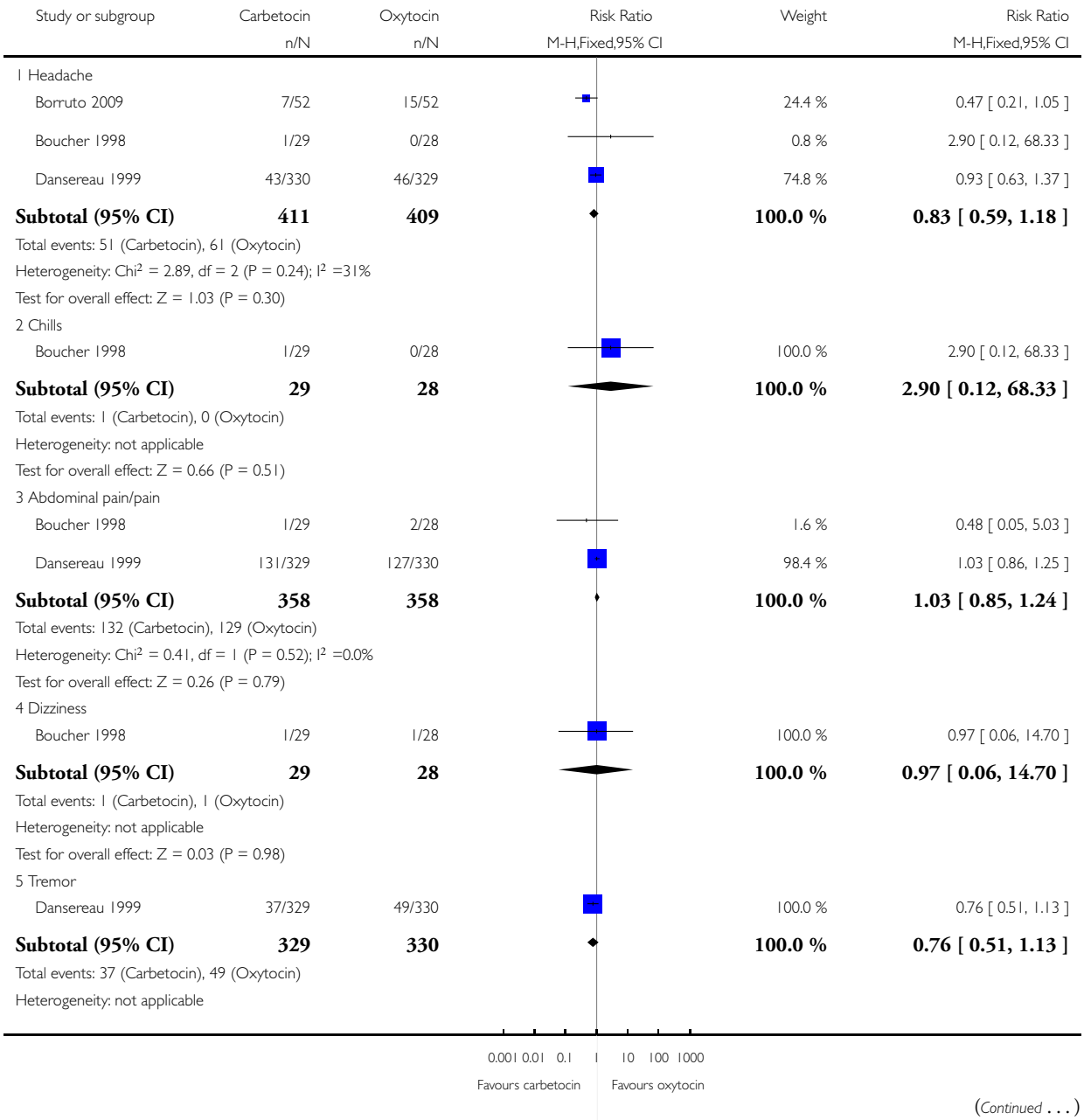


Analysis 1.9. Comparison 1 Carbetocin versus oxytocin, Outcome 9 Maternal adverse drug reactions for caesarean delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 9 Maternal adverse drug reactions for caesarean delivery



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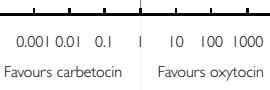
Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.37 (P = 0.17)					
6 Nausea					
Boucher 1998	6/29	6/28		5.9 %	0.97 [0.35, 2.64]
Dansereau 1999	88/329	97/330		94.1 %	0.91 [0.71, 1.16]
Subtotal (95% CI)	**358**	**358**		**100.0 %**	**0.91 [0.72, 1.16]**
Total events: 94 (Carbetocin), 103 (Oxytocin)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 0.75 (P = 0.45)					
7 Vomiting					
Boucher 1998	2/29	5/28		14.9 %	0.39 [0.08, 1.83]
Dansereau 1999	30/329	29/330		85.1 %	1.04 [0.64, 1.69]
Subtotal (95% CI)	**358**	**358**		**100.0 %**	**0.94 [0.59, 1.49]**
Total events: 32 (Carbetocin), 34 (Oxytocin)					
Heterogeneity: Chi^2 = 1.41, df = 1 (P = 0.23); I^2 =29%					
Test for overall effect: Z = 0.26 (P = 0.79)					
8 Back pain					
Dansereau 1999	13/329	16/330		100.0 %	0.81 [0.40, 1.67]
Subtotal (95% CI)	**329**	**330**		**100.0 %**	**0.81 [0.40, 1.67]**
Total events: 13 (Carbetocin), 16 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.56 (P = 0.58)					
9 Pruritis/itching					
Boucher 1998	3/29	3/28		100.0 %	0.97 [0.21, 4.39]
Subtotal (95% CI)	**29**	**28**		**100.0 %**	**0.97 [0.21, 4.39]**
Total events: 3 (Carbetocin), 3 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.05 (P = 0.96)					
10 Feeling of warmth					
Dansereau 1999	65/329	56/330		100.0 %	1.16 [0.84, 1.61]
Subtotal (95% CI)	**329**	**330**		**100.0 %**	**1.16 [0.84, 1.61]**
Total events: 65 (Carbetocin), 56 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					
11 Metallic taste					
Dansereau 1999	20/329	21/330		100.0 %	0.96 [0.53, 1.73]
Subtotal (95% CI)	**329**	**330**		**100.0 %**	**0.96 [0.53, 1.73]**
Total events: 20 (Carbetocin), 21 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.15 (P = 0.88)					
12 Flushing					



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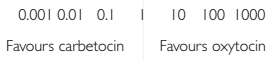
Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dansereau 1999	86/329	76/330		100.0 %	1.14 [0.87, 1.48]
Subtotal (95% CI)	**329**	**330**		**100.0 %**	**1.14 [0.87, 1.48]**
Total events: 86 (Carbetocin), 76 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.93 (P = 0.35)					
13 Sweating					
Dansereau 1999	10/329	10/330		100.0 %	1.00 [0.42, 2.38]
Subtotal (95% CI)	**329**	**330**		**100.0 %**	**1.00 [0.42, 2.38]**
Total events: 10 (Carbetocin), 10 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					
14 Shortness of breath					
Boucher 1998	3/29	0/28		100.0 %	6.77 [0.37, 125.32]
Subtotal (95% CI)	**29**	**28**		**100.0 %**	**6.77 [0.37, 125.32]**
Total events: 3 (Carbetocin), 0 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					
15 Premature ventricular contractions					
Boucher 1998	0/29	1/28		100.0 %	0.32 [0.01, 7.59]
Subtotal (95% CI)	**29**	**28**		**100.0 %**	**0.32 [0.01, 7.59]**
Total events: 0 (Carbetocin), 1 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					



Analysis 1.10. Comparison 1 Carbetocin versus oxytocin, Outcome 10 Maternal adverse drug reactions for vaginal delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 10 Maternal adverse drug reactions for vaginal delivery

Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Headache					
Boucher 2004	6/83	11/77		100.0 %	0.51 [0.20, 1.30]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**0.51 [0.20, 1.30]**
Total events: 6 (Carbetocin), 11 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					
2 Chills					
Boucher 2004	8/83	7/77		100.0 %	1.06 [0.40, 2.79]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**1.06 [0.40, 2.79]**
Total events: 8 (Carbetocin), 7 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.91)					
3 Abdominal pain/pain					
Boucher 2004	5/83	0/77		100.0 %	10.21 [0.57, 181.71]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**10.21 [0.57, 181.71]**
Total events: 5 (Carbetocin), 0 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.58 (P = 0.11)					
4 Dizziness					
Boucher 2004	7/83	6/77		100.0 %	1.08 [0.38, 3.08]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**1.08 [0.38, 3.08]**
Total events: 7 (Carbetocin), 6 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.15 (P = 0.88)					
5 Tremor					
Boucher 2004	5/83	4/77		100.0 %	1.16 [0.32, 4.16]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**1.16 [0.32, 4.16]**
Total events: 5 (Carbetocin), 4 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.23 (P = 0.82)					
6 Nausea					
Boucher 2004	5/83	7/77		100.0 %	0.66 [0.22, 2.00]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**0.66 [0.22, 2.00]**

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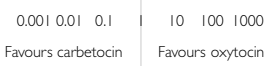
Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 5 (Carbetocin), 7 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.47)					
7 Vomiting					
Boucher 2004	0/83	6/77		100.0 %	0.07 [0.00, 1.25]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**0.07 [0.00, 1.25]**
Total events: 0 (Carbetocin), 6 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.81 (P = 0.071)					
8 Pruritis/itching					
Boucher 2004	0/83	4/77		100.0 %	0.10 [0.01, 1.89]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**0.10 [0.01, 1.89]**
Total events: 0 (Carbetocin), 4 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					
9 Nervous					
Boucher 2004	12/83	9/77		100.0 %	1.24 [0.55, 2.77]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**1.24 [0.55, 2.77]**
Total events: 12 (Carbetocin), 9 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.61)					
10 Cardiovascular					
Boucher 2004	8/83	11/77		100.0 %	0.67 [0.29, 1.59]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**0.67 [0.29, 1.59]**
Total events: 8 (Carbetocin), 11 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.90 (P = 0.37)					
11 Vasodilation					
Boucher 2004	6/83	5/77		100.0 %	1.11 [0.35, 3.50]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**1.11 [0.35, 3.50]**
Total events: 6 (Carbetocin), 5 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.18 (P = 0.85)					
12 Hemic/lymphatic					
Boucher 2004	9/83	10/77		100.0 %	0.83 [0.36, 1.94]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**0.83 [0.36, 1.94]**
Total events: 9 (Carbetocin), 10 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.68)					
13 Leukocytosis					
Boucher 2004	6/83	8/77		100.0 %	0.70 [0.25, 1.91]



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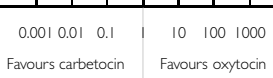
Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**83**	77		**100.0 %**	**0.70 [0.25, 1.91]**
Total events: 6 (Carbetocin), 8 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					
14 Digestive					
Boucher 2004	7/83	10/77		100.0 %	0.65 [0.26, 1.62]
Subtotal (95% CI)	**83**	77		**100.0 %**	**0.65 [0.26, 1.62]**
Total events: 7 (Carbetocin), 10 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.35)					
15 Urogenital					
Boucher 2004	7/83	5/77		100.0 %	1.30 [0.43, 3.92]
Subtotal (95% CI)	**83**	77		**100.0 %**	**1.30 [0.43, 3.92]**
Total events: 7 (Carbetocin), 5 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.64)					
16 Skin/appendages					
Boucher 2004	0/83	5/77		100.0 %	0.08 [0.00, 1.50]
Subtotal (95% CI)	**83**	77		**100.0 %**	**0.08 [0.00, 1.50]**
Total events: 0 (Carbetocin), 5 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.68 (P = 0.092)					



Analysis 1.11. Comparison 1 Carbetocin versus oxytocin, Outcome 11 Headache in caesarean/vaginal delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 11 Headache in caesarean/vaginal delivery

Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Caesarean					
Borruto 2009	7/52	15/52		36.5 %	0.47 [0.21, 1.05]
Boucher 1998	1/29	0/28		4.6 %	2.90 [0.12, 68.33]
Dansereau 1999	46/329	43/330		58.9 %	1.07 [0.73, 1.58]
Subtotal (95% CI)	**410**	**410**		**100.0 %**	**0.83 [0.41, 1.67]**
Total events: 54 (Carbetocin), 58 (Oxytocin)					
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 3.80$, df = 2 (P = 0.15); $I^2 = 47\%$					
Test for overall effect: Z = 0.53 (P = 0.60)					
2 Vaginal					
Boucher 2004	6/83	11/77		100.0 %	0.51 [0.20, 1.30]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**0.51 [0.20, 1.30]**
Total events: 6 (Carbetocin), 11 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					

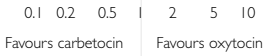
Analysis 1.12. Comparison 1 Carbetocin versus oxytocin, Outcome 12 Nausea for caesarean/vaginal delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 12 Nausea for caesarean/vaginal delivery

Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Caesarean					
Boucher 1998	6/29	6/28		5.9 %	0.97 [0.35, 2.64]
Dansereau 1999	88/329	97/330		94.1 %	0.91 [0.71, 1.16]
Subtotal (95% CI)	**358**	**358**		**100.0 %**	**0.91 [0.72, 1.16]**
Total events: 94 (Carbetocin), 103 (Oxytocin)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 0.75 (P = 0.45)					
2 Vaginal					
Boucher 2004	5/83	7/77		100.0 %	0.66 [0.22, 2.00]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**0.66 [0.22, 2.00]**
Total events: 5 (Carbetocin), 7 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.47)					



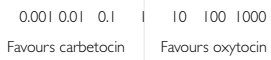
Analysis 1.13. Comparison 1 Carbetocin versus oxytocin, Outcome 13 Vomiting for caesarean/vaginal delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 13 Vomiting for caesarean/vaginal delivery

Study or subgroup	Carbetocin n/N	Oxytocin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Caesarean					
Boucher 1998	2/29	5/28		14.9 %	0.39 [0.08, 1.83]
Dansereau 1999	30/329	29/330		85.1 %	1.04 [0.64, 1.69]
Subtotal (95% CI)	**358**	**358**		**100.0 %**	**0.94 [0.59, 1.49]**
Total events: 32 (Carbetocin), 34 (Oxytocin)					
Heterogeneity: Chi^2 = 1.41, df = 1 (P = 0.23); I^2 =29%					
Test for overall effect: Z = 0.26 (P = 0.79)					
2 Vaginal					
Boucher 2004	0/83	6/77		100.0 %	0.07 [0.00, 1.25]
Subtotal (95% CI)	**83**	**77**		**100.0 %**	**0.07 [0.00, 1.25]**
Total events: 0 (Carbetocin), 6 (Oxytocin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.81 (P = 0.071)					

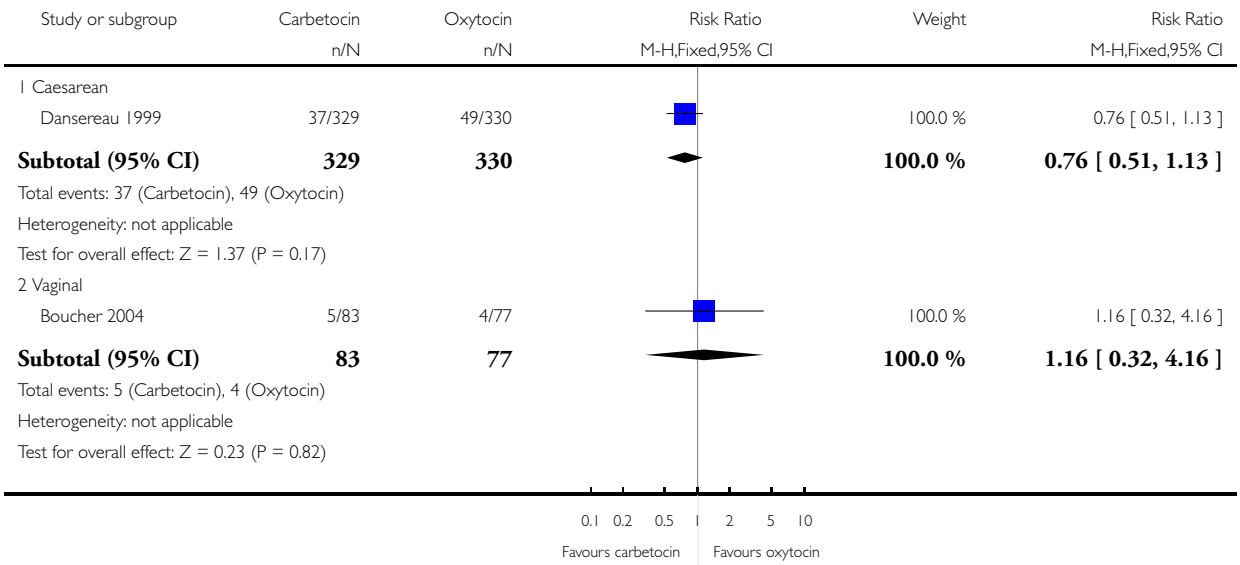


Analysis 1.14. Comparison 1 Carbetocin versus oxytocin, Outcome 14 Tremor for caesarean/vaginal delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 14 Tremor for caesarean/vaginal delivery

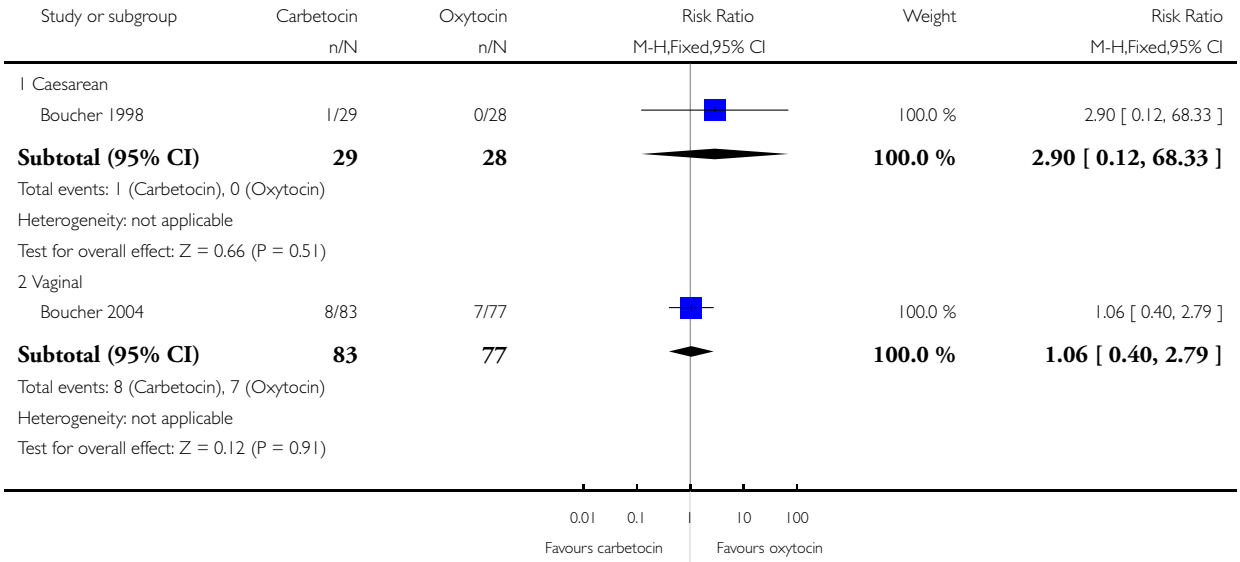


Analysis 1.15. Comparison 1 Carbetocin versus oxytocin, Outcome 15 Chills in caesarean/vaginal delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 15 Chills in caesarean/vaginal delivery

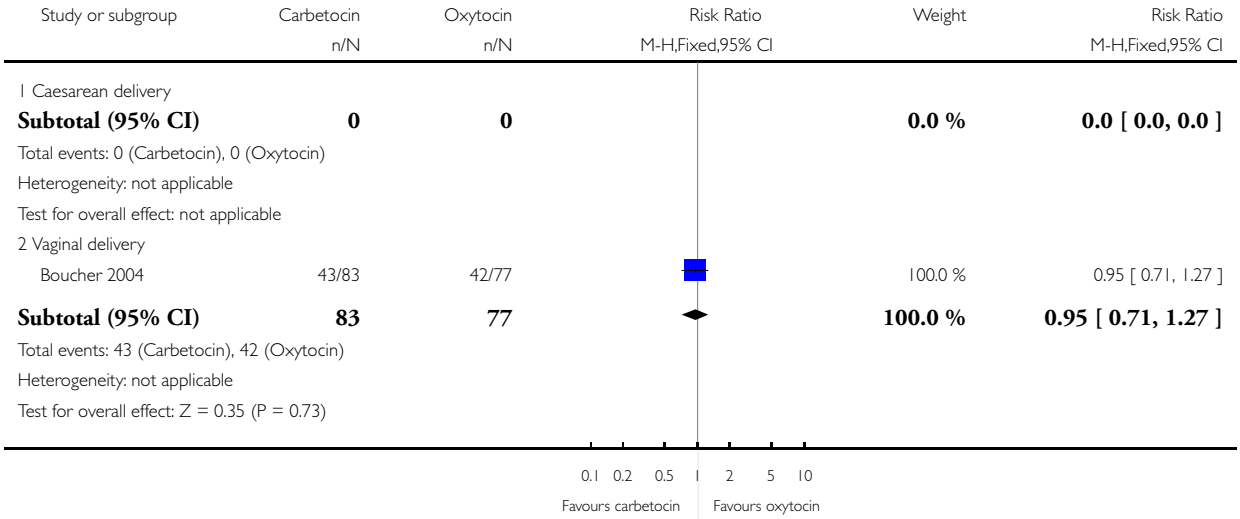


Analysis 1.16. Comparison 1 Carbetocin versus oxytocin, Outcome 16 At least one adverse event.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 1 Carbetocin versus oxytocin

Outcome: 16 At least one adverse event

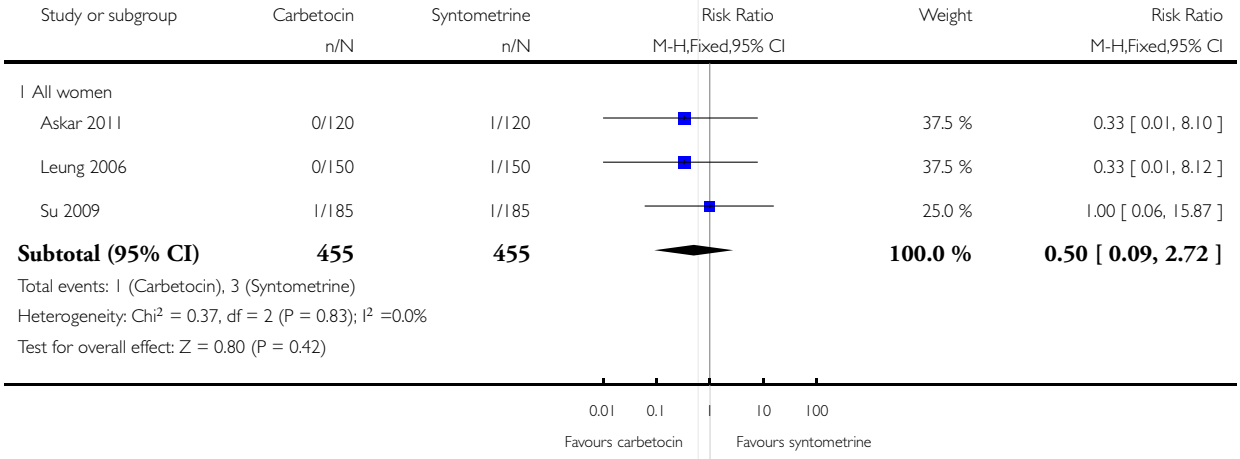


Analysis 2.1. Comparison 2 Carbetocin versus syntometrine, Outcome 1 Severe postpartum haemorrhage (> 1000 ml).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 1 Severe postpartum haemorrhage (> 1000 ml)



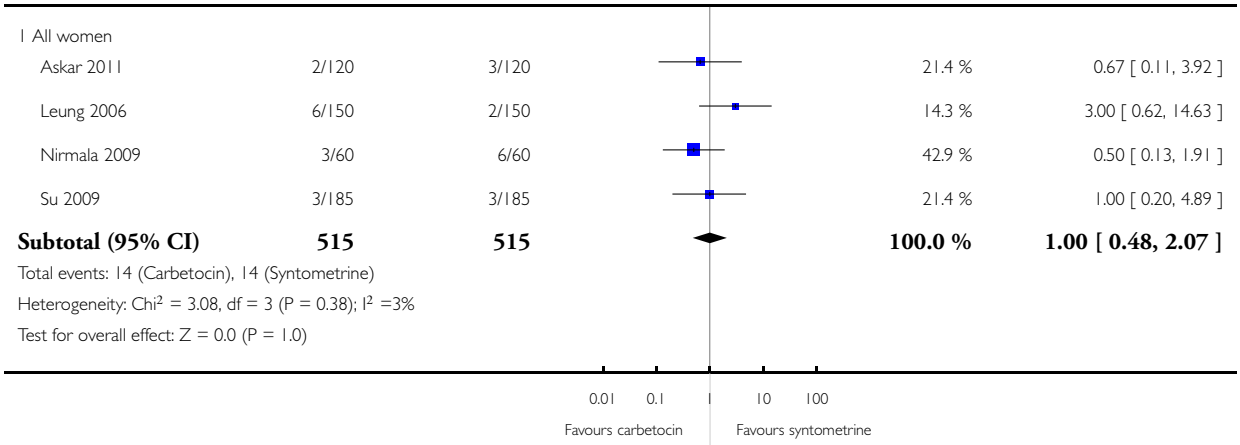
Analysis 2.2. Comparison 2 Carbetocin versus syntometrine, Outcome 2 Postpartum haemorrhage (> 500 ml).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 2 Postpartum haemorrhage (> 500 ml)

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All women					
Askar 2011	2/120	3/120		21.4 %	0.67 [0.11, 3.92]
Leung 2006	6/150	2/150		14.3 %	3.00 [0.62, 14.63]
Nirmala 2009	3/60	6/60		42.9 %	0.50 [0.13, 1.91]
Su 2009	3/185	3/185		21.4 %	1.00 [0.20, 4.89]
Subtotal (95% CI)	**515**	**515**		**100.0 %**	**1.00 [0.48, 2.07]**
Total events: 14 (Carbetocin), 14 (Syntometrine)					
Heterogeneity: Chi^2 = 3.08, df = 3 (P = 0.38); I^2 =3%					
Test for overall effect: Z = 0.0 (P = 1.0)					

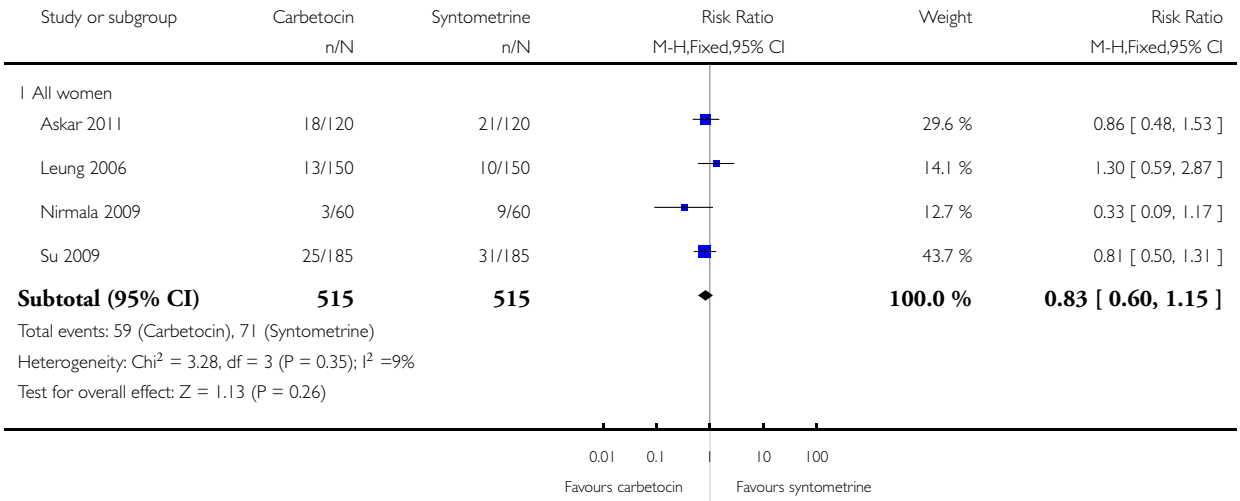


Analysis 2.3. Comparison 2 Carbetocin versus syntometrine, Outcome 3 Use of additional uterotonic therapy.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 3 Use of additional uterotonic therapy

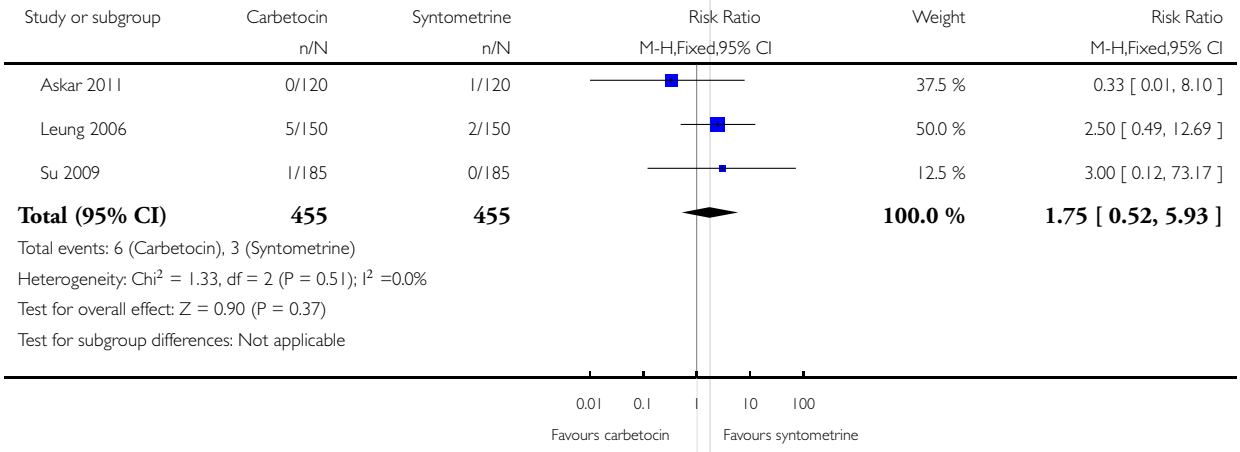


Analysis 2.4. Comparison 2 Carbetocin versus syntometrine, Outcome 4 Need for blood transfusion.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 4 Need for blood transfusion



Analysis 2.5. Comparison 2 Carbetocin versus syntometrine, Outcome 5 Mean blood loss (millimetres).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 5 Mean blood loss (millimetres)

Study or subgroup	Carbetocin N	Mean(SD)	Syntometrine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 All women							
Askar 2011	120	224.6 (110.6)	120	306.1 (95.65)		26.1 %	-81.50 [-107.66, -55.34]
Leung 2006	150	232 (122)	150	249 (175)		24.6 %	-17.00 [-51.14, 17.14]
Nirmala 2009	60	244 (114)	60	343 (143)		22.1 %	-99.00 [-145.27, -52.73]
Su 2009	185	217.4 (99.2)	185	223.1 (76.3)		27.3 %	-5.70 [-23.73, 12.33]
Subtotal (95% CI)	**515**		**515**			**100.0 %**	**-48.84 [-94.82, -2.85]**

Heterogeneity: Tau^2 = 1934.74; Chi^2 = 30.65, df = 3 (P<0.00001); I^2 =90%

Test for overall effect: Z = 2.08 (P = 0.037)

Analysis 2.6. Comparison 2 Carbetocin versus syntometrine, Outcome 6 Vomiting.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 6 Vomiting

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All women					
Askar 2011	3/120	12/120		22.0 %	0.25 [0.07, 0.86]
Leung 2006	1/150	10/150		18.3 %	0.10 [0.01, 0.77]
Nirmala 2009	0/60	2/60		4.6 %	0.20 [0.01, 4.08]
Su 2009	7/185	30/185		55.0 %	0.23 [0.11, 0.52]
Subtotal (95% CI)	**515**	**515**		**100.0 %**	**0.21 [0.11, 0.39]**
Total events: 11 (Carbetocin), 54 (Syntometrine)					
Heterogeneity: Chi^2 = 0.65, df = 3 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 4.91 (P < 0.00001)					

Analysis 2.7. Comparison 2 Carbetocin versus syntometrine, Outcome 7 Nausea.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 7 Nausea

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All women					
Askar 2011	4/120	13/120		18.2 %	0.31 [0.10, 0.92]
Leung 2006	2/150	11/150		15.4 %	0.18 [0.04, 0.81]
Nirmala 2009	0/60	1/60		2.1 %	0.33 [0.01, 8.02]
Su 2009	11/185	46/185		64.3 %	0.24 [0.13, 0.45]
Subtotal (95% CI)	**515**	**515**		**100.0 %**	**0.24 [0.15, 0.40]**
Total events: 17 (Carbetocin), 71 (Syntometrine)					
Heterogeneity: Chi^2 = 0.36, df = 3 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 5.49 (P < 0.00001)					

Analysis 2.8. Comparison 2 Carbetocin versus syntometrine, Outcome 8 Tremor.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 8 Tremor

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 All women				
Nirmala 2009	0/60	0/60		0.0 [0.0, 0.0]
Su 2009	11/185	26/185		0.42 [0.22, 0.83]
Subtotal (95% CI)	**245**	**245**		**0.42 [0.22, 0.83]**
Total events: 11 (Carbetocin), 26 (Syntometrine)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 2.50 (P = 0.012)				

Analysis 2.9. Comparison 2 Carbetocin versus syntometrine, Outcome 9 Retching.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 9 Retching

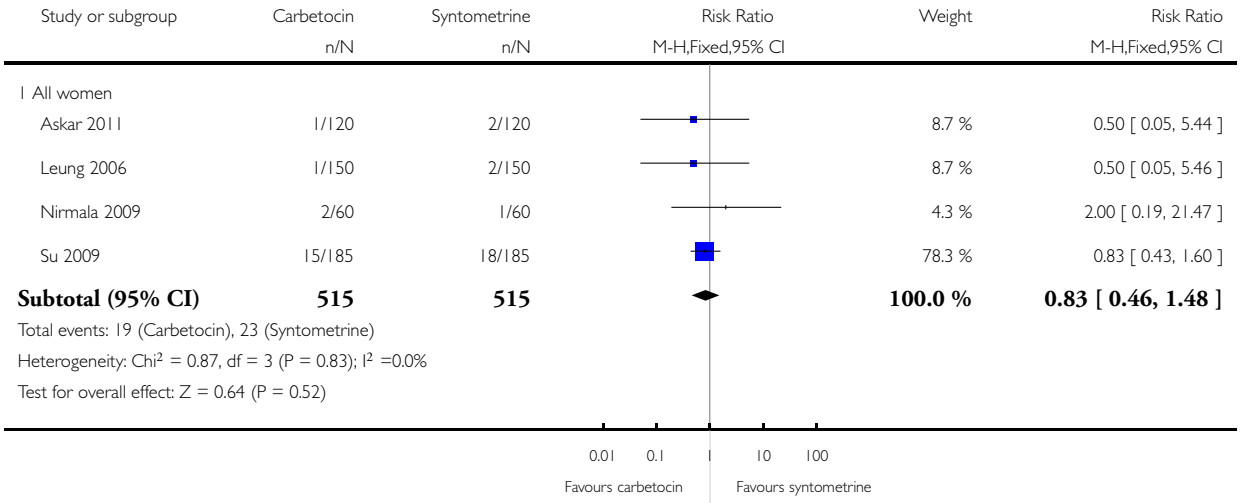
Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All women					
Su 2009	2/185	14/185		100.0 %	0.14 [0.03, 0.62]
Subtotal (95% CI)	**185**	**185**		**100.0 %**	**0.14 [0.03, 0.62]**
Total events: 2 (Carbetocin), 14 (Syntometrine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.60 (P = 0.0094)					

Analysis 2.10. Comparison 2 Carbetocin versus syntometrine, Outcome 10 Headache.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 10 Headache



Analysis 2.11. Comparison 2 Carbetocin versus syntometrine, Outcome 11 Sweating.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 11 Sweating

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All women					
Su 2009	5/185	15/185		100.0 %	0.33 [0.12, 0.90]
Total (95% CI)	**185**	**185**		**100.0 %**	**0.33 [0.12, 0.90]**
Total events: 5 (Carbetocin), 15 (Syntometrine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.17 (P = 0.030)					
Test for subgroup differences: Not applicable					

Analysis 2.12. Comparison 2 Carbetocin versus syntometrine, Outcome 12 Uterine or abdominal pain.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 12 Uterine or abdominal pain

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All women					
Askar 2011	1/120	2/120		5.1 %	0.50 [0.05, 5.44]
Su 2009	21/185	37/185		94.9 %	0.57 [0.35, 0.93]
Total (95% CI)	**305**	**305**		**100.0 %**	**0.56 [0.35, 0.92]**
Total events: 22 (Carbetocin), 39 (Syntometrine)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 2.31 (P = 0.021)					
Test for subgroup differences: Not applicable					

Analysis 2.13. Comparison 2 Carbetocin versus syntometrine, Outcome 13 Facial flushing.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 13 Facial flushing

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All women					
Askar 2011	1/120	4/120		22.9 %	0.25 [0.03, 2.20]
Leung 2006	0/150	3/150		20.0 %	0.14 [0.01, 2.74]
Su 2009	7/185	10/185		57.1 %	0.70 [0.27, 1.80]
Subtotal (95% CI)	**455**	**455**		**100.0 %**	**0.49 [0.22, 1.09]**
Total events: 8 (Carbetocin), 17 (Syntometrine)					
Heterogeneity: Chi^2 = 1.59, df = 2 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 1.76 (P = 0.079)					

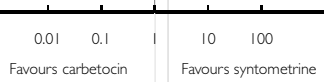
Analysis 2.14. Comparison 2 Carbetocin versus syntometrine, Outcome 14 Shivering.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 14 Shivering

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All women					
Leung 2006	2/150	6/150		100.0 %	0.33 [0.07, 1.63]
Total (95% CI)	**150**	**150**		**100.0 %**	**0.33 [0.07, 1.63]**
Total events: 2 (Carbetocin), 6 (Syntometrine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.36 (P = 0.17)					
Test for subgroup differences: Not applicable					



Analysis 2.15. Comparison 2 Carbetocin versus syntometrine, Outcome 15 Mean haemoglobin difference (g/dL).

Review: Carbetocin for preventing postpartum haemorrhage

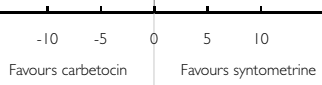
Comparison: 2 Carbetocin versus syntometrine

Outcome: 15 Mean haemoglobin difference (g/dL)

Study or subgroup	Carbetocin N	Mean(SD)	Syntometrine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 All women							
Leung 2006	150	1.4 (1.1)	150	1.5 (1.3)		6.5 %	-0.10 [-0.37, 0.17]
Nirmala 2009	60	0.3 (0.2)	60	0.4 (0.2)		93.5 %	-0.10 [-0.17, -0.03]
Subtotal (95% CI)	**210**		**210**			**100.0 %**	**-0.10 [-0.17, -0.03]**

Heterogeneity: Tau² = 0.0; Chi² = 0.00, df = 1 (P = 1.00); I² =0.0%

Test for overall effect: Z = 2.83 (P = 0.0046)



Analysis 2.16. Comparison 2 Carbetocin versus syntometrine, Outcome 16 Hypertension (blood pressure greater than or equal to 140/90) immediately after delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 16 Hypertension (blood pressure greater than or equal to 140/90) immediately after delivery

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Askar 2011	2/120	4/120		50.0 %	0.50 [0.09, 2.68]
Leung 2006	2/150	4/150		50.0 %	0.50 [0.09, 2.69]
Total (95% CI)	**270**	**270**		**100.0 %**	**0.50 [0.15, 1.64]**

Total events: 4 (Carbetocin), 8 (Syntometrine)

Heterogeneity: Chi² = 0.0, df = 1 (P = 1.00); I² =0.0%

Test for overall effect: Z = 1.14 (P = 0.25)

Test for subgroup differences: Not applicable

Analysis 2.17. Comparison 2 Carbetocin versus syntometrine, Outcome 17 Hypertension (blood pressure greater than or equal to 140/90) 30 minutes after delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 17 Hypertension (blood pressure greater than or equal to 140/90) 30 minutes after delivery

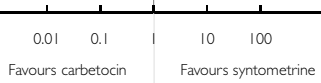
Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Askar 2011	0/120	8/120		50.0 %	0.06 [0.00, 1.01]
Leung 2006	0/150	8/150		50.0 %	0.06 [0.00, 1.01]
Total (95% CI)	**270**	**270**		**100.0 %**	**0.06 [0.01, 0.44]**

Total events: 0 (Carbetocin), 16 (Syntometrine)

Heterogeneity: $Chi^2 = 0.0$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 2.76 (P = 0.0057)

Test for subgroup differences: Not applicable



Analysis 2.18. Comparison 2 Carbetocin versus syntometrine, Outcome 18 Hypertension (blood pressure greater than or equal to 140/90) 60 minutes after delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 2 Carbetocin versus syntometrine

Outcome: 18 Hypertension (blood pressure greater than or equal to 140/90) 60 minutes after delivery

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Askar 2011	0/120	7/120		53.6 %	0.07 [0.00, 1.15]
Leung 2006	0/150	6/150		46.4 %	0.08 [0.00, 1.35]
Total (95% CI)	**270**	**270**		**100.0 %**	**0.07 [0.01, 0.54]**

Total events: 0 (Carbetocin), 13 (Syntometrine)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.94); $I^2 = 0.0\%$

Test for overall effect: Z = 2.56 (P = 0.011)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Carbetocin versus syntometrine, Outcome 1 Severe postpartum haemorrhage (> 1000ml).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 1 Severe postpartum haemorrhage (> 1000ml)

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women without risk factor for PPH					
Askar 2011	0/120	1/120		37.5 %	0.33 [0.01, 8.10]
Leung 2006	0/150	1/150		37.5 %	0.33 [0.01, 8.12]
Su 2009	1/185	1/185		25.0 %	1.00 [0.06, 15.87]
Total (95% CI)	**455**	**455**		**100.0 %**	**0.50 [0.09, 2.72]**
Total events: 1 (Carbetocin), 3 (Syntometrine)					
Heterogeneity: Chi^2 = 0.37, df = 2 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Not applicable					

Analysis 3.2. Comparison 3 Carbetocin versus syntometrine, Outcome 2 Postpartum haemorrhage (> 500 ml).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 2 Postpartum haemorrhage (> 500 ml)

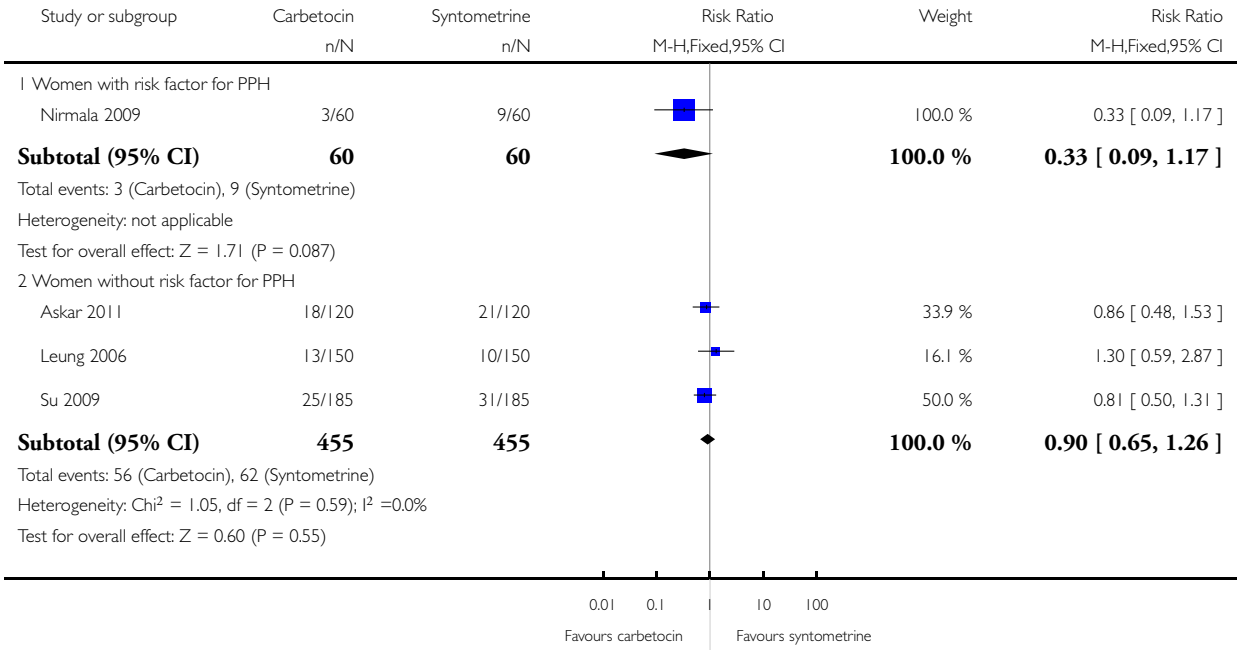
Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women with risk factor for PPH					
Nirmala 2009	3/60	6/60		100.0 %	0.50 [0.13, 1.91]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**0.50 [0.13, 1.91]**
Total events: 3 (Carbetocin), 6 (Syntometrine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
2 Women without risk factor for PPH					
Askar 2011	2/120	3/120		37.5 %	0.67 [0.11, 3.92]
Leung 2006	6/150	2/150		25.0 %	3.00 [0.62, 14.63]
Su 2009	3/185	3/185		37.5 %	1.00 [0.20, 4.89]
Subtotal (95% CI)	**455**	**455**		**100.0 %**	**1.38 [0.56, 3.39]**
Total events: 11 (Carbetocin), 8 (Syntometrine)					
Heterogeneity: Chi^2 = 1.73, df = 2 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 0.69 (P = 0.49)					

Analysis 3.3. Comparison 3 Carbetocin versus syntometrine, Outcome 3 Use of additional uterotonic therapy.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 3 Use of additional uterotonic therapy



Analysis 3.4. Comparison 3 Carbetocin versus syntometrine, Outcome 4 Need for blood transfusion.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 4 Need for blood transfusion

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women without risk factor for PPH					
Askar 2011	0/120	1/120		37.5 %	0.33 [0.01, 8.10]
Leung 2006	5/150	2/150		50.0 %	2.50 [0.49, 12.69]
Su 2009	1/185	0/185		12.5 %	3.00 [0.12, 73.17]
Total (95% CI)	**455**	**455**		**100.0 %**	**1.75 [0.52, 5.93]**
Total events: 6 (Carbetocin), 3 (Syntometrine)					
Heterogeneity: Chi^2 = 1.33, df = 2 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.90 (P = 0.37)					
Test for subgroup differences: Not applicable					

Analysis 3.5. Comparison 3 Carbetocin versus syntometrine, Outcome 5 Mean blood loss (millimetres).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 5 Mean blood loss (millimetres)

Study or subgroup	Carbetocin N	Mean(SD)	Syntometrine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Women with risk factor for PPH							
Nirmala 2009	60	244 (114)	60	343 (143)		100.0 %	-99.00 [-145.27, -52.73]
Subtotal (95% CI)	**60**		**60**			**100.0 %**	**-99.00 [-145.27, -52.73]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.19 (P = 0.000028)							
2 Women without risk factor for PPH							
Askar 2011	120	224.6 (110.6)	120	306.1 (95.65)		33.4 %	-81.50 [-107.66, -55.34]
Leung 2006	150	232 (122)	150	249 (175)		31.4 %	-17.00 [-51.14, 17.14]
Su 2009	185	217.4 (99.2)	185	223.1 (76.3)		35.2 %	-5.70 [-23.73, 12.33]
Subtotal (95% CI)	**455**		**455**			**100.0 %**	**-34.60 [-83.76, 14.57]**
Heterogeneity: Tau^2 = 1702.92; Chi^2 = 22.34, df = 2 (P = 0.00001); I^2 =91%							
Test for overall effect: Z = 1.38 (P = 0.17)							

Analysis 3.6. Comparison 3 Carbetocin versus syntometrine, Outcome 6 Vomiting.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 6 Vomiting

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women with risk factor for PPH					
Nirmala 2009	0/60	2/60		100.0 %	0.20 [0.01, 4.08]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**0.20 [0.01, 4.08]**
Total events: 0 (Carbetocin), 2 (Syntometrine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.30)					
2 Women without risk factor for PPH					
Askar 2011	3/120	12/120		23.1 %	0.25 [0.07, 0.86]
Leung 2006	1/150	10/150		19.2 %	0.10 [0.01, 0.77]
Su 2009	7/185	30/185		57.7 %	0.23 [0.11, 0.52]
Subtotal (95% CI)	**455**	**455**		**100.0 %**	**0.21 [0.11, 0.40]**
Total events: 11 (Carbetocin), 52 (Syntometrine)					
Heterogeneity: Chi^2 = 0.64, df = 2 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 4.80 (P < 0.00001)					

Analysis 3.7. Comparison 3 Carbetocin versus syntometrine, Outcome 7 Nausea.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 7 Nausea

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women with risk factor for PPH					
Nirmala 2009	0/60	1/60		100.0 %	0.33 [0.01, 8.02]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**0.33 [0.01, 8.02]**
Total events: 0 (Carbetocin), 1 (Syntometrine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
2 Women without risk factor for PPH					
Askar 2011	4/120	13/120		18.6 %	0.31 [0.10, 0.92]
Leung 2006	2/150	11/150		15.7 %	0.18 [0.04, 0.81]
Su 2009	11/185	46/185		65.7 %	0.24 [0.13, 0.45]
Subtotal (95% CI)	**455**	**455**		**100.0 %**	**0.24 [0.15, 0.40]**
Total events: 17 (Carbetocin), 70 (Syntometrine)					
Heterogeneity: Chi^2 = 0.33, df = 2 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 5.45 (P < 0.00001)					

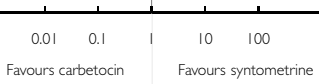
Analysis 3.8. Comparison 3 Carbetocin versus syntometrine, Outcome 8 Tremor.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 8 Tremor

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Women with risk factor for PPH				
Nirmala 2009	0/60	0/60		0.0 [0.0, 0.0]
Subtotal (95% CI)	**60**	**60**		**0.0 [0.0, 0.0]**
Total events: 0 (Carbetocin), 0 (Syntometrine)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Women without risk factor for PPH				
Su 2009	11/185	26/185		0.42 [0.22, 0.83]
Subtotal (95% CI)	**185**	**185**		**0.42 [0.22, 0.83]**
Total events: 11 (Carbetocin), 26 (Syntometrine)				
Heterogeneity: not applicable				
Test for overall effect: Z = 2.50 (P = 0.012)				



Analysis 3.9. Comparison 3 Carbetocin versus syntometrine, Outcome 9 Retching.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 9 Retching

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women without risk factor for PPH					
Su 2009	2/185	14/185		100.0 %	0.14 [0.03, 0.62]
Subtotal (95% CI)	**185**	**185**		**100.0 %**	**0.14 [0.03, 0.62]**
Total events: 2 (Carbetocin), 14 (Syntometrine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.60 (P = 0.0094)					

Analysis 3.10. Comparison 3 Carbetocin versus syntometrine, Outcome 10 Headache.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 10 Headache

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women with risk factor for PPH					
Nirmala 2009	2/60	1/60		100.0 %	2.00 [0.19, 21.47]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**2.00 [0.19, 21.47]**
Total events: 2 (Carbetocin), 1 (Syntometrine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
2 Women without risk factor for PPH					
Askar 2011	1/120	2/120		9.1 %	0.50 [0.05, 5.44]
Leung 2006	1/150	2/150		9.1 %	0.50 [0.05, 5.46]
Su 2009	15/185	18/185		81.8 %	0.83 [0.43, 1.60]
Subtotal (95% CI)	**455**	**455**		**100.0 %**	**0.77 [0.42, 1.42]**
Total events: 17 (Carbetocin), 22 (Syntometrine)					
Heterogeneity: Chi^2 = 0.31, df = 2 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 0.83 (P = 0.41)					

Analysis 3.11. Comparison 3 Carbetocin versus syntometrine, Outcome 11 Sweating.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 11 Sweating

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women without risk factor for PPH					
Su 2009	5/185	15/185		100.0 %	0.33 [0.12, 0.90]
Total (95% CI)	**185**	**185**		**100.0 %**	**0.33 [0.12, 0.90]**

Total events: 5 (Carbetocin), 15 (Syntometrine)
Heterogeneity: not applicable
Test for overall effect: Z = 2.17 (P = 0.030)
Test for subgroup differences: Not applicable

Analysis 3.12. Comparison 3 Carbetocin versus syntometrine, Outcome 12 Uterine or abdominal pain.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 12 Uterine or abdominal pain

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women without risk factor for PPH					
Askar 2011	1/120	2/120		5.1 %	0.50 [0.05, 5.44]
Su 2009	21/185	37/185		94.9 %	0.57 [0.35, 0.93]
Total (95% CI)	**305**	**305**		**100.0 %**	**0.56 [0.35, 0.92]**

Total events: 22 (Carbetocin), 39 (Syntometrine)
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%
Test for overall effect: Z = 2.31 (P = 0.021)
Test for subgroup differences: Not applicable

Analysis 3.13. Comparison 3 Carbetocin versus syntometrine, Outcome 13 Facial flushing.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 13 Facial flushing

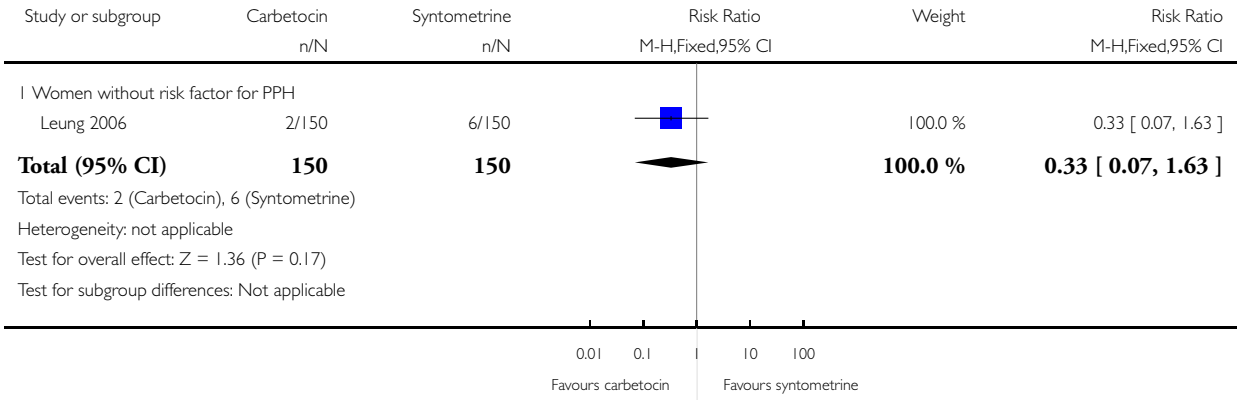
Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Women with risk factor for PPH				
Nirmala 2009	0/60	0/60		0.0 [0.0, 0.0]
Subtotal (95% CI)	**60**	**60**		**0.0 [0.0, 0.0]**
Total events: 0 (Carbetocin), 0 (Syntometrine)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Women without risk factor for PPH				
Askar 2011	1/120	4/120		0.25 [0.03, 2.20]
Leung 2006	0/150	3/150		0.14 [0.01, 2.74]
Su 2009	7/185	10/185		0.70 [0.27, 1.80]
Subtotal (95% CI)	**455**	**455**		**0.49 [0.22, 1.09]**
Total events: 8 (Carbetocin), 17 (Syntometrine)				
Heterogeneity: Chi^2 = 1.59, df = 2 (P = 0.45); I^2 =0.0%				
Test for overall effect: Z = 1.76 (P = 0.079)				

Analysis 3.14. Comparison 3 Carbetocin versus syntometrine, Outcome 14 Shivering.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 14 Shivering

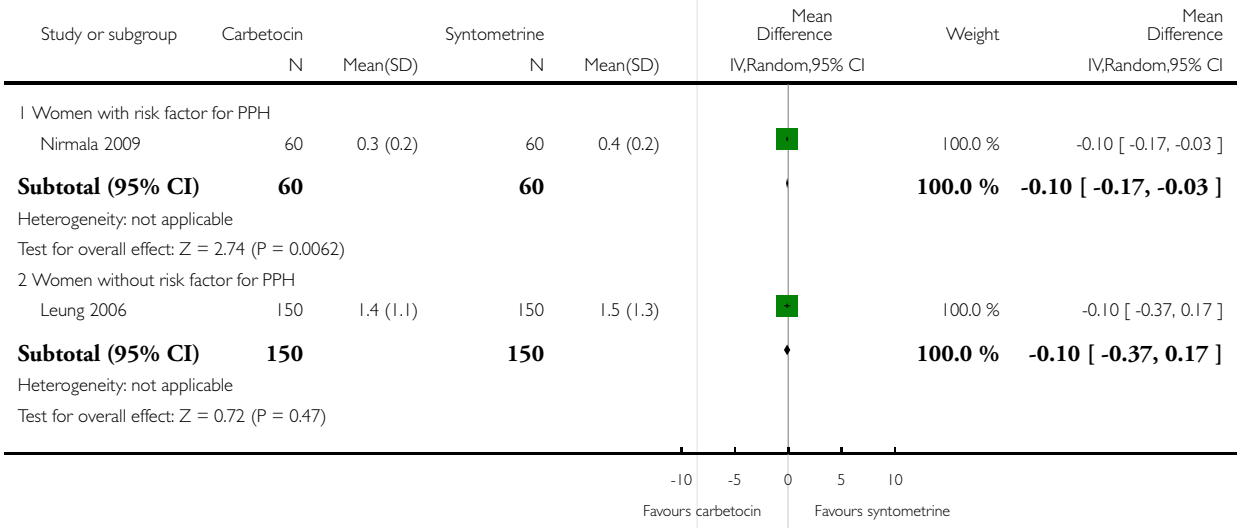


Analysis 3.15. Comparison 3 Carbetocin versus syntometrine, Outcome 15 Mean haemoglobin difference (g/dL).

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 15 Mean haemoglobin difference (g/dL)



Analysis 3.16. Comparison 3 Carbetocin versus syntometrine, Outcome 16 Hypertension (blood pressure greater than or equal to 140/90 mmHg) immediately after delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 16 Hypertension (blood pressure greater than or equal to 140/90 mmHg) immediately after delivery

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women without risk factor for PPH					
Askar 2011	2/120	4/120		50.0 %	0.50 [0.09, 2.68]
Leung 2006	2/150	4/150		50.0 %	0.50 [0.09, 2.69]
Total (95% CI)	**270**	**270**		**100.0 %**	**0.50 [0.15, 1.64]**

Total events: 4 (Carbetocin), 8 (Syntometrine)

Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 1.14 (P = 0.25)

Test for subgroup differences: Not applicable

Analysis 3.17. Comparison 3 Carbetocin versus syntometrine, Outcome 17 Hypertension (blood pressure greater than or equal to 140/90) 30 minutes after delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 17 Hypertension (blood pressure greater than or equal to 140/90) 30 minutes after delivery

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women without risk factor for PPH					
Askar 2011	0/120	8/120		50.0 %	0.06 [0.00, 1.01]
Leung 2006	0/150	8/150		50.0 %	0.06 [0.00, 1.01]
Total (95% CI)	**270**	**270**		**100.0 %**	**0.06 [0.01, 0.44]**

Total events: 0 (Carbetocin), 16 (Syntometrine)

Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 2.76 (P = 0.0057)

Test for subgroup differences: Not applicable

Analysis 3.18. Comparison 3 Carbetocin versus syntometrine, Outcome 18 Hypertension (blood pressure greater than or equal to 140/90) 60 minutes after delivery.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 3 Carbetocin versus syntometrine

Outcome: 18 Hypertension (blood pressure greater than or equal to 140/90) 60 minutes after delivery

Study or subgroup	Carbetocin n/N	Syntometrine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women without risk factor for PPH					
Askar 2011	0/120	7/120		53.6 %	0.07 [0.00, 1.15]
Leung 2006	0/150	6/150		46.4 %	0.08 [0.00, 1.35]
Total (95% CI)	**270**	**270**		**100.0 %**	**0.07 [0.01, 0.54]**

Total events: 0 (Carbetocin), 13 (Syntometrine)

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.94); I^2 =0.0%

Test for overall effect: Z = 2.56 (P = 0.011)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Carbetocin versus placebo, Outcome 1 Use of additional uterotonic therapy.

Review: Carbetocin for preventing postpartum haemorrhage

Comparison: 4 Carbetocin versus placebo

Outcome: 1 Use of additional uterotonic therapy

Study or subgroup	Carbetocin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Caesarean delivery					
Barton 1996	8/62	41/57		100.0 %	0.18 [0.09, 0.35]
Subtotal (95% CI)	**62**	**57**		**100.0 %**	**0.18 [0.09, 0.35]**
Total events: 8 (Carbetocin), 41 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.05 (P < 0.00001)					

APPENDICES

Appendix 1. Search strategy

Authors searched CENTRAL (*The Cochrane Library* 2011, Issue 1 of 4)
#1 oxytocin near agonist*
#2 carbetocin
#3 OXYTOCIN [aa] explode all trees (MeSH)
#4 postpartum near hemorrhage
#5 post-partum near hemorrhage
#6 post partum near hemorrhage
#7 postpartum near haemorrhage
#8 post-partum near haemorrhage
#9 post partum near haemorrhage
#10 POSTPARTUM HEMORRHAGE explode all trees (MeSH)
#11 LABOR STAGE THIRD single term (MeSH)
#12 third stage or 3rd stage
#13 CESAREAN SECTION EXPLODE ALL TREES (MeSH)
#14 cesarean or caesarean or cesarien or caesarien
#15 #1 or #2 or #3
#16 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#17 #15 and #16

Appendix 2. Search strategy

MEDLINE (OVID platform) (1966 to 1 March 2011)
1 (oxytocin adj4 agonist$).mp.
2 carbetocin.af.
3 exp Oxytocin/aa [Analogs & Derivatives]
4 1 or 2 or 3
5 exp Postpartum Hemorrhage/ or (postpartum hemorrhage or post partum hemorrhage or postpartum haemorrhage or post partum haemorrhage).ti,ab.
6 exp Labor Stage, Third/
7 exp Cesarean Section/
8 5 or 6 or 7
9 4 and 8

Appendix 3. Search strategy

EMBASE (Dialog Datastar) (1974 to 1 March 2011)
1 (oxytocin and agonist$)
2 carbetocin
3 exp Oxytocin/aa [Analogs & Derivatives]
4 1 or 2 or 3
5 exp Postpartum Hemorrhage/ or (postpartum hemorrhage or post partum hemorrhage or postpartum haemorrhage or post partum haemorrhage).ti,ab.
6 exp Labor Stage, Third/
7 exp Cesarean Section/
8 5 or 6 or 7
9 4 and 8

Appendix 4. Methods used in the previous version of the review

(1) Selection of trials

Two review authors (Lin Lin Su (LLS) and Miny Samuel (MS)) independently examined the abstracts of studies identified by the search strategy. Full publications were retrieved for qualifying abstracts. Discrepancies were resolved by discussion and by seeking the opinion of the third author (Yap-Seng Chong).

(2) Assessment of methodological quality

Two review authors (LLS and MS) extracted information on participants, methods, interventions, outcomes, and results, and evaluated the methodological quality of each trial. Trial quality was assessed according to methods set out in section six of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005a).
The following features were considered:
(a) method of randomisation;
(b) method of allocation concealment;
(c) blinding of participants, surgeons and outcome assessors;
(d) completeness of follow up;
(e) use of intention-to-treat analysis.
The allocation concealment of each study were scored A (adequate), B (unclear), C (inadequate) or D (not used) according to the rating system outlined in Higgins 2005a.
Trials that were explicitly clear that there were concealment of allocation, blinding of outcome assessment and handling of dropouts and withdrawals with an intention-to-treat analysis were considered to be of high quality (Juni 1999).

(3) Data collection

Data were extracted using methods set out in section seven of the *Cochrane Handbook for Systematic Reviews of interventions* (Higgins 2005b) by two authors (LLS and MS) independently. Discrepancies were resolved by discussion.

(4) Data synthesis

Presentation of statistical data included the use of relative risks for binary data and weighted mean difference for continuous data. When study designs were judged to be homogenous, the results from the various trials were combined by calculating the pooled relative risks/ weighted mean difference and their 95% confidence interval.

Assessment of heterogeneity - we applied tests of heterogeneity between trials using the I^2 statistic. If high levels of heterogeneity among the trials were identified (exceeding 50%), we explored it by prespecified subgroup analysis and performed sensitivity analysis. A random-effects meta-analysis was used as an overall summary if that was considered appropriate. Separate analyses were performed for women who underwent vaginal deliveries and for women who had caesarean deliveries. The other prespecified subgroup analysis was for women at high risk of postpartum haemorrhage (PPH). However, the only trial for vaginal delivery was on women who had risk factor(s) for PPH. No randomised controlled trial has been published so far for the use of oxytocin agonists in women at low risk of PPH.

WHAT'S NEW

Last assessed as up-to-date: 1 August 2011.

Date	Event	Description
9 March 2012	New citation required and conclusions have changed	Outcome data added on severe postpartum haemorrhage. Conclusions now changed for comparison of carbetocin with oxytocin for outcome of postpartum haemorrhage (any) or severe in women undergoing caesarean section. Results have changed from statistically significant to statistically non-significant
9 March 2012	Amended	Added outcome missing from last update, (severe postpartum haemorrhage (PPH)) from Attilakos 2010; Boucher 1998.

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 3, 2007

Date	Event	Description
1 March 2011	New search has been performed	Search updated. Nine trials identified: we have included seven (Askar 2011; Attilakos 2010; Borruto 2009; Del Angel-Garcia 2006; Leung 2006; Nirmala 2009; Su 2009) and two are ongoing trials (Gomez

(*Continued*)

		2011; Kalahroudi 2010). This update now incorporates the Pregnancy and Childbirth Group's hierarchy of reviews on prevention of postpartum haemorrhage (PPH) as well as the set of core outcomes for PPH reviews
1 March 2011	New citation required and conclusions have changed	This updated review now has 11 included studies and the results and conclusions have changed
20 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Su LL - undertook searches, extracted and analysed the data, and wrote the review.

Chong YS - performed data analysis and advised on the review.

Samuel M - undertook searches, extracted data and performed analysis.

DECLARATIONS OF INTEREST

For the Su 2009 trial conducted by Su LL and Chong YS, the carbetocin was purchased from Ferring Inc at a discounted price. All decisions relating to the inclusion of the trial in this review, assessment of risk of bias and data extraction were carried out by the other review author (Miny Samuel) who was not directly involved in the trial.

SOURCES OF SUPPORT

Internal sources

- National University Hospital, Singapore.
- Clinical Trials and Epidemiology Research Unit, Singapore.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

To avoid duplication of data and consistency in reviews, the Pregnancy and Childbirth Group developed a hierarchy of reviews on prevention of postpartum haemorrhage for women giving birth vaginally as well as a set of core outcomes. The hierarchy and core outcomes were derived through consensus between the Editors and review authors and have been incorporated into this review.

We have added an additional outcome (need for uterine massage) which was not prespecified in our published protocol.

We have changed the title of this update because our search strategy did not identify trials of oxytocin agonists apart from carbetocin.

INDEX TERMS

Medical Subject Headings (MeSH)

Delayed-Action Preparations [therapeutic use]; Oxytocics [*therapeutic use]; Oxytocin [agonists; *analogs & derivatives; *therapeutic use]; Postpartum Hemorrhage [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy