CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Carbetocin for the Prevention of Post-Partum Hemorrhage: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	July 29, 2019
Report Length:	59 Pages

CADTH

Authors: Yi-Sheng Chao, Suzanne McCormack

Cite As: Carbetocin for the Prevention of Post-Partum Hemorrhage: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa: CADTH; 2019 Jul. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to Requests@CADTH.ca

Abbreviations

PPH	post-partum hemorrhage
RCT	randomized controlled trial
SR	systematic review

Context and Policy Issues

Maternal blood loss occurs after child birth and the amount of blood loss varies between individuals. Post-partum hemorrhage (PPH) is generally defined as bleeding in excess of 500 mL after a vaginal birth or 1000 mL after a cesarean section in Canada.[1] PPH has been defined differently by various guideline development groups.[1] In clinical practice, PPH should be considered when signs of hypovolemic shock or hemodynamic instability are present.[1] In Canada, the incidence of PPH is 4.8% (95% CI, 4.7 to 4.9) overall and 5.3% (95% CI, 5.2 to 5.4) after vaginal births in 2013.[2]

There are risk factors associated with the occurrence of PPH, including retained placenta, coagulopathy, and vaginal injury.[3] Placenta retention and hemostasis are affected by myometrial contractions.[4] Prophylactic use of uterotonics is the standard of care globally.[4] Two uterotonics, oxytocin and carbetocin are in the Essential Medicines List by the World Health Organization.[5] Oxytocin works on receptors of smooth muscle and stimulate the upper uterine to contract regularly.[1] Carbetocin is a long-acting synthetic oxytocin analogue and also works by stimulating the uterus.[1] There are adverse effects common to both drugs, such as nausea and vomiting.[1] One advantage of carbetocin is its tolerance to heat and does not require cold-chain transport and storage that is needed for oxytocin use.[5] There are studies showing similar or superior effectiveness of carbetocin for the prevention of PPH, when compared to oxytocin.[6] However, the use of carbetocin has not been popular in Canada.[7] There is a need to review the clinical effectiveness, cost-effectiveness, and clinical guidelines to understand the potential role of carbetocin in Canada.

Research Questions

1. What is the clinical effectiveness of carbetocin for individuals undergoing cesarean delivery or having a vaginal delivery who are high risk for post-partum hemorrhage?
2. What is the cost-effectiveness of carbetocin for individuals undergoing cesarean delivery or having a vaginal delivery who are high risk for post-partum hemorrhage?
3. What is the evidence-based guidelines surrounding the use of carbetocin for individuals undergoing cesarean delivery or having a vaginal delivery who are high risk for post-partum hemorrhage?

Key Findings

One systematic review of economic evaluations, two systematic reviews of effectiveness studies, seven randomized controlled trials, five non-randomized studies, two economic evaluations, and five guidelines were included. There is evidence to support the use of carbetocin for the prevention of post-partum hemorrhage (PPH) of ≥500 mL, or ≥1,000 mL based on a network meta-analysis. In a subgroup analysis and a smaller systematic review, carbetocin was more effective than oxytocin for PPH prevention for cesarean delivery, and not vaginal delivery. In the primary studies, carbetocin was associated with similar or more effectiveness regarding the prevention of PPH, reducing additional uterotonic use, or hemoglobin drops. In the systematic review of economic evaluations, carbetocin was more

cost-effective than oxytocin for the prevention of PPH. From a UK perspective, carbetocin, oxytocin and another uterotonic agent were considered the most cost-effective strategies for preventing PPH. However, in a Columbian economic evaluation, carbetocin was less cost-effective for vaginal births than the cost-effectiveness threshold but was less costly and more effective for cesarean delivery. According to a 2018 Canadian guideline, carbetocin is recommended to prevent PPH for cesarean delivery and vaginal delivery with one PPH risk factor. Carbetocin is also considered first-line treatment in a 2018 German guideline. However, three guidelines published before 2018, including a Canadian guideline, do not recommend carbetocin or do not consider it as a first-line option. The limitations of this report included various definitions of PPH and risk factors, pending updates to a key network meta-analysis, and inconsistent guideline recommendations. For health policy making, the clinical effectiveness and cost-effectiveness of carbetocin needs to be further studied in Canadian contexts. The Canadian guidelines may also need to be updated with recent publications.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was carbetocin and post-partum hemorrhage. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and June 12, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Individuals undergoing elective cesarean delivery, intrapartum cesarean delivery, or patients having a vaginal delivery that are at high risk for post-partum hemorrhage (PPH)
Intervention	Carbetocin (any dose)
Comparator	Oxytocin
Outcomes	Q1: Clinical effectiveness (e.g., efficacy of reducing blood loss[i.e., blood loss ≥ 500mL, blood loss ≥ 1000mL, need for transfusion]; safety (e.g., adverse/side effects [nausea, vomiting, flushing, chest pain, EKG changes (prolonged QTc)/arrhythmias) Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, and guidelines

PPH = post-partum hemorrhage

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2 checklist,[8] randomized studies were critically appraised using the Downs and Black checklist,[9] economic studies were assessed using the Drummond checklist,[10] and guidelines were assessed with the AGREE II instrument.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 122 citations were identified in the literature search. Following screening of titles and abstracts, 74 citations were excluded and 48 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 29 publications were excluded for various reasons, and 22 publications met the inclusion criteria and were included in this report. These comprised three systematic reviews (SRs), seven randomized controlled trials (RCTs), five non-randomized studies, two economic evaluations, and five evidence-based guidelines. Appendix 1 presents the PRISMA[12] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Study Design

Systematic reviews

The SR by Lawrie et al. reviewed the cost-effectiveness of uterotonics, including carbetocin and oxytocin, and included 15 economic evaluations.[13] Multiple databases were searched and articles published until 2018 were retrieved.[13] Fourteen of the included studies adopted perspectives relevant to local healthcare and one used a World Health Organization perspective.[13] The SR by Gallos et al. included 140 RCTs available in several databases, published until October 2017, to conduct a network meta-analysis of uterotonics.[6] The start date of the literature search was not reported.[6] In the comparison network for the outcome of PPH ≥ 500 mL and ≥ 1,000 mL, eight and seven studies directly compared carbetocin with oxytocin respectively.[6] Voon et al. searched multiple databases and included seven RCTs published until May 2016.[14] Five of the included primary studies in the SR by Voon et al. were also included in the SR by Gallos et al.[6,14]

The overlap between included SRs were demonstrated in Appendix 5.

RCTs

The RCTs by Amornpetchakul et al.,[15] Mannaerts et al.,[16] Elbohoty et al.,[17] Fahmy, Yousef, and Zaki,[18] and Kabir et al. [19] were single-centre trials and those by Taheripanah et al. [20] and Widmer et al.,[5] were two- and multi-centre respectively. All RCTs blinded patients and outcome assessors,[5,15-18,20] with the exception of Kabir et al. who did not report the blinding status.[19]

Non-randomized studies

Chen et al.[21] and Sotillo et al.,[22] prospectively followed up participants in single medical centres. Wohling et al. and Nucci et al. retrospectively analyzed the data in single medical centres.[23,24] Seow et al. did not specify the type of cohort study conducted in one medical institute.[25]

Economic evaluations

Pickering et al. assessed the cost-effectiveness of uterotonics in a network meta-analysis[6,26] and modeled the treatment strategy within six days.[27] Pickering et al. adopted a UK National Health Service perspective.[27] Gil-Rojas et al. assessed the cost-effectiveness of carbetocin relative to oxytocin using a one-year decision-tree model.[28] Gil-Rojas et al. adopted a third-party payer perspective.[28]

Guidelines

Leduc et al. updated a guideline published in 2000 and the guideline was approved by the Society of Obstetricians and Gynaecologists of Canada.[29] Articles published between 1995 and 2007 were searched in multiple databases.[29] The evidence synthesis method was not reported.[29] Evidence quality was assessed with the Jadad Scale and levels of evidence was rated according to the Canadian Task Force on Preventive Health Care.[29] Lier et al. searched articles published between 2008 and 2015 in the PubMed database.[4] The evidence appraisal tool was not reported and levels of evidence was rated according to the classification of Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF, Association of the Scientific Medical Societies).[4] The guideline was developed by German, Austrian and Swiss Societies of Gynaecology and Obstetrics, German Society of Anaesthesiology and Intensive Care Medicine, and Society of Thrombosis and Haemostasis Research.[4] Mavrides et al. updated a 2009 guideline by searching for articles published from 2007 to 2015 in multiple databases.[30] The guideline was developed based on the Royal College of Obstetricians and Gynaecologists (RCOG) guidance.[30] The evidence was appraised in accordance with RCOG appraisal guidance and the guideline was reviewed by external peers.[30] Bennett et al. updated a 2006 guideline by searching for articles published from 1995 to 2013 in multiple databases.[1] The guideline was developed based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[1] The guideline was reviewed using a modified Appraisal of Guidelines for Research and Evaluation (AGREE) instrument.[1] Sentilhes et al. authored a guideline for the French College of Gynaecologists and Obstetricians and the French Society of Anesthesiology and Intensive Care.[31] English or French articles published through 2014 in multiple databases were reviewed.[31] The evidence was graded and the recommendations were made based on the guidance by the French Health Authority.[31]

Country of Origin

Systematic reviews

The first authors of the SR by Lawrie et al., Gallos et al., and Voon et al. were based in Switzerland, the UK, and Malaysia respectively.[6,13,14]

RCTs

The first authors of the RCTs were based in Thailand (1 study),[15] Belgium (1 study),[16] Iran (1 study),[20] Switzerland (1 study),[5] Egypt (2studies),[17,18] and Bangladesh (1 study).[19]

Non-randomized studies

The first authors of the non-randomized studies were based in Taiwan (2 studies),[21,25] Spain (1 study),[22] Australia (1 study),[23] and France (1 study).[24]

Economic evaluations

The first authors of the economic evaluations were based in the UK (1 study)[27] and Colombia (1 study).[28]

Guidelines

The first authors of the guidelines were based in Canada (2 studies),[1,29] Germany (1 study),[29] the UK (1 study),[30] and France (1 study).[31]

Patient Population

Systematic reviews

In the SR by Lawrie et al., patients in Columbia (1 study), Ecuador (1 study), India (2 studies), Malaysia (1 study), Mexico (1 study), Peru (1 study), Senegal (1 study), Tanzania (1 study), Uganda (1 study), and the UK (4 studies) and a hypothetical cohort (individuals with low access to facility births, simulation details not reported) were synthesized according to type of delivery (vaginal birth or caesarean delivery) and birth settings (community or hospital).[13] The number of patients was not reported.[13] In the SR by Gallos et al., 88,947 patients were included in a network meta-analysis.[6] Most of the patients were in hospital settings with more than 37 weeks of gestation and having a vaginal birth.[6] In the SR by Voon et al., 2,012 patients from Egypt (1 study), Canada (2 studies), Malaysia (1 study), Italy (1 study), UK (study) and Australia (1 study) were analyzed.[14]

RCTs

Amornpetchakul et al. enrolled 350 singleton pregnant patients with mean gestational ages of 38.4 and 38.5 weeks in two groups.[15] At least one risk factors of atonic PPH was required to be included.[15] Mannaerts et al. included 68 singleton pregnant patients planned for cesarean section with gestational ages of 38 to 40 weeks.[16] Taheripanah et al. included 220 patients undergoing emergent cesarean section with at least one risk factor for PPH.[20] The inclusion criteria was gestational age of more than 37 weeks.[20] Widmer et al. recruited 29,645 singleton pregnant patients expected to deliver vaginally from 10 countries (Argentina, Egypt, India, Kenya, Nigeria, Singapore, South Africa, Thailand, Uganda, and the United Kingdom).[5] The median gestational age was 39 weeks.[5] Elbohoty et al. enrolled 263 singleton pregnant patients undergoing an elective cesarean section.[17] The gestational age was 37 weeks or more.[17] Fahmy, Yousef, and Zaki included 60 twin pregnant patients undergoing elective cesarean section.[18] The gestational age was not reported.[18] Kabir et al.

recruited 94 singleton pregnant patients undergoing vaginal deliveries with more than 36 weeks of gestation.[19]

Non-randomized studies

Chen et al. analyzed data from 1,568 patients with cesarean deliveries.[21] The mean gestational ages ranged from 36.9 to 38.7 weeks in four groups.[21] Sotillo et al. followed up 166 twin pregnant patients undergoing an elective or emergent cesarean section with more than 24-week gestation.[22] Wohling et al. analyzed data from 2,499 singleton pregnant patients undergoing cesarean section.[23] The mean gestational ages were 38.6 and 38.7 weeks.[23] Seow et al. included 64 patients with twin pregnancy induced using in vitro fertilization.[25] The mean gestational age was 35.2 weeks.[25] Nucci et al. analyzed data from 60 patients with severe preeclampsia undergoing cesarean section under spinal anaesthesia.[24] The mean gestational age was 31.8 and 31.9 weeks in two groups.[24]

Economic evaluations

Pickering et al. modeled patients approaching the third stage of labour, the period after the birth of the baby and before the removal of the placenta and membranes.[27] Gil-Rojas et al. modeled patients with at least one risk factor for hemorrhage due to uterine atony.[28]

Guidelines

The intended users and target population in the guideline by Leduc et al.[29], Lier et al.,[4] and Sentilhes et al.[31] were clinicians and patients at risk of or with post-partum hemorrhage respectively.[29] The intended users and target population in the guideline by Mavrides et al. were clinicians and patients giving birth respectively.[30] The intended users and target population in the guideline by Bennett et al. were midwives and Ontario midwives' clients respectively.[1]

Interventions and Comparators

Systematic reviews

The intervention and comparator in the SR by Lawrie et al. included carbetocin and oxytocin respectively.[13] The exact dosages were not reported.[13] The interventions and comparators in the network meta-analysis by Gallos et al. were uterotonic drugs for the prevention of PPH, including oxytocin, ergometrine, misoprostol, carbetocin, and their combinations.[6] The intervention and comparator in the SR by Voon et al. were carbetocin (100 µg) and oxytocin (variable doses, not reported) respectively.[14]

RCTs

The intervention and comparator in the RCTs were carbetocin 100 µg and oxytocin.[5,15-20] Oxytocin was injected slowly intravenously 5 IU once[15,16,19] or 10 IU once with subsequent 20 IU over four hours[17] or 20 IU once[18] or 30 IU over two hours.[20]

Non-randomized studies

The intervention and comparator in the non-randomized studies were intravenous injection of carbetocin and oxytocin respectively.[21-25] Except for Chen et al. that reported the use of carbetocin 100 mg,[21] other studies used carbetocin 100 µg.[22-25] The oxytocin doses were 5 IU once,[24] 10 IU once,[21,25] 5 to 10 IU once,[23] and 20 IU once.[22]

Economic evaluations

Pickering et al. based the cost-effectiveness analysis on a network meta-analysis[6] and the intervention and comparator were uterotonics, including carbetocin (100 µg per dose), ergometrine, ergometrine plus oxytocin, misoprostol plus oxytocin, misoprostol, and oxytocin (10 IU per dose).[27] In the economic evaluation by Gil-Rojas et al., the intervention and comparator were carbetocin 100 µg once and oxytocin 5 to 10 IU intramuscularly (vaginal delivery) or 5 IU followed by 30 IU (cesarean section).[28]

Guidelines

Carbetocin was considered in the guidelines by Leduc et al.,[29] Lier et al.,[4] Mavrides et al.,[30] Bennett et al.,[1] and Sentilhes et al.[31]

Outcomes

Systematic reviews

In the SR by Lawrie et al., the outcomes considered were cost-effective for preventing PPH at vaginal delivery, cost-effective for preventing PPH at cesarean delivery, cost-effectiveness of uterotonic agents in community settings without skilled birth attendants, and cost-effectiveness of uterotonic agents in hospital settings where oxytocin quality cannot be guaranteed.[13] In the SR by Gallos et al., the primary outcomes were PPH with more than 500 mL or 1000 ml blood loss and the secondary outcomes included maternal deaths, additional uterotonics requirement, transfusion, and manual removal of the placenta.[6] In the SR by Voon et al., the outcomes were PPH, additional use of uterotonics, and transfusion requirement.[14]

RCTs

PPH was an outcome of interest in the RCTs by Amornpetchakul et al.,[15] Widmer et al.,[5] Fahmy, Yousef, and Zaki,[18] and Kabir et al.[19] The need for additional uterotonics was an outcome of interest in those by Amornpetchakul et al.,[15] Taheripanah et al.,[20] Widmer et al.,[5] Elbohoty et al.,[17] and Kabir et al.[19] Adverse events including nausea and vomiting were an outcome of interest in those by Mannaerts et al.,[16] Elbohoty et al.,[17] and Kabir et al.[19] Additionally, Amornpetchakul et al. studied incidence of post-partum anemia,[15] Mannaerts et al. assessed the need for vasopressors and changes in hemoglobin and hematocrit levels,[16] Taheripanah et al. the hemoglobin drops,[20] Fahmy, Yousef, and Zaki assessed the need for methylergometrine postoperatively and heart rates,[18] and Kabir et al. assessed the need for transfusion.[19]

Non-randomized studies

Chen et al. studied outcomes including fall in hemoglobin and hematocrit levels, blood loss, the need for additional uterotonics, transfusion, and PPH.[21] Sotillo et al. followed up for outcomes including intraoperative bleeding, surgical time, hemoglobin falls, hematocrit drops, additional uterotonic use, and transfusion.[22] Wohling et al. reviewed PPH with more than 1,000 mL blood loss and the need for secondary uterotonics.[23] Seow et al. studied the drop in hemoglobin levels, blood loss, lochia, surgical time, and primary PPH.[25] Nucci et al. reviewed the need for additional uterotonics, time to additional uterotonics, the need for compression balloon, hemoglobin differences, the need for blood products, and admission to an intensive care unit.[24]

Economic evaluations

In the economic evaluation by Pickering et al., the primary outcome of interest was cost (£) per case of PPH avoided (≥ 500 mL blood loss).[27] The secondary outcomes were cost per case of severe PPH avoided (≥ 1000 mL) and cost per major outcome (surgery) averted.[27] Gil-Rojas et al. analysed the incremental costs (Colombian dollars) and effectiveness in terms of quality-adjusted life years (QALYs).[28]

Guidelines

In the guidelines, the outcomes considered were not explicitly reported and various outcomes have been reported.[1,4,29-31] Leduc et al., Mavrides et al., and Bennett et al. reported many outcomes related to maternal and fetal condictiones, such as maternal mortality and morbidity, blood loss, hospitalization, and admission to the Neonatal Intensive Care Unit.[1,29,30] Lier et al. and Sentilhes et al. reported maternal outcomes, such as hemostatic outcomes, placenta retention and PPH.[4,31]

Summary of Critical Appraisal

Systematic reviews

The reporting was central to the quality of the SRs. The population, intervention, comparator, and outcome components were reported in the SRs.[6,13,14] The selection of study design was explained.[6,13,14] Comprehensive literature searches were conducted.[6,13,14] Study selection and data extraction were performed in duplicate.[6,13,14] reducing the potential for human error. Review authors' competing interests were declared.[6,13,14] However, the review protocols were not published *a priori*.[6,13,14] Only Gallos et al. provided a list of excluded studies.[13] However, there were primary studies awaiting further classification and the characteristics and the results of these primary studies were not yet assessed and included in their review.[6] Gallos et al. and Voon et al. described the included studies, whereas Lawrie et al. did not.[6,13,14] Gallos et al. and Voon et al. assessed the risk of bias in the included studies with published tools, whereas Lawrie et al. did not appraise the included studies.[6,13,14] Only Gallos et al. reported the funding sources of the included studies.[6] Only Gallos et al. accounted for the risk of bias when interpreting the results.[6] Gallos et al. and Voon et al. discussed the heterogeneity in the results.[6,14] Only Gallos et al. assessed the publication bias.[6]

Gallos et al. and Voon et al. conducted meta-analyses.[6,14] Appropriate statistical methods were used.[6,14] The risk of bias of the included studies were considered in the analysis.[6,14]

RCTs

Comprehensive reporting was the key to understand the studies. The study objectives, outcomes to be measured, patient characteristics, interventions, distributions of principal confounders, main findings, and estimates of random variability in the outcomes were described.[5,15-20] Actual probability values (***P*** values) were reported, except for the RCT by Widmer et al. that did not report any ***P*** values.[5,15-20] However, adverse events, such as nausea and vomiting, were not reported by Kabir et al. and Fahmy, Yousef and Zaki.[18,19]

The representativeness of the study participants could be assessed from several perspectives. The RCTs were single-centre studies, with the exception of Widmer et al., a multi-centre study conducted in 10 countries.[5] This multi-centre study may be more representative than the single-centre studies.[5,15-20] There was no significant changes to the clinical settings reported and the majority of these study settings were likely representative

of the type of health care received in the populations assessed.[5,15-20] Patients lost to follow-up or the lack of patients lost to follow-up was not reported by Kabir et al.[19]

Trial implementation and analytical methods were important to avoid biases and assess the internal validity. The time periods between intervention and outcome were similar for different groups.[5,15-20] Appropriate statistical methods were used.[5,15-20] Patients' adherence with intravenous injections were reliable and the measurement error was likely minimized.[5,15-20] The outcome measures, such as blood loss and additional use of uterotonics, were accurate and the measurement error was likely minimized.[5,15-20] Patients were blinded in the RCTs by Amornpetchakul et al., Elbohoty et al., Mannaerts et al., Taheripanah et al., and Widmer et al.[5,15-17,20] Though blinding was unlikely to impact patients to subjectively influence the outcomes, such as blood loss and use of additional uterotonics, while delivering. Outcome assessors were blinded in the RCTs by Amornpetchakul et al., Elbohoty et al., Mannaerts et al., Taheripanah et al., Widmer et al., and Fahmy, Yousef, and Zaki, reducing the bias due to subjective assessment.[5,15-18,20]

The risk of selection bias could impact internal validity and be assessed from several points, however this was likely minimal in most studies. Different groups of patients were recruited from the same populations at the same time.[5,15-20] The participants were randomized into different groups.[5,15-20] However, only Amornpetchakul et al. and Elbohoty et al. reported assignment concealment.[15,17] Except for Kabir et al., authors of the other RCTs conducted power analysis for sample sizes before study.[5,15-20]

Non-randomized studies

The clarity of study reporting of the non-randomized studies had been assessed. Comprehensive reporting was the key to understand the studies. The study objectives, outcomes to be measured, patient characteristics, interventions, distributions of principal confounders, main findings, and estimates of random variability in the outcomes were described.[21-25] Actual probability values (***P*** values) were reported.[21-25] However, adverse events, such as nausea and vomiting, were only reported by Nucci et al.[24] Patients lost to follow-up was only reported by Wohling et al.[23]

The representativeness of the study participants was assessed through the following points. The non-randomized studies were all single-centre studies and the representativeness of findings may be limited.[21-25] The patients were recruited from the same population at the same time.[21-25] There was no significant change to the clinical settings reported and was likely representative of the type of health care received in the populations assessed.[21-25]

The efforts to minimize the risk of biases were important to internal validity. The statistical methods were appropriate.[21-25] The compliance to intravenous injections and the outcome measures were reliable.[21-25] However, Nucci et al. and Wohling et al. conducted before-and-after comparisons of the patients and patients were not treated at the same time periods.[23,24] Patients and outcome assessors were not blinded.[21-25]

It's unclear whether selection bias impacted the comparability of different groups. The patients were recruited from the same populations.[21-25] However, Nucci et al. and Wohling et al. compared two cohorts from different time periods and the impact on comparability was unclear.[23,24] Chen et al. allowed clinicians to decide the types of interventions, carbetocin or oxytocin and it is unclear whether selection bias may have impacted the findings.[21] Only Chen et al. adjusted for confounding in the statistical analysis.[21] The patients were not randomized to different groups.[21-25] There was no power analysis for sample sizes.[21-25]

Guidelines

The objectives, health questions, and target populations were described in the included guidelines.[1,4,29-31] Various stakeholders were involved providing different perspectives.[1,4,29-31] Experts from relevant professional groups were involved and the target users were defined or implied.[1,4,29-31] However, the views and preferences of the target populations were not sought.[1,4,29-31] The rigour of development could be determined by examining the literature search methods and guideline development process. Systematic literature searches were conducted and the criteria for selecting the evidence were stated.[1,4,29-31] According to the outcomes reported, the health benefits, sides effects, and risks might have been considered when formulating the recommendations.[1,4,29-31] There were explicit links between the recommendations and the evidence.[1,4,29-31] However, only Lier et al., Mavrides et al., Bennett et al., and Sentilhes et al. reported the methods to formulate the recommendations.[1,4,30,31] External review was reported in the guidelines by Mavrides et al., Bennett et al., and Sentilhes et al.[1,4,29-31] However, the strengths and limitations of the evidence and procedures to update the guidelines were not reported.[1,4,29-31] Though the included guidelines were all updated versions of previous guidelines.[1,4,29-31]

The clarity of presentation was important for users to understand and implement the guidelines. The recommendations were specific and unambiguous.[1,4,29-31] Different options for the prevention of PPH were provided if applicable.[1,4,29-31] The key recommendations were easy to identify.[1,4,29-31]

The applicability of the guidelines affected the usefulness of them in clinical practice. The barriers and facilitators to apply the guidelines, the advice or tools on how to implement the recommendations, and the potential resource implications were reported if available.[1,4,29-31] However, there were no monitoring or auditing criteria reported.[1,4,29-31]

The role of the funding bodies was mentioned in the guidelines by Leduc et al. and Bennett et al.[1,29] The competing interests of the guideline development group members were documented and addressed in the guidelines by Leduc et al., Mavrides et al., and Sentilhes et al.[29-31]

Economics evaluations

The research questions, the economic importance of the questions, the viewpoints, the rationales to choose the interventions, the alternatives, the form of economic evaluations, the choice of economic evaluations, the sources of the effectiveness estimates, the primary outcomes, and the methods to evaluate the benefits, the details of the subjects, the methods to estimate the quantities and unit costs, the currency, the choices of models, the time horizons were reported by Pickering et al. and Gil-Rojas et al.[27,28] Relevant alternatives were compared and incremental analyses were conducted.[27,28] The answers to the research questions and the conclusions with limitations were given.[27,28] However, only Gil-Rojas et al. described the discount rates and the currency of price adjustments for inflation and the conversion rates.[28] In both economic evaluations, the main outcomes were not presented in both aggregated and disaggregated forms.[27,28] Productivity and resource use were not explicitly modeled.[27,28]

In the sensitivity analyses, the approaches and the choices of variables were described.[27,28]

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Clinical Effectiveness of carbetocin

Systematic reviews

According to the results of a network meta-analysis by Gallos et al., carbetocin was more effective than oxytocin for preventing PPH ≥ 500 mL or ≥ 1,000 mL.[6] Gallos et al. concluded that ergometrine plus oxytocin, carbetocin, and misoprostol plus oxytocin were more effective than oxytocin (though combination treatments were not within the scope of this review).[6] For maternal deaths, there was no significant difference between all uterotonics because of rare occurrence.[6] For side effects, carbetocin was associated with similar risks of vomiting, fever, and hypertension compared with oxytocin.[6] Gallos et al. concluded that carbetocin had the more favorable side-effect profile than ergometrine plus oxytocin and misoprostol plus oxytocin.[6]

In the subgroup analyses, the between-drug comparisons showed that carbetocin was not significantly more effective than oxytocin for the prevention of PPH 500 mL or more for vaginal deliveries.[6] However, carbetocin ranked second and oxytocin ranked fourth according to the effectiveness.[6] Carbetocin and oxytocin ranked first and fourth respectively for the prevention of PPH 1,000 mL or more.[6]

For cesarean section deliveries, carbetocin and oxytocin ranked second and third.[6] There was no sufficient evidence for the outcome of PPH 1,000 mL or more.[6]

In the SR by Voon et al., carbetocin was found to be effective in reducing the use of additional uterotonics, reducing PPH and transfusion during cesarean deliveries.[14]

RCTs

For vaginal deliveries, Amornpetchakul et al. found that carbetocin was significantly more effective than oxytocin in reducing blood loss, additional uterotonics, and the incidence of post-partum anemia among singleton pregnant patients.[15] The occurrence of side effects were similar for these two drugs.[15] In a non-inferiority trial, Widmer et al. found that carbetocin was not inferior to oxytocin regarding the frequencies of PPH (blood loss of at least 500 mL or the use of additional uterotonic agents) or frequencies of at least 1,000 mL, or use additional uterotonic agents, or interventions to stop bleeding, or adverse events.[5] Karbir et al. did not conduct a power analysis and did not find a significant difference in PPH (blood loss at least 500 mL) and adverse events between the carbetocin and oxytocin groups, but identified significant differences in massive blood loss, further fundal massage, additional uterotonics, and the average amount of blood loss (favoring carbetocin).[19]

For cesarean section deliveries, Mannaerts et al. found that carbetocin was associated with non-significant reduction in systolic blood pressure, as well as similar need for vasopressors and incidence of nausea and vomiting.[16] Taheripanah et al. identified that carbetocin was associated with significantly less hemoglobin drops, less bleeding volume, less uterine massage frequencies, shorter uterine height, and less side effects (except for puritus).[20] Elbohoty et al. found that carbetocin was associated with significantly less need for further uterotonics and an insignificant difference in the prevention of uterine atony when compared to oxytocin.[17] Fahmy, Yousef, and Zaki also found that carbetocin was significantly more effective than oxytocin for preventing uterine contraction and PPH among multiple pregnant patients.[18]

Non-randomized studies

There was no non-randomized study recruiting patients delivering vaginally.

For cesarean section deliveries, Chen et al. carbetocin was associated with significantly lower hemoglobin and hematocrit drops and less need for additional uterotonics among patients with prior cesarean section deliveries and other risk factors.[21] Sotillo et al. reported that carbetocin was associated with less reductions in the hemoglobin levels, less need for blood transfusion, less likely to treat anemia, and less need for additional uterotonics.[22] In contrast, Wohling et al. found carbetocin was associated with a significant decrease in the incidence of PPH 500 mL or more and secondary uterotonic treatment, but not associated with a significant decrease in the incidence of PPH 1,000 mL or more.[23] Seow et al. only found carbetocin was associated with significantly shorter operative time when compared with oxytocin.[25] The differences in blood loss and drops in hemoglobin levels were not significant between two drugs.[25] Nucci et al. did not identify significant differences in additional uterotonic administration between carbetocin and oxytocin.[24]

Cost-Effectiveness of carbetocin

There were one SR of economic evaluations and two primary economic evaluations (based in the UK and Colombia) included.[13,27,28]

Systematic reviews

Lawrie et al. found that carbetocin was more effective at vaginal delivery than oxytocin in preventing PPH and was associated with an incremental cost-effectiveness ratio (ICER) of US$1,193.59 per additional PPH with 500 mL or more blood loss avoided and US$ 29,464.19 per additional PPH with 1,000 mL or more blood loss in the UK.[13]

For cesarean section deliveries, carbetocin (100 µg) was reported to be more cost-effective than oxytocin (5 or 10 IU, if doses reported) in seven primary studies and uncertain in one primary study.[13]

Lawrie et al concluded that the cost-effectiveness of uterotonics were not generalizable and carbetocin or misoprostol plus oxytocin were more cost-effective than oxytocin alone.[13]

Economic evaluations

Pickering et al. concluded that carbetocin was the most effective strategy based on a network meta-analysis by Gallos et al.[6,27] Excluding adverse events, the incremental cost-effectiveness ratios (ICERs) for preventing PPH 500 mL or more and 1,000 mL or more were £1,889 and £30,013 per case respectively, when compared with oxytocin.[27] Including adverse events, the ICERs for preventing PPH 500 mL or more and 1,000 mL or more were £928 and £22,900 per case respectively.[27] Pickering et al. concluded that carbetocin, oxytocin and ergometrine plus oxytocin were the most cost-effective strategy for preventing PPH, but a clear-cut conclusion as to which uterotonics was the most cost-effective could not be made due to mixed findings[27].

Gil-Rojas et al. found that carbetocin was associated with an ICER above the cost-effectiveness threshold adopted by Colombia for vaginal delivery, but carbetocin was less costly and more effective with a saving per avoided hemorrhagic event for cesarean section deliveries.[28]

Guidelines

Carbetocin 100 µg intravenously is recommended for elective cesarean section for the prevention of PPH and for the reduction of additional uterotonics in the 2018 Society of Obstetricians and Gynaecologists of Canada guideline (fair evidence to recommend).[29] At vaginal delivery, carbetocin 100 µg intramuscularly is recommended for the reduction in the need for uterine massage and PPH prevention among patients with one risk factor for PPH (fair evidence to recommend).[29]

In the German guideline updated in 2018 by Lier et al., the first-line uterotonics include oxytocin and carbetocin.[4] If first-line options are not available or effective, sulprostone is recommended (consensus of the committee).[4]

In the 2017 Royal College of Obstericians and Gynaecologists guideline, a 2012 Cochrane review has been summarized and carbetocin is associated with a significant reduction in the need for further uterotonics at cesarean section (high-quality studies with a very low risk of bias).[30] A 2009 Society of Obstetricians and Gynaecologists of Canada guideline has been mentioned to support he use of carbetocin to prevent PPH at cesarean section (well-conducted studies with a low risk of bias).[30] In contrast, according to a 2011 National Institute for Health and Care Excellence guideline that reviewed the literature, oxytocin 5 IU is recommended for the same indication (well-conducted studies with a low risk of bias).[30]

In the 2016 Association of Ontario Midwives, oxytocin is recommended as the first-line uterotonic for the treatment of PPH due to uterine atony (strong recommendation).[1] Carbetocin is considered a second-line uterotonic and the choice of second-line uterotonics depends on clinical context because there is no clear evidence favoring any of the second-line uterotonics (strong recommendation).[1]

In the 2016 French guideline, oxytocin is recommended to prevent PPH after cesarean section based on professional consensus (professional consensus).[31]

Limitations

There were several limitations to this report. PPH was defined differently across guideline development groups.[1] In the Cochrane review by Gallos et al., there were still references to be screened, some of which might be eligible for meta-analysis.[6] One trial mentioned by Gallos et al. (Widmer et al.)[5] was recently published and remained to be meta-analyzed.[6] Thus, it remains unclear whether the exclusion of the RCT by Widmer et al.[5] would have changed the overall interpretation of the Gallos et al meta-analysis. It is also unclear whether there were reporting errors in one of the included studies, Chen et al., as the dose of carbetocin used by, 100 mg,[21] was 1,000-time higher than the dose reported in other studies, 100 µg.[6,29] The risk factors for PPH were defined differently.[1,20,28] There was heterogeneity between the trials or reviews that used PPH risk factors in the inclusion criteria. The recommendations about the use of carbetocin varied between guidelines[1,29] and within the Royal College of Obstetricians and Gynaecologists guideline.[30] Two recent guidelines supported the use of carbetocin for the prevention of PPH[4,29] and older guidelines recommended oxytocin[1,31] or provided mixed recommendations.[30] There was inconsistency in the recommendations regarding carbetocin use between the guidelines published before and after 2018. Two economic evaluations adopted UK and Colombian perspectives and might not be applicable to Canadian contexts.[27,28]

Conclusions and Implications for Decision or Policy Making

One SR of economic evaluations,[13] two SRs of effectiveness studies,[6,14] seven RCTs,[5,15-20] five non-randomized studies,[21-25] two economic evaluations,[27,28] and five guidelines were included.[1,4,29-31] There is evidence to support the use of carbetocin for the prevention of PPH 500 mL or more or 1,000 mL or more based on a network meta-analysis.[6] In a subgroup analysis and a smaller SR, carbetocin was more effective than oxytocin for PPH prevention of cesarean section deliveries, but not vaginal deliveries.[6,14] In a RCT recruiting patients delivering vaginally, carbetocin was not inferior to oxytocin regarding the prevention of PPH (500 mL or more or additional uterotonic use; 1,000 mL or more) In the other RCTs, carbetocin was found to be more or similarly effective than oxytocin in outcomes, such as reducing blood loss among singleton pregnant patients [15] and additional uterotonics.[15,19]

For cesarean section deliveries, carbetocin was found to be similarly or more effective than oxytocin regarding several outcomes in RCTs, such as PPH,[18] additional uterotonic use,[17] and blood pressure drops.[16] In non-randomized studies, carbetocin was associated with significantly less hemoglobin drops,[21,22] additional uterotonic use,[21] and PPH incidence.[23] In two other studies, similar levels of hemoglobin drops and additional uterotonic use between two drugs were observed.[24,25]

In the SR of economic evaluations by Lawrie et al., the ICERs for preventing PPH 500 mL or more and 1,000 mL or more were US$ 1,193.59 and 29,464.19 respectively in the UK.[13] In seven of the eight primary studies, carbetocin was more cost-effective than oxytocin, while one reported uncertainty.[13] Lawrie et al. concluded the cost-effectiveness of uterotonics was not generalizable and carbetocin was more cost-effective than oxytocin.[13] In the primary economic evaluations, Pickering et al. concluded that carbetocin, oxytocin and 'ergometrine plus oxytocin' were the most cost-effective strategies to prevent PPH, compared with other uterotonics.[27] Gil-Rojas et al. concluded that carbetocin was not cost-effective based on the cost-effectiveness threshold in Colombia for vaginal deliveries, but carbetocin was less costly and more effective in preventing PPH for cesarean section deliveires.[28]

In the 2018 Canadian guideline, carbetocin is recommended for elective cesarean section for the prevention of PPH and the reduction in additional uterotonic use.[29] For vaginal deliveries, carbetocin is also recommended for patients with one risk factor for PPH.[29] In the 2018 German guideline, carbetocin is considered first-line treatment.[4] However, carbetocin is not recommended in the three guidelines published before 2018.[1,30,31]

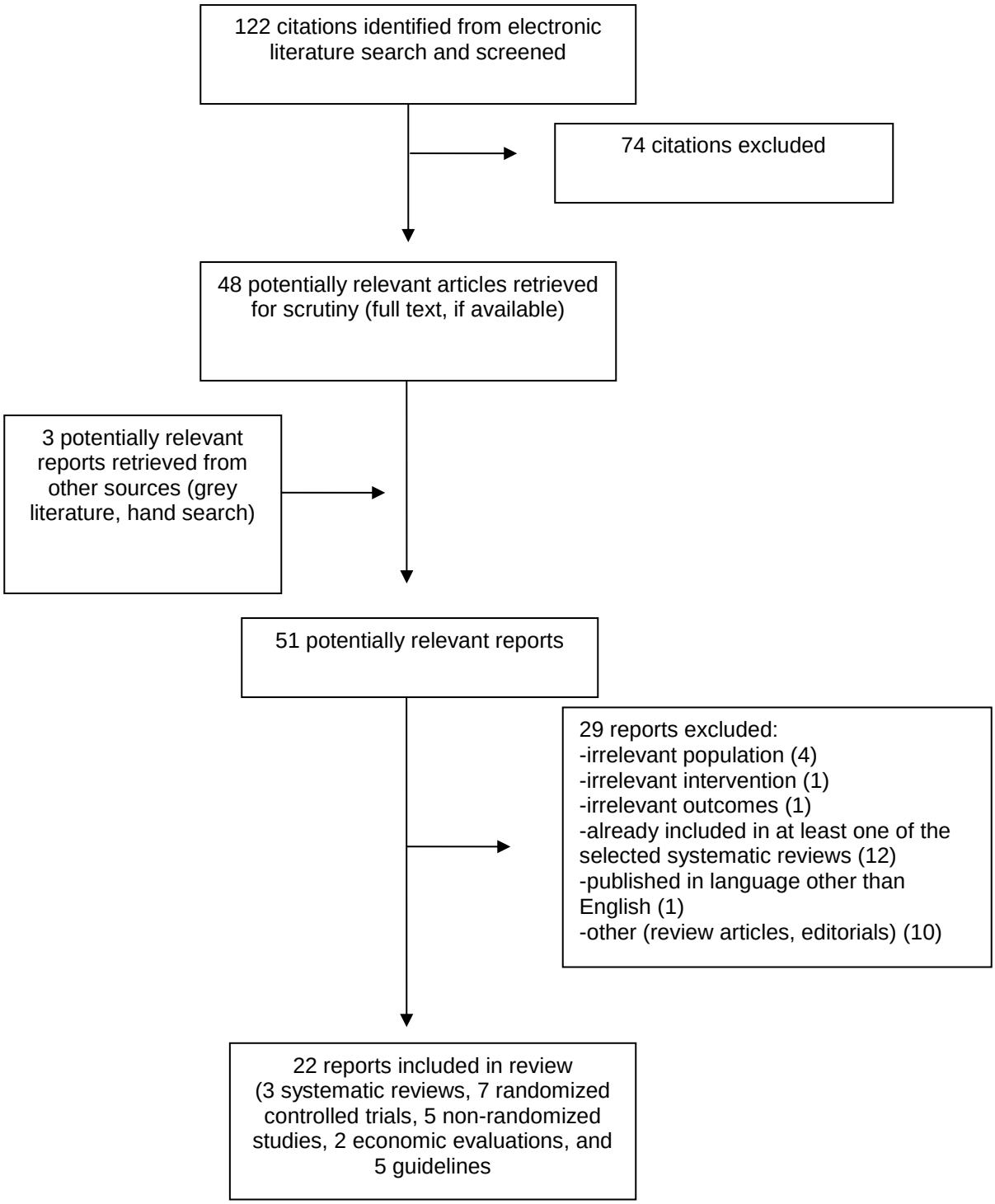
The limitations of this report included differences in the definition of PPH and the risk factors of PPH across primary studies and guidelines.[1] A network meta-analysis is needed to be updated with the studies awaiting classification and major trials, including the one by Widmer et al.[6] It was unclear whether there was a potential reporting error in the carbetocin dose in one of the included studies.[21] There was inconsistency in the recommendations regarding the use of carbetocin between guidelines published before and after 2018.

In conclusion, there was evidence demonstrating carbetocin is similarly or more effective than oxytocin for the prevention of PPH, especially for cesarean section deliveries.[6,14] Carbetocin was considered more cost-effective than oxytocin in certain studies.[13] For policy making, the effectiveness and cost-effectiveness of carbetocin need to be further studied in Canadian contexts. The Canadian guidelines may need to be updated with recent publications.

References

1. PPH CPG Work Group. Postpartum Hemorrhage. *(Clinical Practice Guideline 17)*. Toronto (ON): Association of Ontario Midwives; 2016: https://www.ontariomidwives.ca/sites/default/files/2017-12/CPG-Postpartum-hemorrhage-PUB_1.pdf. Accessed 2019 Jul 15.
2. Bonnet M-P, Basso O, Bouvier-Colle M-H, et al. Postpartum haemorrhage in Canada and France: a population-based comparison. *PLoS One.* 2013;8(6):e66882-e66882.
3. Akhter P, Pal SN, Begum S. Comparison between Carbetocin and Oxytocin in Active Management of 3rd Stage of Labour in Preventing Post Partum Hemorrhage. *Mymensingh Med J.* 2018;27(4):793-797.
4. Lier H, Von Heymann C, Korte W, Schlembach D. Peripartum Haemorrhage: Haemostatic Aspects of the New German PPH Guideline. *Transfus Med Hemother.* 2018;45(2):127-135.
5. Widmer M, Piaggio G, Nguyen TMH, et al. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. *N Engl J Med.* 2018;379(8):743-752.
6. Gallos ID, Williams HM, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. *Cochrane Database Syst Rev.* 2018;4:CD011689.
7. Thorneloe B, Carvalho JCA, Downey K, Balki M. Uterotonic drug usage in Canada: a snapshot of the practice in obstetric units of university-affiliated hospitals. *Int J Obstet Anesth.* 2019;37:45-51.
8. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008.
9. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384.
10. Higgins JPT, Green S, editors. Figure 15.5.a: Drummond checklist (Drummond 1996). *Cochrane handbook for systematic reviews of interventions*. London (GB): The Cochrane Collaboration; 2011: http://handbook-5-1.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm. Accessed 2019 Jul 15.
11. AGREE Next Steps Consortium. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 Jul 15.
12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
13. Lawrie TA, Rogozinska E, Sobiesuo P, Vogel JP, Ternent L, Oladapo OT. A systematic review of the cost-effectiveness of uterotonic agents for the prevention of postpartum hemorrhage. *Int J Gynaecol Obstet.* 2019;146(1):56-64.
14. Voon HY, Suharjono HN, Shafie AA, Bujang MA. Carbetocin versus oxytocin for the prevention of postpartum hemorrhage: A meta-analysis of randomized controlled trials in cesarean deliveries. *Taiwan J Obstet Gynecol.* 2018;57(3):332-339.
15. Amornpetchakul P, Lertbunnaphong T, Boriboonhiransarn D, Leetheeragul J, Sirisomboon R, Jiraprasertwong R. Intravenous carbetocin versus intravenous oxytocin for preventing atonic postpartum hemorrhage after normal vaginal delivery in high-risk singleton pregnancies: a triple-blind randomized controlled trial. *Arch Gynecol Obstet.* 2018;298(2):319-327.
16. Mannaerts D, Van der Veeken L, Coppejans H, Jacquemyn Y. Adverse Effects of Carbetocin versus Oxytocin in the Prevention of Postpartum Haemorrhage after Caesarean Section: A Randomized Controlled Trial. *J Pregnancy.* 2018;2018:1374150.
17. Elbohoty AE, Mohammed WE, Sweed M, Bahaa Eldin AM, Nabhan A, Abd-El-Maeboud KH. Randomized controlled trial comparing carbetocin, misoprostol, and oxytocin for the prevention of postpartum hemorrhage following an elective cesarean delivery. *Int J Gynaecol Obstet.* 2016;134(3):324-328.
18. Fahmy NG, Yousef HM, Zaki HV. Comparative study between effect of carbetocin and oxytocin on isoflurane-induced uterine hypotonia in twin pregnancy patients undergoing cesarean section. *Egypt J Anaesth.* 2016;32(1):117-121.
19. Kabir N, Akter D, Daisy TA, et al. Efficacy and safety of carbetocin in comparison to oxytocin in the active management of third stage of labour following vaginal delivery: An open label randomized control trial. *Bangladesh Journal of Obstetrics & Gynecology.* 2015;30(1):3-9.
20. Taheripanah R, Shoman A, Karimzadeh MA, Zamaniyan M, Malih N. Efficacy of oxytocin versus carbetocin in prevention of postpartum hemorrhage after cesarean section under general anesthesia: a prospective randomized clinical trial. *J Matern Fetal Neonatal Med.* 2018;31(21):2807-2812.
21. Chen YT, Chen SF, Hsieh TT, Lo LM, Hung TH. A comparison of the efficacy of carbetocin and oxytocin on hemorrhage-related changes in women with cesarean deliveries for different indications. *Taiwan J Obstet Gynecol.* 2018;57(5):677-682.
22. Sotillo L, De la Calle M, Magdaleno F, Bartha JL. Efficacy of carbetocin for preventing postpartum bleeding after cesarean section in twin pregnancy. *J Matern Fetal Neonatal Med.* 2018:1-5.
23. Wohling J, Edge N, Pena-Leal D, Wang R, Mol BW, Dekker G. Clinical and financial evaluation of carbetocin as postpartum haemorrhage prophylaxis at caesarean section: A retrospective cohort study. *Aust N Z J Obstet Gynaecol.* 2018;09:09.
24. Nucci B, Aya A, Aubry E, Ripart J. Carbetocin for prevention of postcesarean hemorrhage in women with severe preeclampsia: a before-after cohort comparison with oxytocin. *J Clin Anesth.* 2016;35:321-325.
25. Seow KM, Chen KH, Wang PH, Lin YH, Hwang JL. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in infertile women with twin pregnancy undergoing elective cesarean delivery. *Taiwan J Obstet Gynecol.* 2017;56(3):273-275.
26. Gallos I, Williams H, Price M, et al. Uterotonic drugs to prevent postpartum haemorrhage: a network meta-analysis. *Health Technol Assess.* 2019;23(9):1-356.
27. Pickering K, Gallos ID, Williams H, et al. Uterotonic Drugs for the Prevention of Postpartum Haemorrhage: A Cost-Effectiveness Analysis. *Pharmacoeconom Open.* 2019;3(2):163-176.
28. Gil-Rojas Y, Lasalvia P, Hernandez F, Castaneda-Cardona C, Rosselli D. Cost-effectiveness of Carbetocin versus Oxytocin for Prevention of Postpartum Hemorrhage Resulting from Uterine Atony in Women at high-risk for bleeding in Colombia. *Rev Bras Ginecol Obstet.* 2018;40(5):242-250.
29. Leduc D, Senikas V, Lalonde AB. No. 235-Active Management of the Third Stage of Labour: Prevention and Treatment of Postpartum Hemorrhage. *J Obstet Gynaecol Can.* 2018;40(12):e841-e855.
30. Mavrides E, Allard S, Chandraharan E, et al., on behalf of the Royal College of Obstetricians and Gynaecologists. Prevention and Management of Postpartum Haemorrhage: Green-top Guideline No. 52. *BJOG.* 2017;124(5):e106-e149.
31. Sentilhes L, Vayssiere C, Deneux-Tharaux C, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). *Eur J Obstet Gynecol Reprod Biol.* 2016;198:12-21.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Lawrie et al. 2019, Switzerland[13]	15 studies Inclusion criteria: comparative economic evaluations, cost-utility analyses, and resource-utilization studies. Databases searched: Medline (1980 to 2018), Embase (1980 to 2018), and the National Health Services Economic Evaluation database (1995 to 2015, database closure) Perspectives: relevant healthcare (14 studies) and WHO (1 study) Model: model-based using decision analytical models (decision trees) (11 studies); using data from RCTs (2 studies); using data from an observational study (1 study); and using data from a service composite clinical and financial analysis study (1 study) 1 study based on a network meta-analysis using a UK perspective[6,26]	Patients from Columbia (1 study), Ecuador (1 study), India (2 studies), Malaysia (1 study), Mexico (1 study), Peru (1 study), Senegal (1 study), Tanzania (1 study), Uganda (1 study), the UK (4 studies), and one international study with a hypothetical cohort 11 of these studies: conducted from 2011 to 2018 and 4 conducted from 2007 to 2010	Carbetocin versus oxytocin across various facility settings (8 studies, dosages not reported) Misoprostol versus third stage management without any uterotonics (five studies) or oxytocin (one study) in settings with low access to facility births	1. Cost-effective for preventing PPH at vaginal birth 2. Cost-effective for preventing PPH at cesarean delivery 3. Cost-effectiveness of uterotonic agents in community settings without skilled birth attendants 4. Cost-effectiveness of uterotonic agents in hospital settings where oxytocin quality cannot be guaranteed
Gallos et al. 2018, UK[6] Another SR, Gallos et al. 2019[26],	140 RCTs Inclusion criteria: "*All randomised controlled comparisons or cluster trials of effectiveness or*	88,947 patients 917 in 8 studies and 1,026 patients in 7 studies comparing carbetcoin with	Uterotonic drugs to prevent PPH is part of the active management of the third stage of labour	Primary outcomes "*1. PPH ≥ 500 mL; and 2. PPH ≥ 1000 mL*" (p. 9) Secondary outcomes

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
considered the same as Gallos et al. 2018[6] by Lawrie et al. based on the same network and similar studies (137 RCTs)	*side-effects of uterotonic drugs for preventing PPH*" (p. 1) Databases searched: Cochrane Pregnancy and Childbirth's Trials Register, CENTRAL, MEDLINE, Embase and CINAHL Search date: 27 October 2017	oxytocin for the outcomes of PPH ≥ 500 mL and 1,000 mL respectively Mostly in hospital settings and predominantly more than 37 weeks of gestation having a vaginal birth.	Oxytocin, ergometrine, misoprostol, carbetocin, and combination drugs compared to one another	"*1. maternal deaths; 2. maternal deaths or severe morbidity events*" (p. 9) "*3. additional uterotonics requirement; 4. transfusion requirement; 5. manual removal of the placenta; 6. mean volumes of blood loss (mL); 7. mean durations of the third stage of labour (minutes); 8. change in haemoglobin measurements before and after birth (g/L); 9. clinical signs of excessive blood loss (as defined by the trialists); 10. neonatal unit admission requirement; 11. breastfeeding at discharge; and 12. side-effects such as nausea, vomiting, hypertension, headache, tachycardia, hypotension, abdominal pain, fever and shivering in the first 24 hours postpartum*" (p. 9)
Voon et al. 2018, Malaysia[14]	7 RCTs Databases searched: Medline, Database of Abstract of Reviews of Effects (DARE), Cochrane Controlled Trials Register (CENTRAL), Cochrane Database of Systematic reviews and Cumulative Index to	2,012 participants Sample size range: 57 to 635 Conducted in Egypt (1 study), Canada (2 studies), Malaysia (1 study), Italy (1 study), UK (study) and Australia (1 study)	Carbetocin 100 µg versus oxytocin (variable doses, not reported) in the context of cesarean deliveries	Post-partum hemorrhage, additional use of uterotonic and transfusion requirement

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Nursing and Allied Health Literature (CINAHL) until May 2016 No language restriction Inclusion criteria: RCTs			

CENTRAL = Cochrane Controlled Trials Register; CINAHL = Cumulative Index to Nursing and Allied Health Literature; DARE = Database of Abstract of Reviews of Effects; PPH = post-partum hemorrhage; RCT = randomized controlled trial; WHO = World Health Organization

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized controlled trials				
Amornpetchakul et al. 2018, Thailand[15]	RCT, triple-blind, single-centre Registration: TCTR20160715004	350 singleton pregnant patients Age ≥ 35 years: 19 and 26 of the oxytocin (n = 174) and carbetocin (n = 176) respectively Mean gestational age (weeks): 38.4 ± 1.2 and 38.5 ± 1.3 respectively Inclusion criteria: 20 years or older, a gestational age of at least 34 weeks, a vaginal delivery, and at least one risk factor for atonic post-partum hemorrhage At least one risk factors of atonic PPH needed for inclusion: "*(1) a previous history of PPH; (2) induction or augmentation of labor > 4 h; (3)*	100 µg of carbetocin versus 5 U of oxytocin intravenously Immediately after childbirth but before placental delivery	Postpartum blood loss, incidence of atonic PPH, usage of additional uterotonic drugs, and incidence of postpartum anemia

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		exposure to tocolytic agents within 4 h prior to delivery; (4) a prolonged active phase of labor > 12 h; (5) precipitated labor; (6) grand multipara (parity > 4); (7) polyhydramnios; and (8) presence of uterine leiomyoma" (p. 320)		
Mannaerts et al. 2018, Belgium[16]	RCT, double-blind, single-centre Registration: ISRCTN 95504420	68 patients Inclusion criteria: "singleton pregnancies undergoing a planned cesarean section at term (≥37 weeks) under combined spinal/epidural anaesthesia" (p. 2) Gestational ages: 38 to 40 weeks.	100 µg of carbetocin (Pabal®, Ferring NV, Aalst, Belgium) single dose over 3 minutes versus oxytocin (Syntocinon, Sigma-Tau, Rome, Italy), 5 IU over 3 minutes followed by 10 IU oxytocin over 24 hours	Nausea, vomiting, blood pressure, heart rate, nausea/vomitus, need for vasopressors, preoperative and postoperative haemoglobin and haematocrit levels Follow-up 48 hours
Taheripanah et al. 2018, Iran[20]	RCT, two-centre, double-blind Registration: NCT02079558	220 patients Mean age (years) in 2 groups: 27.69 ± 5.7 and 26.93 ± 5.4, ***P*** = 0.643 Gestational age > 37 weeks Inclusion criteria: "*presence of at least one risk factor for postpartum hemorrhage among patients who could not give birth and then underwent emergency cesarean delivery (prolonged third stage of labor, mediolateral episiotomy, previous postpartum*	Single 100 µg IV dose of carbetocin versus 30-international unit IV infusion of oxytocin during 2 hours after delivery of placenta	Postpartum hemorrhage requiring additional uterotonic drugs, bleeding volume, and the hemoglobin drops

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		hemorrhage, arrest of descent, soft-tissue lacerations, augmented labor, forceps or vacuum delivery, Asian or Hispanic ethnicity, midline episiotomy, and nulliparity), and lack of hypersensitivity to oxytocin and carbetocin" (p. 2808)		
Widmer et al. 2018, Switzerland[5]	RCT, multi-centre (10 countries), double-blind, non-inferiority, active-controlled Carbetocin Haemorrhage Prevention (CHAMPION) Registration: ACTRN12614000870651; EudraCT 2014-004445-26 and, CTRI/ 2016/ 05/ 006969.)	29,645 patients randomized 29,539 modified intent-to-treat patients Median age: 25 years Median gestational age: 39 weeks Inclusion criteria: "*Women who expected to give birth vaginally and who had a singleton pregnancy and cervical dilatation of 6 cm or less*" (p. 745)	Heat-stable carbetocin (at a dose of 100 µg) versus oxytocin (at a dose of 10 IU) immediately after vaginal birth	Primary outcomes: proportion of patients with blood loss of at least 500 ml or the use of additional uterotonic agents, and the proportion of patients with blood loss of at least 1,000 ml Secondary outcomes "*proportion of women with blood loss of at least 1000 ml at 1 hour and up to 2 hours for women who continued to bleed after 1 hour*" (p. 746)
Elbohoty et al. 2016, Egypt[17]	RCT, double-blind, single-centre Registration: NCT02053922	263 patients undergoing an elective cesarean delivery Inclusion criteria: singleton pregnancy, full term (duration of pregnancy ≥37 weeks)	Carbetocin: single 100 µg (Pabal; Draxis/Multipharma, Egypt) following the delivery versus oxytocin single 10 IU (Syntocinon; Novartis Pharma, Berne, Switzerland) slowly intravenously following neonatal delivery with 20 IU oxytocin intravenous infusion over 4 hours	Primary outcome: occurrence of uterine atony necessitating additional uterotonics Secondary outcomes: total blood loss, the difference in hemoglobin level before and 24 hours after delivery, and the development of any adverse events

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			versus misoprostol: two tablets (each tablet 200 µg) (Misotac; Sigma Pharmaceuticals, Egypt) following the cesarean delivery	
Fahmy, Yousef, and Zaki 2016, Egypt[18]	RCT, single-centre, single blind (clinicians)	60 multiple pregnancy patients undergoing elective cesarean delivery Gestational age: not reported Inclusion criteria: twin pregnancy patients ASA physical status I, and aged 28 to 36 years	100 µg carbetocin versus 20 IU oxytocin	Need for methylergometrine postoperative, blood loss, blood pressure, and heart rates
Kabir et al. 2015, Bangladesh[19]	RCT, single-centre, no blinding reported	94 pregnant patients undergoing vaginal deliveries Inclusion criteria: "*women with a single pregnancy undergoing vaginal delivery above 36 weeks of gestation (gestational age was recorded according to the last menstrual period and was confirmed by ultrasound report)*" (p. 4)	Intravenous 100 micro gram carbetocin versus intramuscular 10 IU oxytocin in third stage of labour.	Massive blood loss, primary PPH, blood transfusion, additional uterotonics, adverse effects
Non-randomized studies				
Chen et al. 2018, Taiwan[21]	Retrospective cohort study, single-centre	1,568 patients with cesarean deliveries "*before labor onset (elective CS, n = 1,153) or during labor (intrapartum CS, n =*	Carbetocin (100 mg intravenously infused over 1 min) versus oxytocin (10 units as a bolus, intravenously	Fall in hemoglobin and hematocrit levels after CS, estimated blood loss, need for additional uterotonic agents, blood transfusion, and rate

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		415) after 24 weeks' gestation" (p. 677) Mean ages of 4 groups: 33.1 to 35.0 years Ranges of mean gestational ages: 36.9 to 38.7 weeks in 4 groups	infused) administration after delivering the newborn "*then received intravenous infusion of oxytocin at a rate of 1.0 - 1.2 units per hour until the next morning to control for the operative hemorrhage*" (p. 677)	of postpartum hemorrhage
Sotillo et al. 2018, Spain[22]	Prospective cohort study, single-centre	166 twin pregnancies at term undergoing elective or emergency cesarean section Inclusion criteria: "*patients older than18 years, elective or nonelective cesarean performed in twin gestations over 24 weeks, cesarean section performed through low segment hysterotomy, absence of maternal contraindications for the use of carbetocin (serious cardiovascular disorders, liver or kidney failure, and/or eclampsia), and cesarean section under epidural or spinal anesthesia*" (p. 2)	Single 100 µg dose of carbetocin versus oxytocin 20 IU in 10 to 15 min	"*intraoperative bleeding (estimated by the anesthetist from the amount of blood collected in the aspirator and the number of compresses used during the intervention), surgical time (from the skin incision to the skin closure), hemoglobin fall, hematocrit drop, additional uterotonic use (Methylergometrine and/or misoprostol), need for blood transfusion, and/or IV iron therapy*" (p. 2) "*proportion of patients who needed additional treatments during the postpartum period, understanding as such the need for additional uterotonic (Methylergometrine and/or misoprostol) and/or the need for treatment for anemia (IV iron therapy and/or blood transfusion)*" (p. 2)

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Wohling et al. 2018, Australia[23]	Retrospective cohort study, single-centre, before-and-after	2,499 singleton pregnancies undergoing CS from 2008 to 2010 Mean maternal ages: 29.2 ± 5.8 and 29.0 ± 5.9 years Mean gestational ages: 38.6 and 38.7 weeks in 2 groups	Prophylactic oxytocin 5 to 10 units slow push intravenously at delivery from January 2008 to 24 March 2009 versus 100 µg intravenous carbetocin after 24 March 2009, until 2010	PPH (≥1000 mL) and the requirement of secondary uterotonics
Seow et al. 2017, Taiwan[25]	Cohort study, single-centre	64 patients Mean ages: 34.5 ± 4.2 and 33.7 ± 3 years, carbetocin and control respectively (***P*** > 0.05) Mean gestational age: 35.2 weeks Cesarean delivery: all Inclusion criteria: "*twin pregnancy induced using in vitro fertilization-embryo transfer (IVF-ET)*" (p. 274)	100 µg carbetocin intravenously, single dose, as soon as the baby was delivered but before the placenta was delivered versus continuous IV infusion of 10 IU oxytocin as soon as the baby was delivered and for 24 h afterward	Primary outcome: drop in hemoglobin level by comparing the maternal hemoglobin concentration on admission before cesarean delivery with that measured 24 h after delivery Secondary outcomes: "*blood loss during surgery, and lochia within 2 h after delivery, the duration of the operation, the incidence of primary PPH (defined as blood loss more than 1000 mL), and blood transfusion*" (p. 274) Blood loss: estimated after excluded amniotic fluid volume in each case Maternal pulse rate and fetal body weight, and need for additional uterotonic agents
Nucci et al. 2016, France[24]	Retrospective cohort study, single-centre, before-and-after	60 patients with severe preeclampsia undergoing cesarean	100 µg intravenous carbetocin	Need for additional uterotonics, time interval to additional

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		delivery under spinal anaesthesia, ASA 3 Mean gestational age: 31.8 and 31.9 weeks Sever preeclampsia: 2009 French Society of Anesthesiology and Critical Care Medicine guideline	(first 18 months between July 2011 and August 2013) versus 5 IU oxytocin (last 8 months between the same period) after the birth of the infant	uterotonics, need for compression balloon, hemoglobin difference, loss of hemoglobin, need for blood products, red blood cells, fresh frozen plasma, and admission to intensive care unit

ASA = American Society of Anesthesiologists; CHAMPION = Carbetocin Haemorrhage Prevention; IU = international unit; IV = intravenous; PPH = post-partum hemorrhage; RCT = randomized controlled trial; U = unit

Table 4: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Pickering et al. 2019, UK[27]	Cost-effectiveness, model-based, decision tree Maximal length of treatment stage: 6 days UK National Health Service perspective	"*relative cost effectiveness for the full range of uterotonic drugs available for preventing postpartum haemorrhage (PPH)*" (p. 163) Primary outcome: cost per case of PPH avoided (≥ 500 mL blood loss) Secondary outcomes: cost per	Patients approaching the third stage of labour (vaginal delivery) Third stage of labour: the period of time after the birth of the baby and before removal of the placenta and membranes	Carbetocin, ergometrine, 'ergometrine plus oxytocin', 'misoprostol plus oxytocin', misoprostol, and oxytocin compared to each other Given at the prevention stage (Stage 0) of the model	Network meta-analysis-based[26]	UK costs from published sources Primary outcome: cost per case of PPH avoided (≥ 500 mL blood loss) Secondary outcome: cost per case of severe PPH avoided (≥ 1000 mL) and cost per major outcome	"*after receiving a particular prevention strategy at stage 0, a woman will have a probability of either bleeding (PPH ≥ 500 mL) or experiencing no PPH*" (p. 164) 1 prevention stage and 4 treatment stages assumed in the management strategy

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
		case of severe PPH avoided (≥ 1000 mL); cost per major outcome (surgery) averted				(surgery) averted	
Gil-Rojas et al. 2018, Colombia[28]	Cost-effectiveness analysis, decision tree Costs in 2016 Colombian pesos (1 USD = 3,051 Col$). Time horizon: 1 year Third-party payer perspective No discount	Use of carbetocin and oxytocin for prevention of PPH and related consequence Outcome: incremental costs and effectiveness in terms of quality-adjusted life years (QALYs)	Patients with at least one risk factor for hemorrhage due to uterine atony (vaginal delivery and cesarean section) Risk factors: "*multiple gestation, polyhydramnios, macrosomia, large multiparous, severe hydrocephalus, prolonged labor and chorioamnionitis*" (p. 244)	Carbetocin, single dose of 100 µg (vaginal and cesarean deliveries) versus Oxytocin: vaginal delivery 5 to 10 IU, intramuscularly, cesarean section, an IV bolus of 5 IU followed by an infusion of 30 IU	Trial-based analysis (5 studies)	"*only direct medical costs required to prevent and treat hemorrhagic events with each of the alternatives*" (p. 245) Cost data sources: 2016 Report of the Drug Price Information System and official documents of price regulation for medicines issued by the Ministry of Health, the Social Security Institute (ISS, in the Spanish acronym) Fee Manual (Agreement	Not reported

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
						256 of 2001)	

IU = international unit; PPH = post-partum hemorrhage; RCT = randomized controlled trial; USD = United States dollar

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Leduc et al. 2018, Canada[29] Society of Obstetricians and Gynaecologists of Canada						
Intended users: clinicians **Target population: patients at risk of or with postpartum hemorrhage**	Drugs (oxytocin, ergonovine, carbetocin) and non-drug interventions for the prevention and treatment of postpartum hemorrhage Risk factors of postpartum hemorrhage: Tone (uterine atony, distended bladder), Tissue (retained placenta and clots), Trauma (vaginal, cervical, or uterine injury), and Thrombin [coagulopathy (pre-existing or acquired)]	Maternal and neonatal outcomes including retained placenta, PPH, and length of third stage	An update of a 2000 guideline Databases searched: Medline, PubMed, the Cochrane Database of Systematic Reviews, ACP Journal Club, and BMJ Clinical Evidence Articles published between 1995 and 2007 retrieved Synthesis methods not reported in this article	Jadad Scale	Levels of evidence defined by the Canadian Task Force on Preventive Health Care	Approved by Board of The Society of Obstetricians and Gynaecologists of Canada

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Lier et al. 2018, German[29] German, Austrian and Swiss Societies of Gynaecology and Obstetrics German Society of Anaesthesiology and Intensive Care Medicine Society of Thrombosis and Haemostasis Research						
Intended users: clinicians **Target population: patients at risk of or with postpartum hemorrhage**	Pharmaceutical and non-pharmaceutical treatment and diagnosis of peripartum haemorrhage	Maternal outcomes including hemostatic outcomes	Update to an AWMF's 2008 guideline Databases searched: PubMed Articles published between 2008 to 2015 retrieved Synthesis based on 142 articles; structured, consensus-based	Appraisal tools not reported	AWMF's classification of the strength of consensus	Not reported
Mavrides et al. 2017, UK[30] Royal College of Obstetricians and Gynaecologists						
Intended users: clinicians **Target population: patients giving birth**	Pharmaceutical and non-pharmaceutical interventions for the prevention and treatment of PPH	Maternal and neonatal outcomes including bleeding, hospitalization, PPH, and fertility	An update of a 2009 guideline Databased searched: Cochrane Library (including the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects	"*developed in accordance with standard methodology for producing RCOG Green-top Guidelines*" (p. e114) Guideline development website: http://www.rcog.org.uk/green-top-	"*developed in accordance with standard methodology for producing RCOG Green-top Guidelines*" (p. e114) Guideline development website: http://www.rcog.org.uk/green-top-development Grades of recommendations explained in the	Peer reviewed by external experts

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
			[DARE]), EMBASE, Trip, MEDLINE, PubMed, National Library for Health and the National Guideline Clearinghouse Articles published from 2007 to 2015 retrieved Synthesis: "*Where possible, recommendations are based on available evidence and the areas where evidence is lacking are annotated as 'good practice points*'" (p. e114)	development Classification of evidence levels explained in the Appendix I of the guideline	Appendix I of the guideline	
Bennett et al. 2016, Canada[1] Association of Ontario Midwives						
Intended users: Ontario midwives **Target population: Ontario**	Pharmaceutical and non-pharmaceutical interventions for the prevention and treatment of PPH	Critical and important maternal and neonatal outcomes including mortality, morbidity, blood loss,	An update of a 2006 guideline Databases searched: Medline and CINAHL databases	Grading of Recommendations Assessment, Development and Evaluation (GRADE)	Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for guideline development	"*reviewed using a modified version of the AGREE instrument, the AOM Values-based Approach to CPG Development, as*

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
midwives' clients		hysterectomy, blood transfusion, and admission to NICU	and Cochrane library Articles published from 1995 to 2013 retrieved Synthesis: not reported	methodology for guideline development		*well as consensus of the Postpartum Hemorrhage Work Group; the CPG Committee; the Quality, Insurance and Risk Management Program Steering Committee; the AOM Board of Directors; and member consultation*" (p.5)
Sentilhes et al. 2016, France[31] French College of Gynaecologists and Obstetricians French Society of Anesthesiology and Intensive Care						
Intended users: clinicians **Target population: Ontario midwives' clients**	Pharmaceutical and non-pharmaceutical interventions including methods of delivery, oxytocin, and cord drainage	Maternal outcomes including placenta retention and PPH	Databases searched: MEDLINE database and the Cochrane Library English or French articles published through 2014 retrieved "*synthesis of recommendations was drafted by the organizing committee based on the replies given by the expert*	"*level of evidence based on the quality of its data, in accordance with the framework defined by the HAS (French Health Authority)*" (p. 13)	"*level of evidence based on the quality of its data, in accordance with the framework defined by the HAS (French Health Authority)*" (p. 13)	Reviewed by external experts

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
			authors" (p. 13)			

ACP = American College of Physicians; AGREE = Appraisal of Guidelines for Research and Evaluation; AOM = Association of Ontario Midwives; AWMF = Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies); BMJ = British Medical Journal; CPG = clinical practice guideline; DARE = Database of Abstracts of Reviews of Effects; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HAS = French Health Authority; PPH = post-partum hemorrhage; RCOG = Royal College of Obstericians and Gynecologists; RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2 checklist[8]

Strengths	Limitations
Lawrie et al., 2019 [13]	
- PICO components included in the research questions - Selection of study design explained - Comprehensive literature search strategies - Study selection in duplicate - Data extraction in duplicate - Review authors' conflict of interest reported	- Review protocol not published *a priori* - A list of excluded studies not provided - Included studies not described - Risk of bias in the included studies not assessed with published tools - Sources of funding of the included studies not reported - Risk of bias in the included studies considered when interpreting the results - Heterogeneity in the results discusses - Publication bias assessed
Gallos et al., 2018 [6]	
- PICO components included in the research questions - Selection of study design explained - Comprehensive literature search strategies - Study selection in duplicate - Data extraction in duplicate - A list of excluded studies provided - Included studies described - Risk of bias in the included studies assessed with published tools - Sources of funding of the included studies reported - Appropriate statistical methods used in meta-analysis - Risk of bias in the included studies considered in meta-analysis - Risk of bias in the included studies considered when interpreting the results - Heterogeneity in the results discusses - Publication bias assessed - Review authors' conflict of interest reported	- Review protocol not published *a priori*
Voon et al., 2018 [14]	
- PICO components included in the research questions - Selection of study design explained - Comprehensive literature search strategies - Study selection in duplicate - Data extraction in duplicate - Included studies described - Risk of bias in the included studies assessed with published tools - Appropriate statistical methods used in meta-analysis - Risk of bias in the included studies considered in meta-analysis - Heterogeneity in the results discusses - Review authors' conflict of interest reported	- Review protocol not published *a priori* - A list of excluded studies not provided - Sources of funding of the included studies not reported - Risk of bias in the included studies not considered when interpreting the results - Publication bias not assessed - Funded by the manufacturer

PICO = population, intervention, comparator, and intervention

Table 7: Strengths and Limitations of Clinical Studies using Downs and Black checklist[9]

Strengths	Limitations
Randomized controlled trials	
Amornpetchakul et al., 2018[15]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided - Adverse events reported - No lost to follow-up - Actual probability values (***P*** values) for the outcomes reported - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared - Patients blinded for the intervention status - Outcome assessors blinded for the intervention status - Time periods between the intervention and outcome the same for different groups - Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable - Outcome measures accurate - Different groups of patients recruited from the same population - Different groups of patients recruited from the same period of time - Patients randomized to different groups - Assignment concealed from the patients - No lost to follow-up reported - Power analysis for sample sizes conducted	- Single-centre trial
Mannaerts et al., 2018[16]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided - Adverse events reported - Patients lost to follow-up reported - Actual probability values (***P*** values) for the outcomes reported - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared - Patients blinded for the intervention status - Outcome assessors blinded for the intervention status - Time periods between the intervention and outcome the same for different groups - Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable	- Single-centre trial - Assignment concealment not reported

Table 7: Strengths and Limitations of Clinical Studies using Downs and Black checklist[9]

Strengths	Limitations
- Outcome measures accurate - Different groups of patients recruited from the same population - Different groups of patients recruited from the same period of time - Patients randomized to different groups - Patients lost to follow-up excluded from analysis - Power analysis for sample sizes conducted	
Taheripanah et al., 2018[20]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided - Adverse events reported - No lost to follow-up - Actual probability values (***P*** values) for the outcomes reported - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared - Patients blinded for the intervention status - Outcome assessors blinded for the intervention status - Time periods between the intervention and outcome the same for different groups - Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable - Outcome measures accurate - Different groups of patients recruited from the same population - Different groups of patients recruited from the same period of time - Patients randomized to different groups - Power analysis for sample sizes conducted	- Single-centre trial - Assignment concealment not reported
Widmer et al., 2018[5]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided - Adverse events reported - Patients lost to follow-up reported - Multi-centre trial - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared - Patients blinded for the intervention status	- Probability values (*P* values) not reported - Assignment concealment not reported

Table 7: Strengths and Limitations of Clinical Studies using Downs and Black checklist[9]

Strengths	Limitations
- Outcome assessors blinded for the intervention status - Time periods between the intervention and outcome the same for different groups - Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable - Outcome measures accurate - Different groups of patients recruited from the same population - Different groups of patients recruited from the same period of time - Patients randomized to different groups - Patients lost to follow-up excluded from analysis - Power analysis for sample sizes conducted	
Elbohoty et al., 2016[17]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided - Adverse events reported - Lost to follow-up reported - Actual probability values (***P*** values) for the outcomes reported - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared - Patients blinded for the intervention status - Outcome assessors blinded for the intervention status - Time periods between the intervention and outcome the same for different groups - Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable - Outcome measures accurate - Different groups of patients recruited from the same population - Different groups of patients recruited from the same period of time - Patients randomized to different groups - Assignment concealed from the patients - Lost to follow-up excluded from analysis - Power analysis for sample sizes conducted	- Single-centre trial
Fahmy, Yousef, and Zaki, 2016[18]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided	- Single-centre trial - Adverse events such as nausea not reported - Patient blinding not reported - Assignment concealment from the patients not reported

Table 7: Strengths and Limitations of Clinical Studies using Downs and Black checklist[9]

Strengths	Limitations
- Lost to follow-up not reported - Outcome assessors blinded for the interventions - Actual probability values (***P*** values) for the outcomes reported - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared - Time periods between the intervention and outcome the same for different groups - Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable - Outcome measures accurate - Different groups of patients recruited from the same population - Different groups of patients recruited from the same period of time - Patients randomized to different groups - Power analysis for sample sizes conducted	
Kabir et al., 2015[19]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided - Lost to follow-up not reported - Actual probability values (***P*** values) for the outcomes reported - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared - Time periods between the intervention and outcome the same for different groups - Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable - Outcome measures accurate - Different groups of patients recruited from the same population - Different groups of patients recruited from the same period of time - Patients randomized to different groups	- Single-centre study - Adverse events not reported - Patient blinding for the intervention status not reported - Outcome assessor blinding for the intervention status not reported - Assignment concealment not reported - Power analysis for sample sizes not conducted
Non-randomized studies	
Chen et al., 2018[21]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided	- Single-centre study - Adverse events such as nausea and vomiting not reported - Patient blinding not reported - Outcome assessor blinding not reported - Interventions assigned based on clinicians' choices

Table 7: Strengths and Limitations of Clinical Studies using Downs and Black checklist[9]

Strengths	Limitations
- Lost to follow-up not reported - Actual probability values (***P*** values) for the outcomes reported - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared - Time periods between the intervention and outcome the same for different groups - Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable - Outcome measures accurate - Different groups of patients recruited from the same population - Different groups of patients recruited from the same period of time - Confounding adjusted in the analysis	
Sotillo et al., 2018[22]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided - Lost to follow-up not reported - Actual probability values (***P*** values) for the outcomes reported - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared - Time periods between the intervention and outcome the same for different groups - Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable - Outcome measures accurate - Different groups of patients recruited from the same population - Different groups of patients recruited from the same period of time	- Single-centre study - Adverse events such as nausea and vomiting not reported - Patient blinding not reported - Outcome assessor blinding not reported - Interventions assignment not explained - Confounding not adjusted in the analysis
Wohling et al., 2018[23]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided - Lost to follow-up reported - Actual probability values (***P*** values) for the outcomes reported - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared	- Single-centre study - Patient blinding not reported - Outcome assessor blinding not reported - Interventions assigned based on the time of treatment (before -after design) - Different time periods between the intervention and outcome for two groups - Confounding not adjusted in the analysis - Different groups of patients not recruited from the same period of time

Table 7: Strengths and Limitations of Clinical Studies using Downs and Black checklist[9]

Strengths	Limitations
- Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable - Outcome measures accurate - Different groups of patients recruited from the same population - Adverse events reported	
Seow et al., 2017[25]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided - Lost to follow-up not reported - Actual probability values (***P*** values) for the outcomes reported - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared - Time periods between the intervention and outcome the same for different groups - Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable - Outcome measures accurate - Different groups of patients recruited from the same population - Different groups of patients recruited from the same period of time	- Single-centre study - Adverse events such as nausea and vomiting not reported - Patient blinding not reported - Outcome assessor blinding not reported - Interventions assignment not explained - Confounding not adjusted in the analysis
Nucci et al., 2016[24]	
- Research hypothesis described - Outcomes to be measured described - Characteristics of patients described - Interventions described - Distributions of principal confounders described - Main findings described - Estimates of random variability in the outcome data provided - Lost to follow-up not reported - Actual probability values (***P*** values) for the outcomes reported - No differences in the staff, places, and facilities where trial patients were treated and those for the majority of patients declared - Statistical tests to assess the outcomes appropriate - Compliance with the intervention reliable - Outcome measures accurate - Different groups of patients recruited from the same population - Adverse events reported	- Representativeness of the patients unclear - Patient blinding not reported - Outcome assessor blinding not reported - Interventions assigned based on the time of treatment (before -after design) - Different time periods between the intervention and outcome for two groups - Confounding not adjusted in the analysis - Different groups of patients not recruited from the same period of time

Table 8: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline				
	Leduc et al. 2018, Canada[29] Society of Obstetricians and Gynaecologists of Canada	Lier et al. 2018, German[4] German, Austrian and Swiss Societies of Gynaecology and Obstetrics German Society of Anaesthesiology and Intensive Care Medicine Society of Thrombosis and Haemostasis Research	Mavrides et al. 2017, UK[30] Royal College of Obstetricians and Gynaecologists	Bennett et al. 2016, Canada[1] Association of Ontario Midwives	Sentilhes et al. 2016, France[31] French College of Gynaecologists and Obstetricians French Society of Anesthesiology and Intensive Care
Domain 1: Scope and Purpose					
1. The overall objective(s) of the guideline is (are) specifically described.	Strongly agreed	Strongly agreed	Strongly agreed	Strongly agreed	Strongly agreed
2. The health question(s) covered by the guideline is (are) specifically described.	Agreed	Agreed	Strongly agreed	Strongly agreed	Strongly agreed
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Agreed	Agreed	Strongly agreed	Strongly agreed	Strongly agreed
Domain 2: Stakeholder Involvement					
4. The guideline development group includes individuals from all relevant professional groups.	Partly agreed	Strongly agreed	Strongly agreed	Strongly agreed	Strongly agreed
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Disagreed	Disagreed	Disagreed	Disagreed	Disagreed
6. The target users of the guideline are clearly defined.	Partly agreed	Partly agreed	Strongly agreed	Strongly agreed	Strongly agreed
Domain 3: Rigour of Development					
7. Systematic methods were used to search for evidence.	Strongly agreed	Strongly agreed	Strongly agreed	Strongly agreed	Strongly agreed
8. The criteria for selecting the evidence are clearly described.	Strongly agreed	Strongly agreed	Strongly agreed	Agreed	Agreed

Table 8: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline				
	Leduc et al. 2018, Canada[29] Society of Obstetricians and Gynaecologists of Canada	Lier et al. 2018, German[4] German, Austrian and Swiss Societies of Gynaecology and Obstetrics German Society of Anaesthesiology and Intensive Care Medicine Society of Thrombosis and Haemostasis Research	Mavrides et al. 2017, UK[30] Royal College of Obstetricians and Gynaecologists	Bennett et al. 2016, Canada[1] Association of Ontario Midwives	Sentilhes et al. 2016, France[31] French College of Gynaecologists and Obstetricians French Society of Anesthesiology and Intensive Care
9. The strengths and limitations of the body of evidence are clearly described.	Disagreed	Disagreed	Disagreed	Disagreed	Disagreed
10. The methods for formulating the recommendations are clearly described.	Disagreed	Agreed	Agreed	Agreed	Agreed
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Agreed	Agreed	Agreed	Agreed	Agreed
12. There is an explicit link between the recommendations and the supporting evidence.	Strongly agreed	Strongly agreed	Strongly agreed	Strongly agreed	Strongly agreed
13. The guideline has been externally reviewed by experts prior to its publication.	Disagreed	Disagreed	Strongly agreed	Agreed	Strongly agreed
14. A procedure for updating the guideline is provided.	Disagreed	Disagreed	Disagreed	Disagreed	Disagreed
Domain 4: Clarity of Presentation					
15. The recommendations are specific and unambiguous.	Strongly agreed	Agreed	Strongly agreed	Strongly agreed	Strongly agreed
16. The different options for management of the condition or health issue are clearly presented.	Strongly agreed	Agreed	Strongly agreed	Strongly agreed	Strongly agreed
17. Key recommendations are easily identifiable.	Strongly agreed	Agreed	Strongly agreed	Strongly agreed	Agreed
Domain 5: Applicability					

Table 8: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline				
	Leduc et al. 2018, Canada[29] Society of Obstetricians and Gynaecologists of Canada	Lier et al. 2018, German[4] German, Austrian and Swiss Societies of Gynaecology and Obstetrics German Society of Anaesthesiology and Intensive Care Medicine Society of Thrombosis and Haemostasis Research	Mavrides et al. 2017, UK[30] Royal College of Obstetricians and Gynaecologists	Bennett et al. 2016, Canada[1] Association of Ontario Midwives	Sentilhes et al. 2016, France[31] French College of Gynaecologists and Obstetricians French Society of Anesthesiology and Intensive Care
18. The guideline describes facilitators and barriers to its application.	Agreed	Strongly agreed	Strongly agreed	Strongly agreed	Strongly agreed
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Agreed	Strongly agreed	Strongly agreed	Strongly agreed	Strongly agreed
20. The potential resource implications of applying the recommendations have been considered.	Agreed	Agreed	Agreed	Agreed	Strongly agreed
21. The guideline presents monitoring and/or auditing criteria.	Disagreed	Disagreed	Disagreed	Disagreed	Disagreed
Domain 6: Editorial Independence					
22. The views of the funding body have not influenced the content of the guideline.	Agreed	Disagreed (not reported)	Disagreed (not reported)	Strongly agreed	Disagreed (not declared)
23. Competing interests of guideline development group members have been recorded and addressed.	Strongly agreed	Disagreed (not reported)	Strongly agreed	Disagreed	Strongly agreed

Table 9: Strengths and Limitations of Economic Studies using the Drummond Checklist[10]

Strengths	Limitations
Gil-Rojas et al., 2018 [28]	
- Research questions stated - Economic importance of the research question stated - Viewpoints stated and justified - Rationales for the interventions stated - Alternatives being compared described - The form of economic evaluation stated and justified - Sources of effectiveness estimates stated - Primary outcome measures stated - Methods to evaluate the benefits stated - Details of the subjects from whom valuations were obtained described - Methods to estimate the quantities and unit costs stated - Currency and price data reported - Details in currency adjustment for inflation stated - Details of the models used given - The choice of model and key parameters justified - Time horizon stated - Discount rate stated and justified - Approach to sensitivity analysis explained - Variables for sensitivity analysis explained - The ranges over which the variables were varied given - Relevant alternatives compared - Incremental analysis reported - Answers to the study questions provided - Conclusions reported with caveats	- Productivity change not stated - Quantities of resources not reported separately from the unit costs - Major outcomes not presented in both aggregated and disaggregated forms
Pickering et al., 2019[27]	
- Research questions stated - Economic importance of the research question stated - Viewpoints stated and justified - Rationales for the interventions stated - Alternatives being compared described - The form of economic evaluation stated and justified - Sources of effectiveness estimates stated - Primary outcome measures stated - Methods to evaluate the benefits stated - Details of the subjects from whom valuations were obtained described - Methods to estimate the quantities and unit costs stated - Currency and price data reported - Details of the models used given - The choice of model and key parameters justified - Time horizon stated - Approach to sensitivity analysis explained - Variables for sensitivity analysis explained - The ranges over which the variables were varied given - Relevant alternatives compared - Incremental analysis reported - Answers to the study questions provided - Conclusions reported with caveats - Design and results of the effectiveness study described - Meta-analysis of the estimates described	- Productivity change not stated - Quantities of resources not reported separately from the unit costs - Major outcomes not presented in both aggregated and disaggregated forms - Details in currency adjustment for inflation not stated - Discount rate not stated

Appendix 4: Main Study Findings and Authors' Conclusions

Table 10: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Lawrie et al., 2019[13]	
Which uterotonic agents are cost-effective for preventing PPH at vaginal birth? - "*When adverse events were considered, oxytocin (which ranked fourth in effectiveness) was the least costly uterotonic agent*" (p. 59) - "*Compared with oxytocin, carbetocin (which ranked as a more effective agent) was associated with an ICER of approximately US $1193.58 per additional PPH of greater than or equal to 500 mL avoided, and US $29 464.19 per additional PPH greater than or equal to 1000 mL avoided*" (p. 59) Which uterotonic agents are cost-effective for preventing PPH at cesarean delivery? - "*The ICER for averting one case of PPH greater than or equal to 1000 mL in the UK context was reported as approximately US $2927.30 with carbetocin versus the misoprostol plus oxytocin combination, and averting a major adverse outcome was US $114 347.78*" (p. 59) according to one included study - Carbetocin (100 µg) to oxytocin (5 or 10 IU, where dose was reported): carbetocin cost-effective at cesarean delivery compared with oxytocin in 7 studies; uncertain in 1 study Uterotonic agents in community settings without skilled birth attendants - "*The cost-effectiveness of misoprostol was evaluated in settings with low access to modern birth facilities (lack of skilled birth attendants, inadequate transport and storage facilities, or oxytocin not available) in six studies*" (p. 60)	- "*Evidence on the cost-effectiveness of various uterotonic agents was not generalizable. As the number of competing uterotonics increases, rigorous economic evaluations including contextual factors are needed*" (p. 56) Which uterotonic agents are cost-effective for preventing PPH at cesarean delivery? - "*these two uterotonic options (i.e. carbetocin or misoprostol plus oxytocin) were both more cost-effective than misoprostol or oxytocin alone*" (p. 59)
Gallos et al., 2018[6]	
Outcome of PPH ≥ 500 mL, compared with oxytocin - RR of ergometrine plus oxytocin = 0.69 (95% CI, 0.57 to 0.83), moderate-quality evidence - RR of carbetocin = 0.72 (95% CI, 0.52 to 1.00), very low-quality evidence - RR of misoprostol plus oxytocin = 0.73 (95% CI, 0.60 to 0.90), moderate-quality evidence - "*about 10.5% women given oxytocin would experience a PPH of ≥ 500 mL compared with 7.2% given ergometrine plus oxytocin combination, 7.6% given carbetocin, and 7.7% given misoprostol plus oxytocin*" (p. 2) - "*Oxytocin was ranked fourth with close to 0% cumulative probability of being ranked in the top three for PPH ≥ 500 mL*" (p. 2) Outcome of PPH ≥ 1000 mL - similar to those of PPH ≥ 500 mL	- "*The three most effective drugs for prevention of PPH ≥ 500 mL were ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination*" (p. 2) - "*These three options were more effective at preventing PPH≥500mL compared with oxytocin, the drug currently recommended by the WHO*" (p. 2) - "*Ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination were more effective for preventing PPH ≥ 500 mL than the current standard oxytocin*" (p. 2) - "*Ergometrine plus oxytocin combination was more effective for preventing PPH ≥ 1000 mL than oxytocin*" (p. 2) - "*Misoprostol plus oxytocin combination evidence is less consistent and may relate to different routes and doses of misoprostol used in the studies*" (p. 2) - "*Carbetocin had the most favourable side-effect profile amongst the top three options; however, most carbetocin trials were small and at high risk of bias*" (p. 2)

Table 10: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
- Ergometrine plus oxytocin combination more effective than oxytocin: RR = 0.77 (95% CI, 0.61 to 0.95), high-quality evidence) - Ergometrine plus oxytocin combination more certain than that for carbetocin: RR = 0.70 (95% CI, 0.38 to 1.28), low-quality evidence) - Ergometrine plus oxytocin combination more certain than misoprostol plus oxytocin combination: RR = 0.90 (95% CI, 0.72 to 1.14), moderate-quality evidence Maternal deaths or severe morbidity - No meaningful differences between all drugs because of rare occurrence in the included randomised trials Side effects - Poorest rankings for side-effects: ergometrine plus oxytocin combination and misoprostol plus oxytocin combination - Ergometrine plus oxytocin combination with higher risk for vomiting [RR = 3.10 (95% CI, 2.11 to 4.56), high-quality evidence; 1.9% versus 0.6%) and hypertension [RR = 1.77 (95% CI, 0.55 to 5.66), low-quality evidence; 1.2% versus 0.7%) when compared with oxytocin - Misoprostol plus oxytocin combination with higher risk for fever [RR = 3.18 (95% CI, 2.22 to 4.55), moderate-quality evidence; 11.4% versus 3.6%] when compared with oxytocin - Carbetocin: similar risk for side-effects compared with oxytocin (very low-quality evidence for vomiting and fever, and low-quality evidence for hypertension) Subgroup analysis Vaginal birth Outcome PPH ≥ 500 mL (85 trials) - "*Ergometrine plus oxytocin, and misoprostol plus oxytocin were found to be more effective when compared with the standard agent oxytocin*" (p. 63) - "*The highest ranked agents were ergometrine plus oxytocin, carbetocin, and misoprostol plus oxytocin with an almost 100% probability of these three agents being ranked first, second or third. Oxytocin was ranked fourth and its probability of being ranked in the top three agents was close to 0%*" (p. 63) PPH ≥ 1000 mL (71 trials) - "*The highest ranked agents were carbetocin, ergometrine plus oxytocin, and misoprostol plus oxytocin. Oxytocin was ranked fourth and its probability in being ranked in the top two agents was close to 0%*" (p. 65) Cesarean section PPH ≥ 500 mL (15 trials) - "*only misoprostol plus oxytocin is better than oxytocin alone in preventing PPH ≥ 500 mL for women undergoing cesareans, but most of the comparisons were based on single studies*" (p. 65)	

Table 10: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
- "*The highest ranked agents were misoprostol plus oxytocin and carbetocin. Oxytocin was ranked third and its probability in being ranked in the top two agents was close to 5%*" (p. 65) PPH ≥ 1000 mL (19 trials) - "*lack of evidence that any agent is worse or better than any other in preventing PPH ≥ 1000 mL in women undergoing cesareans, but many of the comparisons were based on single studies*" (p. 67)	
Voon et al., 2018[14]	
Carbetocin versus oxytocin - Statistically significant reduction in the rates of postpartum hemorrhage [RR = 0.79 (95% CI, 0.66 to 0.94), P = 0.009], use of additional uterotonics [RR = 0.57 (95% CI, 0.49 to 0.65), ***P*** < 0.001] and transfusion [RR = 0.31 (95% CI, 0.15 to 0.64), ***P*** = 0.002) - Significant heterogeneity across studies (extreme heterogeneity for the outcome of additional uterotonic usage)	- "*Carbetocin is effective in reducing the use of additional uterotonics, reduction in postpartum hemorrhage and transfusion when used during cesarean deliveries*" (p. 332)

CI = confidence interval; ICER = incremental cost-effectiveness ratio; IU = international unit; PPH = post-partum hemorrhage; RR = risk ratio; WHO = World Health Organization

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized controlled trials	
Amornpetchakul et al., 2018[15]	
Carbetocin versus oxytocin (vaginal delivery) - Less postpartum blood loss (146.7 ± 90.4 vs. 195.1 ± 146.2 mL; ***P*** < 0.01) - Lower incidence of atonic PPH (0 vs. 6.3%; ***P*** < 0.01) - Less usage of additional uterotonic drugs (9.1 vs. 27.6%; ***P*** < 0.01) - Lower incidence of postpartum anemia (Hb ≤ 10 g/dL) (9.1 vs. 18.4%; ***P*** < 0.05) - No significant differences in side effects	- "*Intravenous carbetocin is more effective than intravenous oxytocin for the prevention of atonic PPH among singleton pregnancies with at least one risk factor for PPH*" (p. 319)
Mannaerts et al., 2018[16]	
Carbetocin versus oxytocin (cesarean section) Hypotensive effect - Difference in systolic blood pressure(14.4 ± 2.4mmHg versus 8.5 ± 1.8mmHg respectively, ***P*** = 0.1) - Difference in diastolic blood pressure(7.8 ± 1.6mmHg versus 8.9 ± 3.0mmHg, ***P*** = 0.7) - Needs for vasopressors: similar - Nausea: not rare, statistically insignificant difference (***P*** = 0.4) - Average blood loss: insignificant difference (***P*** = 0.8)	- "*In planned CS, a possible clinical significant lower incidence of nausea after carbetocin was noted but this was not statistically significant. There were no differences regarding BP, heart rate, the need for vasopressor, and blood loss*" (p. 1)
Taheripanah et al., 2018[20]	

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Carbetocin versus oxytocin (cesarean section) - Hemoglobin drops: 1.01 versus 2.05, ***P*** = 0.01 - Bleeding volume: 430.68 mL versus 552.6 mL, ***P*** < 0.001 - Uterine massages frequency: 3.7 versus 4.26, ***P*** < 0.001 - Uterine height at 2, 4, and 24 hours: ***P*** < 0.001 - Side effects: oxytocin significantly higher in comparison with the carbetocin (except pruritus observed in 27% of patients in the carbetocin versus no cases in the oxytocin group)	- "*carbetocin is a good alternative modality to conventional uterotonic agents such as oxytocin for the prevention of postpartum hemorrhage after cesarean sections*" (p. 2807)
Widmer et al., 2018 [5]	
Carbetocin versus oxytocin (vaginal delivery) - Frequency of blood loss of at least 500 ml or the use of additional uterotonic agents: 14.5% versus 14.4% [relative risk = 1.01 (95% CI, 0.95 to 1.06), consistent with noninferiority] - Frequency of blood loss of at least 1000 ml: 1.51% versus 1.45% [relative risk = 1.04 (95% CI, 0.87 to 1.25), CI crossing the margin of noninferiority] - Use of additional uterotonic agents: not statistically significant - Interventions to stop bleeding: not statistically significant - Adverse effects: not statistically significant	- "*Heat-stable carbetocin was noninferior to oxytocin for the prevention of blood loss of at least 500 ml or the use of additional uterotonic agents*" (p. 743) - "*Noninferiority was not shown for the outcome of blood loss of at least 1000 ml; low event rates for this outcome reduced the power of the trial*" (p. 743)
Elbohoty et al., 2016[17]	
Carbetocin versus oxytocin versus misoprostol (cesarean delivery) - Need for further uterotonics: 5 (6%, lowest, ***P*** = 0.004), 11 (13%), and 20 (22%) - Prevention of uterine atony: carbetocin comparable with oxytocin [RR = 0.41 (95% CI, 0.14 to 1.25)] and superior to misoprostol [RR = 0.21 (95% CI, 0.07 to 0.58)]	- "*Additional uterotonics were needed less frequently by patients treated with carbetocin. Carbetocin was comparable to oxytocin and superior to misoprostol in the prevention of uterine atony following an elective cesarean delivery*" (p. 324)
Fahmy, Yousef, and Zaki., 2016[18]	
Carbetocin versus oxytocin (cesarean delivery) - "*As regards uterine contraction group O needed methylergometrine postoperative significantly more than group C and as regards blood loss; it was significantly decreased more in group C and though less reduction in blood pressure and less effect on heart rate than group O*" (p. 117)	- "*Single dose of carbetocin appears to be more effective than oxytocin for several hours on uterine contraction and though preventing postpartum hemorrhage in multiple pregnancy patients undergoing elective caesarian section*" (p. 117)
Kabir et al., 2015[19]	
Carbetocin versus oxytocin (vaginal delivery) - Massive blood loss: 0% versus 8.5% (***P*** = 0.002) - Further fundal massage: 0% versus 10.6% (***P*** = 0.002) - Immediate blood transfusion: 0% versus 6.4% (***P*** = 0.07) - Additional uterotonics: 0% versus 10.6% (***P*** = 0.002) - Average amount of blood loss: 64 ml less in carbetocin group (***P*** = 0.003) - Adverse effects: similar - Primary PPH: 0% versus 6.4% (***P*** = 0.07)	- "*Carbetocin appears to be an effective new drug in the active management of third stage of labour in vaginal delivery*" (p. 3) - "*A single dose of 100 microgram IV carbetocin is more effective than oxytocin for maintaining adequate uterine tone, less blood loss and preventing postpartum bleeding in women undergoing vaginal delivery*" (p. 3)
Non-randomized studies	
Chen et al., 2018[21]	

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Carbetocin versus oxytocin (cesarean section) - "*For women with elective CS, decreased Hb and Hct falls were noted with carbetocin treatment compared to oxytocin treatment in women with indications for prior CS, fetal malpresentation, and multiple gestation*" (p. 677) - "*The need for additional uterotonics was less in CS for prior CS, fetal malpresentation, and cephalopelvic disproportion and fewer transfusions in CS for multiple gestation in women with carbetocin compared to women with oxytocin treatment*" (p. 677) - "*For women with intrapartum CS, carbetocin was associated with decreased use of additional uterotonic agents and transfusion in CS for dysfunctional labor*" (p. 677)	"*Carbetocin and oxytocin had differential effects on hemorrhage-related changes in women with CS for different indications*" (p. 677)
Sotillo et al., 2018[22]	
Carbetocin versus oxytocin (cesarean section) - Fall in the hemoglobin level: 1.2 versus 1.7 (P = 0.02) - Need for blood transfusion: 13% versus 9.3% (P = 0.03) - Treatment for anemia as a composite variable (intravenous (IV) iron therapy and/or blood transfusion): 3.85% versus 16.3%, OR = 0.2 (95% CI, 0.05 to 0.72) - Reduction in the need to administer additional treatments (uterotonic and/or treatment for anemia) during the postpartum period: OR = 0.32 (95% CI, 0.12 to 0.88)	"*In our population of twin pregnancies delivered by cesarean section, carbetocin appears more effective than oxytocin in preventing PPH*" (p. 1)
Wohling et al., 2018[23]	
Carbetocin versus oxytocin (cesarean section) - Incidence of PPH ≥1000 mL: 7.8% versus 9.7%; OR = 0.79 (95% CI, 0.59 to 1.05) - Moderate blood loss >500 mL: 27.3% versus 39.4%; OR = 0.57 (95% CI, 0.49 to 0.68) - Secondary uterotonic treatment: 20.0% reduction with carbetocin; OR = 0.42 (95% CI, 0.35 to 0.49) - Average drug costs: $36.42 versus $4.74/patient - Cost-effectiveness ratio: $1,667 with carbetocin to prevent one case of PPH ≥1000 mL	- "*Carbetocin reduced moderate blood loss >500 mL, but not PPH ≥1000 mL*" (p. 1) - "*Carbetocin conferred a 20% reduction in secondary uterotonic treatment, as well as lowering direct medical costs*" (p. 1)
Seow et al., 2017[25]	
Carbetocin versus oxytocin (cesarean delivery) - Mean estimated blood loss during surgery: lower in the carbetocin group; 871 ± 305 and 922.8 ± 430 mL, respectively (***P*** = 0.06) - Drop in hemoglobin level between two groups: no significant difference - Mean operative time: significantly shorter in the carbetocin group (***P*** = 0.001)	"*Carbetocin is as effective as oxytocin in preventing primary postpartum hemorrhage in infertile women with twin pregnancy undergoing elective cesarean delivery*" (p. 273)
Nucci et al., 2016[24]	
Carbetocin versus oxytocin (cesarean section) - Additional uterotonic administration: 15% versus 10% (***P*** = 0.70)	"*carbetocin appears to be as effective and safe as oxytocin in preeclampsia women*" (p. 321)

C = carbetocin; CI = confidence interval; ICER = incremental cost-effectiveness ratio; IU = international unit; IV = intravenous; O =oxytocin; OR = odds ratio; PPH = post-partum hemorrhage; RR = risk ratio; WHO = World Health Organization

Table 12: Summary of Findings of Included Economic Evaluations

Main Study Findings	Authors' Conclusion
Pickering et al., 2019[27]	
Uterotonic agents compared in a network (vaginal delivery) - Carbetocin: the most effective strategy Excluding adverse events - Ergometrine plus oxytocin: the least costly strategy - Incremental cost-effectiveness ratio for prevention of PPH with carbetocin: £1,889 per case of PPH ≥ 500 mL avoided; £30,013 per case of PPH ≥ 1000 mL avoided; and £1,172,378 per major outcome averted, when compared with prevention with ergometrine plus oxytocin Including adverse events - Oxytocin: the least costly strategy - Incremental cost-effectiveness ratio for prevention of PPH with carbetocin: £928 per case of PPH ≥ 500 mL avoided; £22,900 per case of PPH ≥ 1000 mL avoided; and £894,514 per major outcome averted, when compared with oxytocin	- "*The results suggest carbetocin, oxytocin and 'ergometrine plus oxytocin' could all be favourable options for being the most cost-effective strategy for preventing PPH*" (p. 163) - "*Carbetocin could be the preferred choice, especially if the price of carbetocin decreased*" (p. 163) - "*Mixed findings mean a clear-cut conclusion cannot be made as to which uterotonic is the most cost effective*" (p. 163)
Gil-Rojas et al., 2018 [28]	
Carbetocin versus oxytocin Vaginal delivery model - Average cost of care for a patient: Col$ 347,750 and Col$ 262,491 - QALYs: 0.9980 and 0.9979 - Incremental cost-effectiveness ratio: above the cost-effectiveness threshold adopted by Colombia (Col$ 53,090.188) Cesarean section - Average cost of a patient: Col$ 461,750 and Col$ 481,866 - QALYs: 0.9959 and 0.9926 - Carbetocin: lower cost and more effective, with a saving of Col$ 94,887 per avoided hemorrhagic event	- "*In case of elective cesarean delivery, carbetocin is a dominant alternative in the prevention of PPH compared with oxytocin; however, it presents higher costs than oxytocin, with similar effectiveness, in cases of vaginal delivery*" (p. 242)

Col = Colombia; PPH = post-partum hemorrhage; QALY: quality-adjusted life year

Table 13: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Leduc et al. 2018, Canada[29] Society of Obstetricians and Gynaecologists of Canada	
"*6. Carbetocin, 100 µg given as an IV bolus over 1 minute, should be used instead of continuous oxytocin infusion in elective Cesarean section for the prevention of PPH and to decrease the need for therapeutic uterotonics*" (p. e842)	I-B (Evidence obtained from at least one properly randomized controlled trial; There is fair evidence to recommend the clinical preventive action)

Table 13: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
"*7. For women delivering vaginally with 1 risk factor for PPH, carbetocin 100 µg IM decreases the need for uterine massage to prevent PPH when compared with continuous infusion of oxytocin*" (p. e842)	I-B (Evidence obtained from at least one properly randomized controlled trial; There is fair evidence to recommend the clinical preventive action)
Lier et al. 2018, German[4] German, Austrian and Swiss Societies of Gynaecology and Obstetrics German Society of Anaesthesiology and Intensive Care Medicine Society of Thrombosis and Haemostasis Research	
First-line uterotonics: including oxytocin and carbetocin	
"*If first-line uterotonics are not available or effective, sulprostone should be used immediately. Continuous haemodynamic monitoring is recommended*" (p. 129)	Consensus of the committee
Mavrides et al. 2017, UK[30] Royal College of Obstetricians and Gynaecologists	
"*A Cochrane review[44] has addressed the use of a longer-acting oxytocin derivative, carbetocin, in the prevention of PPH. Carbetocin is licensed in the UK specifically for the indication of prevention of PPH in the context of cesarean delivery. Use of carbetocin resulted in a statistically significant reduction in the need for further uterotonics compared with oxytocin for those undergoing a cesarean, but not for vaginal delivery. However, there were no statistically significant differences between carbetocin and oxytocin in terms of risk of PPH*" (p. 12)	I ++ (High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias)
"*Guidelines from the Society of Obstetricians and Gynaecologists of Canada[30] recommend that carbetocin (100 micrograms given as an intravenous bolus over 1 minute) should be used for the prevention of PPH in elective cesarean deliveries. Randomised trials[45–50] have compared different uterotonics (oxytocin, ergometrine–oxytocin, misoprostol, carbetocin and 15-methyl prostaglandin F2a) for prophylaxis in women delivering by cesarean section. Appraisal of the evidence from these trials, together with consideration of standard practice in the UK, led the development group for the NICE cesarean section guideline[51] to recommend oxytocin 5 iu by slow intravenous injection for prophylaxis in the context of cesarean delivery*" (p. 13)	I + (Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias)
Bennett et al. 2016, Canada[1] Association of Ontario Midwives	
"*9. Midwives should use oxytocin as the first line uterotonic for the treatment of PPH due to uterine atony*" (p. 28)	"*Strong recommendation; moderate-quality evidence. No high-quality evidence has shown superior efficacy of any uterotonic drug vs oxytocin in settings where it is available. The CMO requires that midwives carry at least 2 uterotonics: oxytocin plus 1 additional drug. The comparative effectiveness of uterotonics for treatment of PPH is identified as a research gap*" (p. 28)

Table 13: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
"*10. Available research does not clearly support the use of one particular uterotonic over another for second-line treatment of primary PPH due to uterine atony (ergot alkaloids, prostaglandins and carbetocin). Midwives should choose their second-line uterotonic based on clinical context*" (p. 28)	"*Strong recommendation; very low-quality evidence* *Access to each drug may vary by community. In the absence of clear evidence, midwives should use their clinical experience, community standards, and the clinical context of the client and birth to guide second-line uterotonic use*" (p. 28)
Sentilhes et al. 2016, France[31] French College of Gynaecologists and Obstetricians French Society of Anesthesiology and Intensive Care	
"*Carbetocin reduces the risk of PPH, but in the absence of a noninferiority trial, oxytocin remains the preventive treatment of reference for preventing PPH after cesarean deliveries (professional consensus). Tranexamic acid must not be used routinely for PPH prevention*" (p. 15)	Professional consensus

IM = intramuscular; IU = international unit; IV = intravenous; PPH = post-partum hemorrhage; QALY: quality-adjusted life year

Appendix 5: Overlap between Included Systematic Reviews

Table 14: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Lawrie et al., 2019[13] (n = 14)	Gallos et al., 2018[6] (n = 140)	Voon et al., 2018[14] (n = 7)
Del Angel-Garcia 2006	X		
Rueda 2013	X		
Henriquez-Trujillo 2017	X		
Sutherland 2010	X		
Sutherland 2009	X		
Voon 2018	X		
Caceda 2018	X		
Vlassoff 2016	X		
Bradley 2007	X		
Lubinga 2015	X		
Gallos 2019	X		
Luni 2017	X		
van der Nelson 2017	X		
Higgins 2011	X		
Abdel-Aleem 2010		X	
Acharya 2001		X	
Adanikin 2012		X	
Afolabi 2010		X	
Ahmed 2014		X	
Al-Sawaf 2013		X	
Amant 1999		X	
Amin 2014		X	
Askar 2011		X	
Attilakos 2010		X	X
Atukunda 2014		X	
Badejoko 2012		X	
Balki 2008		X	
Bamigboye 1998a		X	
Bamigboye 1998b		X	
Barton 1996		X	

Table 14: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Lawrie et al., 2019[13] (n = 14)	Gallos et al., 2018[6] (n = 140)	Voon et al., 2018[14] (n = 7)
Baskett 2007		X	
Begley 1990		X	
Bellad 2012		X	
Benchimol 2001		X	
Bhullar 2004		X	
Borruto 2009		X	X
Boucher 1998		X	X
Boucher 2004		X	
Bugalho 2001		X	
Butwick 2010		X	
Caliskan 2002		X	
Caliskan 2003		X	
Carbonell 2009		X	
Cayan 2010		X	
Chaudhuri 2010		X	
Chaudhuri 2012		X	
Chaudhuri 2015		X	
Chhabra 2008		X	
Choy 2002		X	
Cook 1999		X	
Dansereau 1999		X	X
Dasuki 2002		X	
de Groot 1996b		X	
Derman 2006		X	
Dhananjaya 2014		X	
Docherty 1981		X	
Eftekhari 2009		X	
El Behery 2015		X	X
El Tahan 2012		X	
El-Refaey 2000		X	
Elgafor 2013		X	

Table 14: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Lawrie et al., 2019[13] (n = 14)	Gallos et al., 2018[6] (n = 140)	Voon et al., 2018[14] (n = 7)
Elsedeek 2012		X	
Enakpene 2007		X	
Ezeama 2014		X	
Fararjeh 2003		X	
Fawole 2011		X	
Fazel 2013		X	
Fekih 2009		X	
Fenix 2012		X	
Fu 2003		X	
Garg 2005		X	
Gavilanes 2016		X	
Gerstenfeld 2001		X	
Gulmezoglu 2001		X	
Gupta 2006		X	
Hamm 2005		X	
Harriott 2009		X	
Hofmeyr 1998		X	
Hofmeyr 2001		X	
Hofmeyr 2011		X	
Hoj 2005		X	
Hong 2007		X	
Is 2012		X	
Jago 2007		X	
Jangsten 2011		X	
Jerbi 2007		X	
Jirakulsawas 2000		X	
Karkanis 2002		X	
Kerekes 1979		X	
Khan 1995		X	
Kikutani 2006		X	
Kumru 2005		X	

Table 14: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Lawrie et al., 2019[13] (n = 14)	Gallos et al., 2018[6] (n = 140)	Voon et al., 2018[14] (n = 7)
Kundodyiwa 2001		X	
Lam 2004		X	
Lapaire 2006		X	
Leung 2006		X	
Lokugamage 2001		X	
Lumbiganon 1999		X	
Maged 2016		X	
McDonald 1993		X	
Mitchell 1993		X	
Mobeen 2011		X	
Moertl 2011		X	
Moir 1979		X	
Moodie 1976		X	
Mukta 2013		X	
Musa 2015		X	
Nasr 2009		X	
Ng 2001		X	
Ng 2007		X	
Nirmala 2009		X	
Nordstrom 1997		X	
Oboro 2003		X	
Ogunbode 1979		X	
Orji 2008		X	
Ortiz-Gomez 2013		X	
Owonikoko 2011		X	
Parsons 2006		X	
Parsons 2007		X	
Penaranda 2002		X	
Prendiville 1988		X	
Rajaei 2014		X	
Ramirez 2001		X	

Table 14: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Lawrie et al., 2019[13] (n = 14)	Gallos et al., 2018[6] (n = 140)	Voon et al., 2018[14] (n = 7)
Rashid 2009		X	
Ray 2001		X	
Reyes 2011a		X	
Reyes 2011b		X	
Rogers 1998		X	
Rosseland 2013		X	
Rozenberg 2015		X	
Sadiq 2011		X	
Samimi 2013		X	
Shrestha 2011		X	
Singh 2009		X	
Soltan 2007		X	
Sood 2012		X	
Stanton 2013		X	
Su 2009		X	
Sultana 2007		X	
Surbek 1999		X	
Tewatia 2014		X	
Thilaganathan 1993		X	
Ugwu 2014		X	
Un Nisa 2012		X	
Uncu 2015		X	
Vagge 2014		X	
Vaid 2009		X	
Verma 2006		X	
Vimala 2004		X	
Vimala 2006		X	
Walley 2000		X	
Whigham 2014		X	
Yuen 1995		X	
Zachariah 2006		X	

Table 14: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Lawrie et al., 2019[13] (n = 14)	Gallos et al., 2018[6] (n = 140)	Voon et al., 2018[14] (n = 7)
Razali 2016			X
Whigham 2016			X

Appendix 6: Additional References of Potential Interest

Eligible study without full texts available

Akhter P, Pal SN, Begum S. Comparison between Carbetocin and Oxytocin in Active Management of 3rd Stage of Labour in Preventing Post Partum Hemorrhage. *Mymensingh Med J.* 2018;27(4):793-797

Guidelines with unclear methodology

Sentilhes L, Goffinet F, Vayssiere C, Deneux-Tharaux C. Comparison of postpartum haemorrhage guidelines: discrepancies underline our lack of knowledge. *BJOG.* 2017;124(5):718-722.

Vogel JP, Oladapo OT, Dowswell T, Gulmezoglu AM. Updated WHO recommendation on intravenous tranexamic acid for the treatment of post-partum haemorrhage. *Lancet Glob Health.* 2018;6(1):e18-e19.

Practice Bulletin No. 183 Summary: Postpartum Hemorrhage. *Obstet Gynecol.* 2017;130(4)

Reviews with unclear methodology

Health Technology Assessment Study Group – Health Policy Development and Planning Bureau. Carbetocin for the prevention of postpartum hemorrhage. *(Technology Review).* Manila (PH): Department of Health; 2016: https://www.doh.gov.ph/sites/default/files/publications/TR_Carbetocin.pdf.

Dahlke JD, Mendez-Figueroa H, Maggio L, et al. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. *Am J Obstet Gynecol.* 2015;213(1):76.e71-76.e10.

Bohlmann MK, Rath W. Medical prevention and treatment of postpartum hemorrhage: a comparison of different guidelines. *Arch Gynecol Obstet.* 2014;289(3):555-567