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REPORTS OF ORIGINAL INVESTIGATIONS

Carbetocin compared with oxytocin in non-elective Cesarean delivery: a systematic review, meta-analysis, and trial sequential analysis of randomized-controlled trials

Comparaison de la carbétocine à l'ocytocine pour un accouchement par césarienne non planifié : revue systématique, méta-analyse et analyse séquentielle des études randomisées contrôlées

Desire N. Onwochei, MBBS · Adetokunbo Owolabi, MBBS · Preet Mohinder Singh, MD · David T. Monks, MBChB

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Abstract

Purpose *Carbetocin has been shown to reduce the requirement for additional uterotonics in women exclusively undergoing elective Cesarean delivery (CD). The aim of this review was to determine whether this effect could also be demonstrated in the setting of non-elective CD.*

Methods *Medline, Embase, CINAHL, Web of Science and Cochrane databases were searched for randomized-controlled trials (RCTs) in any language comparing carbetocin to oxytocin. Studies with data on women undergoing non-elective CD, where carbetocin was compared with oxytocin, were included. The primary outcome was the need for additional uterotonics. Secondary outcomes included incidence of blood transfusion, estimated blood loss (mL), incidence of postpartum hemorrhage (PPH; > 1000 mL) and mean hemoglobin drop ($g \cdot dL^{-1}$*

Results *Five RCTs were included, with a total of 1,214 patients. The need for additional uterotonics was reduced with carbetocin compared with oxytocin (odds ratio, 0.30; 95% CI, 0.11 to 0.86; I^2, 90.60%). Trial sequential analysis (TSA) confirmed that the information size needed to show a significant reduction in the need for additional uterotonics had been exceeded. No significant differences were shown with respect to any of the secondary outcomes, but there was significant heterogeneity between the studies.*

Conclusions *Carbetocin reduces the need for additional uterotonics in non-elective CD compared with oxytocin. TSA confirmed that this analysis was appropriately powered to detect the pooled estimated effect. Further trials utilizing consistent core outcomes are needed to determine an effect on PPH.*

Trial registration *PROSPERO CRD42019147256, registered 13 September 2019.*

Résumé

Objectif *Il a été démontré que la carbétocine réduisait les besoins en utérotoniques supplémentaires exclusivement chez les femmes subissant un accouchement par césarienne planifié. L'objectif de ce compte rendu était de déterminer si cela pouvait également être démontré dans le cas d'un accouchement par césarienne non planifié.*

Méthode *Les bases de données Medline, Embase, CINAHL, Web of Science et Cochrane ont été passées en revue pour en extraire les études randomisées contrôlées (ERC), toutes langues confondues, comparant la carbétocine à l'ocytocine. Les études comportant des*

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D. N. Onwochei, MBBS (✉) · A. Owolabi, MBBS
Department of Anaesthesia, Guy's & St. Thomas' NHS Foundation Trust, Great Maze Pond, London SE1 9RT, UK
e-mail: desire.onwochei@gstt.nhs.uk

P. M. Singh, MD · D. T. Monks, MBChB
Department of Anesthesiology, Washington University in St. Louis, St. Louis, MO, USA

données concernant des femmes subissant un accouchement par césarienne non planifié et comparant la carbétocine à l'ocytocine ont été incluses. Le critère d'évaluation principal était le besoin d'utérotoniques supplémentaires. Les critères secondaires comprenaient l'incidence de transfusion sanguine, la perte de sang estimée (mL), l'incidence d'hémorragie postpartum (HPP; > 1000 mL) et la baisse moyenne du taux d'hémoglobine ($g \cdot dL^{-1}$).

Résultats *Cinq ERC ont été retenues, incluant 1214 patientes au total. Les besoins en utérotoniques supplémentaires étaient plus faibles lors de l'utilisation de carbétocine par rapport à l'ocytocine (rapport de cotes, 0,30; IC 95 %, 0,11 à 0,86; I^2, 90,60 %). L'analyse séquentielle des essais a confirmé que la taille des informations démontrant une réduction significative du besoin d'utérotoniques supplémentaires avait été dépassée. Aucune différence significative n'a été démontrée en ce qui touchait nos critères d'évaluation secondaires, mais l'hétérogénéité des études était considérable.*

Conclusion *La carbétocine réduit le besoin d'utérotoniques supplémentaires lors d'un accouchement par césarienne non planifié comparativement à l'ocytocine. L'analyse séquentielle des essais a confirmé que cette analyse disposait de suffisamment de puissance pour détecter l'effet estimé pondéré. Des études supplémentaires portant sur des critères constants sont nécessaires afin de déterminer un effet sur l'HPP.*

Enregistrement de l'étude *PROSPERO CRD42019147256, enregistrée le 13 septembre 2019.*

Keywords Carbetocin · non-elective Cesarean · oxytocin · postpartum hemorrhage · trial sequential analysis

Postpartum hemorrhage (PPH) is a significant cause of maternal morbidity and mortality worldwide,[1] with uterine atony being the cause in the majority of cases.[2] Management of uterine atony includes the use of uterotonic agents, of which oxytocin is now the most widely used in the developed world. Oxytocin has been shown in Cochrane reviews to be reduce blood loss and the need for additional uterotonics in the management of PPH.[3,4]

Oxytocin binds to oxytocin receptors in the myometrium to stimulate uterine smooth muscle. It has a fast onset but is of short duration and a maintenance infusion in the immediate perioperative period is recommended.[5] Carbetocin is a longer acting synthetic analogue of oxytocin. When given intravenously, it causes continuous uterine contractions within two minutes, followed by rhythmic contractions for 60 min.[6] Recent trials suggest that carbetocin may be just as effective as oxytocin, with less adverse effects, avoiding a continuous infusion and greater heat-stability, particularly where maintaining a cold supply chain is not feasible.[7] As such, interest in carbetocin continues to rise, with its use increasing in popularity.

In the United Kingdom, of the births with a recorded delivery method, the incidence of Cesarean delivery (CD) between 2017 and 2019 was 11–17%,[8] making CD an important scenario for investigation. Previous meta-analyses comparing oxytocin and carbetocin have been performed on mixed patient populations, with an absence of data specific to elective or non-elective CD. Data from dose-finding studies of oxytocin and carbetocin have suggested marked differences between the effective doses needed for each drug depending on whether the context is elective or non-elective CD.[9–12] This phenomenon is thought to be related, at least in part, to the downregulation of myometrial oxytocin receptors in response to elevated levels of oxytocin during spontaneous or augmented labour. We have recently shown that carbetocin reduces the need for additional uterotonics by 53% compared with oxytocin at elective CD.[13] Trial sequential analysis (TSA) confirmed the significance of this result. Since the context of CD is known to produce different uterine responses to oxytocin receptor agonists, it is unclear how oxytocin and carbetocin compare with each other when used to achieve uterine contraction after non-elective CD. Hence, an analysis of the available data in this specific context was warranted.

Trial sequential analysis is an advanced meta-analytical technique used to address the increased risk of type I errors associated with multiple hypothesis testing in data synthesis, as well as type II errors due to inadequate participant and trial numbers.[14] As each trial is added, the significance threshold (alpha-spending boundary) is adjusted to minimize the risks of prematurely declaring a significant treatment effect. Trial sequential analysis can also employ an estimate of effect (with a low risk of bias) from the included studies to determine the information size required to reject such a treatment effect.[15]

The aim of this systematic review and meta-analysis was to compare the efficacy of carbetocin and oxytocin as a first-line uterotonic in non-elective CD. Non-elective CD (unscheduled) was defined as a previously unplanned CD occurring after the start of labour, as per the study definitions. The primary outcome, need for additional uterotonics, is a commonly used surrogate to assess the efficacy of PPH prophylaxis. Our secondary outcomes were incidence of blood transfusion, estimated blood loss (mL), incidence of PPH (> 1000 mL), and mean hemoglobin drop ($g \cdot dL^{-1}$).

Methods

This study was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[16] and the was protocol registered on PROSPERO (CRD42019147256, http://www.crd.york.ac.uk/PROSPERO).

Search strategy

Medline, Embase, CINAHL, Web of Science, and the Cochrane database were searched for peer-reviewed literature. The search included all studies published in any language from the start of the databases to 22 July 2019. Search terms including and relating to *carbetocin*, *uterotonics, postpartum hemorrhage, and cesarean section,* were used as key words and medical subject heading (MeSH) terminologies. An outline of the search strategy for each database is presented in the supporting information (Electronic Supplementary Material [ESM] eFig. 1). Hand searching of full-text reference lists as a secondary search was undertaken. Records were managed using a reference management tool (Mendeley Desktop Version 1.19.5 ©2008-2019 Mendeley Ltd).

Selection criteria

Randomized-controlled trials comparing the use of carbetocin with oxytocin in non-elective CD in any language were eligible for inclusion. Studies were excluded if they did not compare carbetocin with oxytocin or if they focused on carbetocin use in elective CD or vaginal delivery populations. Systematic reviews, conference abstracts, and letters were also excluded. The primary outcome was the need for additional uterotonics. Secondary outcome variables of interest were incidence of blood transfusion, estimated blood loss (mL), incidence of PPH (> 1000 mL), and mean hemoglobin drop ($g{\cdot}dL^{-1}$).

Data extraction

The search was conducted by a single investigator (D.O.). All papers selected as potentially eligible for inclusion were reviewed and the data extracted independently by two investigators (A.O. and D.O.) using a predesigned data extraction tool in Microsoft Excel 2019 (Microsoft Corp, Redmond, WA, USA). Any disagreements were resolved through discussion or arbitration by a third investigator (D.M.). Extracted data included geographical location, cohort size, other risk factors for PPH apart from non-elective CD, interventions, and primary and secondary outcome measures. Statistical results (e.g., relative risks, p values) were extracted and reported if provided in the manuscript. Authors were contacted for further information if there was inadequate data for analysis, and specifically for data on non-elective CD rather than a mixture of urgencies or delivery modes.

Statistical analysis

The main findings and recommendations of each study were summarized in tabular format. The statistical analysis of the pooled data was performed using Comprehensive Meta-Analysis, Version 3.0 (Biostat Inc, USA). Meta-analysis was performed using random effects modelling. The I^2 statistic was used to quantify heterogeneity between the trials. I^2 values $< 40\%$ were considered non-significant heterogeneity, 40–60% were considered moderate heterogeneity, and $> 60\%$ were considered high heterogeneity. For frequency variables, the pooled results were reported as Mantel–Haenszel odds ratios (MH odds ratio) along with their 95% confidence intervals (CIs). For continuous variables, results were expressed as pooled means or pooled mean differences with 95% CIs. For mean blood loss, where studies provided estimates as medians with associated interquartile ranges and attempts to retrieve raw data from the study authors were unsuccessful, the mean and standard deviation were estimated for pooling using Hozo's method.[17] If mean blood loss was reported without the associated variance, in the absence of raw data, these missing variances were imputed as per Cochrane collaboration recommendations. The mean variance was used, which was calculated from the other available variances of the included studies.[18,19] A value of $P < 0.05$ was considered statistically significant for pooled results of the above variables.

To determine whether the cumulative sample size was appropriately powered for the obtained pooled effect estimate and to avoid random error, TSA was performed using the TSA Module 2017 (Copenhagen Trial Unit, Denmark). Both conventional (with alpha of 5%) and trial sequential monitoring boundaries (for random effects modelling with alpha of 5% and a beta of 20%) were constructed for the need for additional uterotonics as a binary outcome variable. The heterogeneity correction in the TSA was set to variance-based (random effects model), and relative risk reduction for low risk of bias over a baseline of 51.59% in the control group was used to construct the alpha-spending boundary. A cumulative sequential z-score curve was constructed and used to evaluate adequacy of the present evidence. The required information size was defined and calculated using the above modelling as the number of participants and events necessary to detect or reject an *a priori* assumed intervention effect in the meta-analysis.

Risk of bias assessment

Risk of bias was assessed using the revised Cochrane risk of bias tool for randomized trials (RoB 2).[20] Two authors (A.O. and D.O.) assessed risk of bias and consensus was reached through arbitration by a third author (PMS). The GRADEpro Guideline Development Tool was used to produce a summary of findings table rating the evidence for the outcomes as high, moderate, low, or very low, as per the GRADE approach.[21] Possible publication bias was assessed visually using a funnel plot, and subsequently quantified using the Egger's test.

Results

A total of 2,026 articles were identified after removal of duplicates. Non-pertinent titles and abstracts were excluded, leaving 12 full-text articles that were assessed for eligibility (Fig. 1). After exclusions, five RCTs were included in the review,[22–26] with a total of 1,214 patients. Table 1 outlines the study characteristics. All the studies included patients undergoing non-elective CD under regional anesthesia, except one, which looked specifically at non-elective CD under general anesthesia.[25] None of the studies specified whether regional anesthesia was intrathecal, epidural, or a combined technique. One study originally included data from a mixed population of elective and non-elective cases, but the author was successfully contacted and provided raw data for the non-elective cases.[22] Two of the studies included patients with risk factors for PPH other than non-elective CD, one looking at women with a body mass index (BMI) over 30 and the other looking at general anesthesia only.[23,25] The dose of carbetocin was 100 μg *iv* in all of the studies, being compared with a single bolus dose of oxytocin 5 international units (IU) *iv* in two of the studies and a bolus dose of 10 IU *iv* in one study.[22,24,26] Two studies used an oxytocin infusion of 20 or 30 IU over four and two hours, respectively.[23,25] The need for additional uterotonics was used as the primary outcome measure in all but one of the studies, which used PPH (> 1000 mL) as the primary outcome and need for additional uterotonics as a secondary outcome.[23] The most frequent secondary outcome measures were estimated blood loss, hemoglobin drop, and need for blood transfusion.

Meta-analysis

Pooled results were generated for the parameters below.

Primary outcome

Need for additional uterotonics

Data were available from all five trials and included 617 patients in the carbetocin group and 597 patients in the oxytocin group. In the carbetocin group, 28.20% (95% CI, 24.79 to 31.88) of patients required additional uterotonics whereas, in the oxytocin group, 51.59% (95% CI, 47.59 to 55.58) of patients needed uterotonic supplementation. The MH odds ratio for the need for additional uterotonics was 0.30 (95% CI, 0.11 to 0.86) for patients in the carbetocin group (random effects I^2, 90.60%; Fig. 2). To explore the heterogeneity in the above pooled estimate, a sensitivity analysis was performed using the "single-study removal method" revealing that the study by El Behery *et al.*[23] contributed most to the heterogeneity of the estimate. Removing this trial reduced heterogeneity to an I^2 of 79.01%. For the conventional boundary, the alpha error was set to 0.05 and the estimated required information size was 335. The alpha-spending boundary was constructed using the O'Brien spending function. The model was adjusted for the heterogeneity observed in the meta-analysis (heterogeneity-adjusted, information size). The relative risk reduction, used by the model to construct the alpha boundary, was estimated based on a 51.59% need for additional uterotonics (the incidence in the control arm of trials with a low risk of bias). Trial sequential analysis calculations were performed for a power of 80%. The information size required for a conclusion based upon the alpha-spending function was calculated to be 850. The total sample size of 1,214 exceeded the required information size for both models (Fig. 3). Thus, a type I error was unlikely.

Secondary outcomes

Incidence of blood transfusion

No patients required a blood transfusion in one trial,[25] and data for blood transfusion were available from the remaining four trials, including 507 patients in the carbetocin group and 487 patients in the oxytocin group. The pooled incidence of blood transfusion was 2.17% (95% CI, 1.22 to 3.84) in the carbetocin group and 5.95% (95% CI, 4.18 to 8.42) in the oxytocin group. The MH odds ratio for blood transfusion incidence with carbetocin was 0.46 (95% CI, 0.14 to 1.59). This pooled estimate failed to achieve statistical significance in the random effects model (P = 0.22; I^2, 47.74%; eFig. 1 [ESM]). Trial sequential analysis estimated a required information size of 994 for the conventional boundary and 3,342 for the alpha-

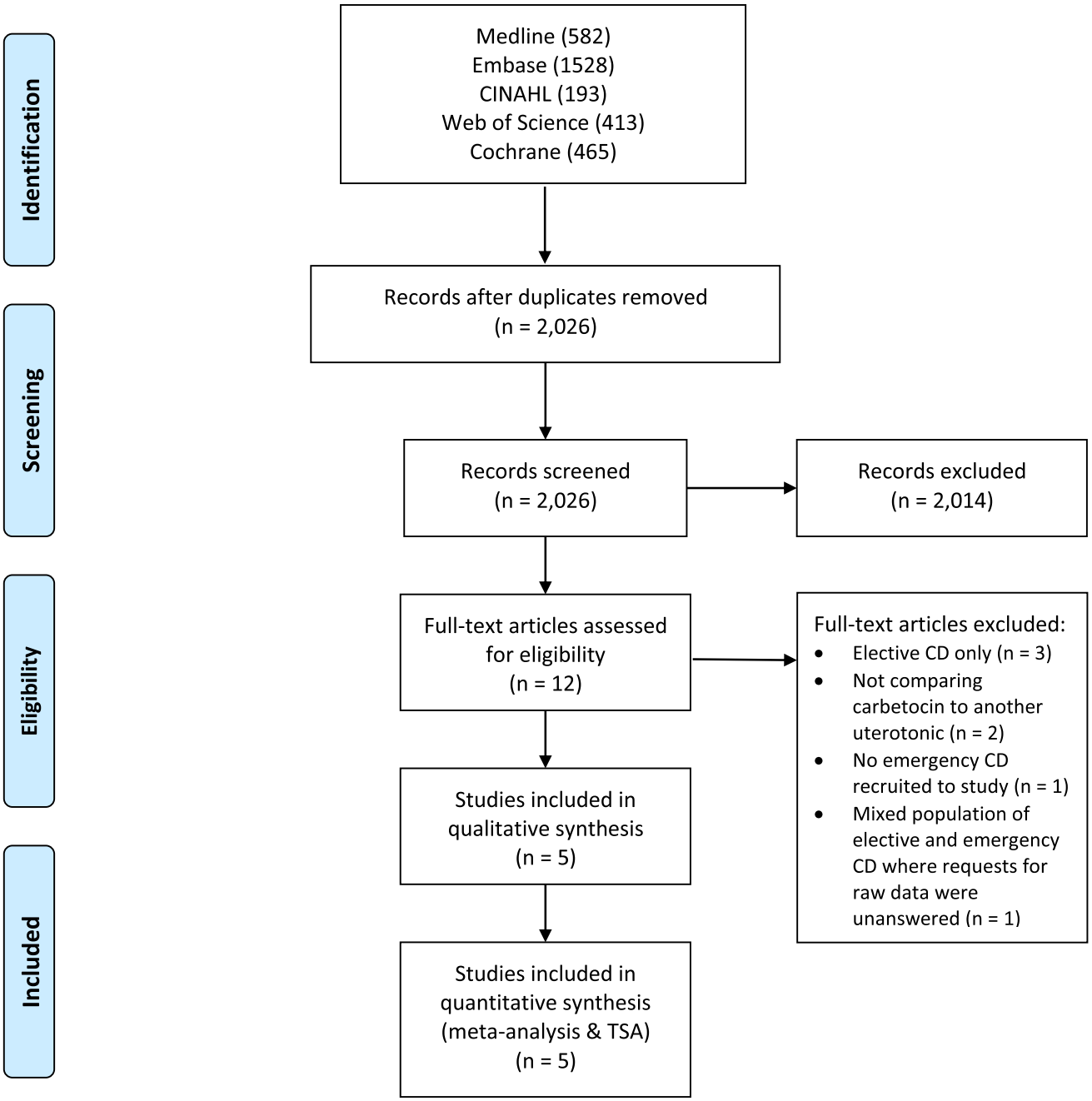

Fig. 1 PRISMA flowchart of systematic research

spending function. Thus, the present sample size (994) was inadequate to make a definitive conclusion.

Estimated blood loss

Data were available from all five trials. Pooled mean difference of blood loss failed to achieve statistical significance and suffered from high heterogeneity (random effects I^2, 97.47%; eFig. 2 [ESM]). The mean difference in blood loss (carbetocin to oxytocin) was 46.60 mL (95% CI, -71.95 to 165.15; P = 0.44). Presently available information from the trials was inadequate to construct an alpha boundary for TSA.

Incidence of PPH (> 1000 mL)

Four trials reported this outcome, but the pooled results failed to achieve statistical significance. The MH odds ratio for PPH with carbetocin was 0.75 (95% CI, 0.31 to 1.80; P = 0.52; random effects I^2, 57.26%; eFig. 3 [ESM]).

Table 1 Demographics of included studies

Author (year)	Location	Cohort size	Other PPH risk factors present	Type of anesthesia	Intervention	Primary outcome	Secondary outcomes
Attilakos[22] (2010)	UK	155	No	Regional anesthesia	- Carbetocin 100 μg *iv* (*n* = 82) - Oxytocin 5 IU *iv* bolus (*n* = 73)	Need for additional uterotonics	- EBL - EBL > 1000 mL - Need for blood transfusion
El Behery[23] (2016)	Egypt	180	Yes (BMI > 30)	Regional anesthesia	- Carbetocin 100 μg *iv* (*n* = 90) - Oxytocin 20 IU IV infusion over 4 hr (*n* = 90)	Postpartum hemorrhage (PPH) (> 1000 mL)	- EBL - Need for additional uterotonics - Need for blood transfusion - Hemoglobin difference (admission-postpartum)
Razali[24] (2016)	Malaysia	547	No	Regional anesthesia	- Carbetocin 100 μg *iv* (*n* = 276) - Oxytocin 10 IU *iv* bolus (*n* = 271)	Need for additional uterotonics	- EBL - Hemoglobin drop - Need for blood transfusion - PPH (> 1000 mL)
Taheripanah[25] (2018)	Iran	220	Yes (GA)	General anesthesia	- Carbetocin 100 μg *iv* (*n* = 110) - Oxytocin 30 IU *iv* over 2 hr (*n* = 110)	Need for additional uterotonics	- Bleeding volume - Hemoglobin drop - Need for blood transfusion
Whigham[26] (2016)	Australia	112	No	Regional anesthesia	- Carbetocin 100 μg *iv* (*n* = 59) - Oxytocin 5 IU *iv* bolus (*n* = 53)	Need for additional uterotonics	- EBL - Hemoglobin drop - Need for blood transfusion - PPH (> 1000 mL)

BMI = body mass index; EBL = estimated blood loss; IU = international units.

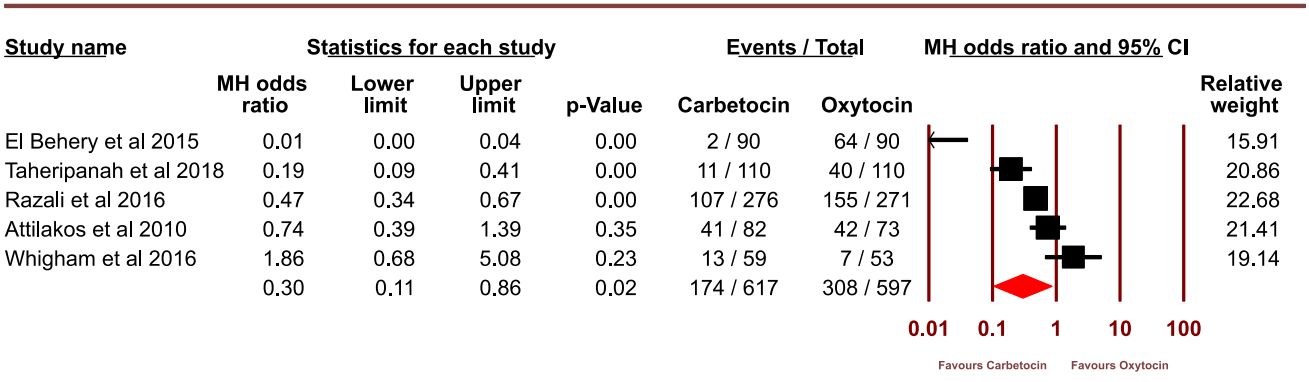

Fig. 2 Mantel–Haenszel odds ratios (MH odds ratio) for need for additional uterotonics

Mean change in hemoglobin

Data were available from four trials. Pooled results failed to achieve statistical significance. The difference in mean drop of hemoglobin (carbetocin to oxytocin) was 0.07 $g \cdot dL^{-1}$ (95% CI, -0.59 to 0.74; $P = 0.83$; random effects I^2, 96.45%; eFig. 4 [ESM]).

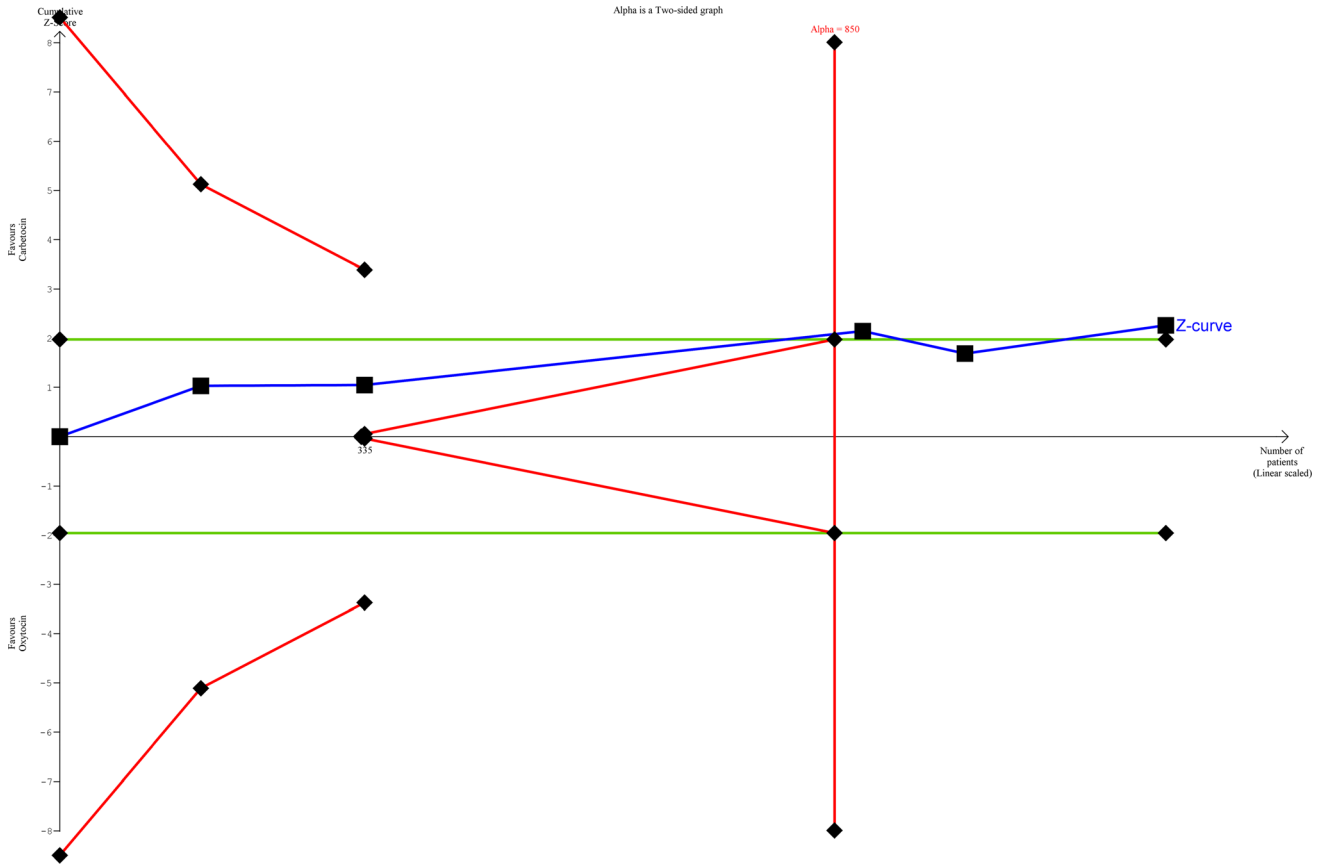

Fig. 3 Trial sequential analysis (TSA) for incidence of need for additional uterotonics, showing superiority of carbetocin over oxytocin. The lower half of the graph below the zero axis represents the area of advantage with oxytocin and the upper half represents the advantage area with carbetocin. The solid black squares indicate the accumulative z-score with the addition of each of the five trials in chronological order. The green lines at +1.96 and -1.96 on the Y-axis represent the conventional model boundaries for TSA with an α of 5%. The red lines represent the alpha-spending boundary (upper O'Brien Fleming with a of 5%, low risk of bias). The minimum required information size for the alpha-spending boundary model is 850 (vertical line intersecting X-axis in red). The cumulative z-score line (blue) crosses the conventional boundaries (green lines) indicating the superiority of carbetocin over oxytocin based upon the conventional model. The statistical significance of this result is confirmed (accounting for repeated hypothesis tests) as the cumulative z-score also crosses the alpha-spending boundary (for interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Quality

A risk of bias assessment was performed on the studies (Fig. 4). Primary outcome measurements had an unclear risk of bias in one study because the methods for estimating blood loss were subjective,[23] and in another study because randomization was unblinded after recruitment and prior to analysis.[26] The generalisability of two of the studies was unclear because of the exclusive recruitment of patients with high BMI and general anesthesia.[23,25] Nevertheless, this did not contribute to the risk of bias assessment using the revised RoB 2 tool.[20] The quality of the evidence, rated using the GRADE framework, is shown in Table 2.

Publication bias

Publication bias was evaluated visually with a funnel plot (eFig. 5 [ESM]) and subsequently by Egger's Regression test. No publication bias was suggested by these tests. The regression test was statistically non-significant and showed an X-axis intercept at -2.43 with $P = 0.55$ (two-tailed).

Discussion

Our analysis showed that carbetocin reduces the need for additional uterotonics at non-elective CD compared with oxytocin. Nevertheless, the estimated reduction in odds (70%) is imprecise as represented by the wide 95% CI (14% to 89%). Trial sequential analysis confirmed that the meta-analysis was adequately powered to detect the effect

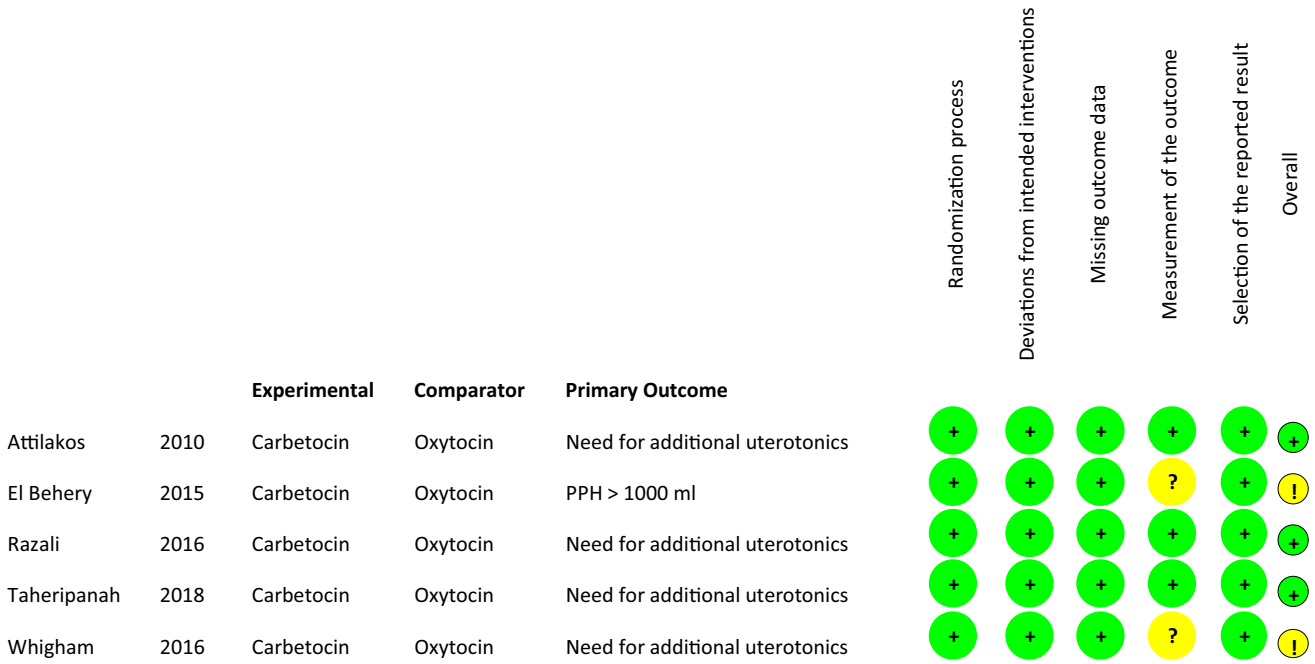

Fig. 4 Risk of bias assessment using version 2 of the Cochrane risk of bias tool. Low risk (green), high risk (red), unclear (yellow).

size observed in included studies with a low risk of bias (after adjustment for heterogeneity), and that the required information size (n = 850 participants) was achieved after addition of the third trial. This finding suggests that carbetocin has greater uterotonic efficacy than oxytocin and is consistent with previous meta-analyses that have compared these two uterotonic agents either in mixed populations (elective and non-elective CD)[27,28] or exclusively in elective CD.[13]

This is the first analysis of which the authors are aware that provides pooled estimates for reduced additional uterotonic requirement when comparing carbetocin with oxytocin in women undergoing non-elective CD. This population is at higher risk of PPH but carbetocin is more expensive and, as such, this finding could prove valuable in assessing the cost effectiveness of this agent in this population. It should be noted, however, that "need for additional uterotonic" is only a surrogate for uterotonic effect, and that other factors might explain the differences observed in this outcome. For example, although the dose of carbetocin was consistent across included studies, the dose and method of oxytocin administration varied considerably and this could have affected the efficacy of oxytocin. Problems with the external validity of the pharmacodynamic data relating to oxytocin, and the absence of relevant pharmacokinetic data, contribute to clinical uncertainty about the optimal dosing strategies in this context.[29]

The thoroughness of the database searches and the retrieval of some raw data strengthen the validity of the analysis. There was, however, high heterogeneity (I^2, 90.60%) between studies for the primary outcome. The likely sources of this heterogeneity are: 1) a true difference in effects between different study populations; 2) biased estimates due to deficiencies in study design and; 3) variability in administration of the interventions. The first source should be suspected because the populations in each study differ on the basis of potential risk factors for atonic PPH, such as higher BMI or use of general anesthesia. This does not necessarily weaken this meta-analysis as it increases its external validity. A sensitivity analysis systematically excluding each of the studies to explore their relative contribution to the heterogeneity found that the study by El Behery *et al.*[23] contributed the most heterogeneity. Nevertheless, removing this study only reduced the overall heterogeneity to 79.01%. This study, from a university hospital in Egypt, was performed exclusively on women with a BMI greater than 30 $kg.m^{-2}$. The mean BMI of their population (32.6 in the study group and 32.3 in the control group) was only modestly elevated compared with the mean BMI of the other studies (27.3 to 29.3). The removal of Taheripanah *et al.* (in addition to El Behery *et al.*), which included women who had CD under general anesthesia, only reduced the overall heterogeneity to 71.63%. Nevertheless, the removal of both studies would substantially reduce the power of the meta-analysis as well as the generalizability of the pooled estimate. Furthermore, a random effects model was used to adjust the CIs to account for this large heterogeneity.

Table 2 GRADE Framework: GRADEPro summary of findings table

Carbetocin compared with oxytocin for postpartum hemorrhage in non-elective Cesarean delivery

Patient or population: Postpartum hemorrhage in non-elective Cesarean delivery
Setting: Non-elective Cesarean delivery
Intervention: Carbetocin
Comparison: Oxytocin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with oxytocin	Risk with carbetocin				
Need for additional uterotonics	516 per 1,000	242 per 1,000 (105 to 478)	**OR 0.30** (0.11 to 0.86)	1,214 (5 RCTs)	⨁⨁⨁◯ MODERATE [a,b]	Use of carbetocin reduced the need for additional uterotonics. Pooled results had 1,214 patients, which was well past the predicted requirement by TSA for avoiding false positives.
Need for blood transfusion	60 per 1,000	28 per 1,000 (9 to 91)	**OR 0.46** (0.14 to 1.59)	994 (4 RCTs)	⨁◯◯◯ VERY LOW [a,c]	Random effects model failed to achieve statistical significance because of high heterogeneity. Pooled results had 994 patients; this failed to meet the required "information size" by TSA (3,342).
Estimated blood loss	The mean blood loss was 617.33 mL	Mean 46.6 mL less (-165.15 to 71.95)	-	1,214 (5 RCTs)	⨁◯◯◯ VERY LOW [a,d]	No statistically significant effect could be shown. Comparison suffered high risk of methodological bias and possible inconsistency in transfusion triggers.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Methodological bias present. High heterogeneity between studies
b. Threshold for use of additional uterotonics could vary across trials
c. No standardized transfusion threshold
d. Measurement method for blood loss not standardized
CI = confidence interval; OR = odds ratio; RCT = randomized-controlled trial; TSA = trial sequential analysis

The second two sources of heterogeneity could threaten the strength of our findings. The eligibility criteria for the systematic literature search was designed to select studies with a low risk of bias. One study, however, was judged to have an unclear risk of bias because of uncertainties surrounding blinding of the outcome assessment; this is a possible risk of bias at the analysis stage and is an unclear risk of attrition bias.[26] Excluding this study did not affect the heterogeneity. As previously mentioned, whilst the method of administration and dose of carbetocin were consistent, these varied considerably for oxytocin between studies. Three studies administered oxytocin as an intravenous bolus of 5, 5, and 10 IU, respectively. The two other studies employed oxytocin infusions of 30 IU over two hours in one study and 20 IU over four hours in the other. This difference in interventions may increase the variability in effect observed between groups and reduce the precision of the pooled estimates.

Bleeding-related outcomes are arguably more important and relevant to patients than our choice of primary outcome, which is an inexact surrogate of efficacy. These outcomes, however, were inconsistently assessed in the included studies and our choice of primary outcome was based on a prior knowledge of the evidence from a previous review of the literature comparing carbetocin and oxytocin in the context of elective CD.[13] A previous Cochrane review of the same comparison in all CDs included 11 studies, only two of which evaluated a primary outcome directly related to bleeding.[27] Only one of our five studies assessed such a primary outcome, the rest using need for additional uterotonic as their main outcome.

The current analysis suggests that further comparisons of the need for additional uterotonics between carbetocin and oxytocin may be unnecessary, although this is uncertain because of the marked variation in administration of oxytocin. The recent international expert consensus statement will hopefully lead to greater standardization of oxytocin administration in studies.[5] Future research should look for a meaningful difference in bleeding prevention between these interventions. All the

studies contributing to our analysis assessed "bleeding volume" or "estimated blood loss" but none employed an objective method, or even the same method, of calculation. This is an obstacle to synthesis of bleeding-related outcome data. The incidence of blood transfusion was the only bleeding outcome that permitted TSA. The required information size was calculated as a sample of 3,342 participants. This reflects the low baseline incidence of blood transfusion in this context and the small difference between the groups observed in the studies at low risk of bias. The information size required to detect or reject a clinically meaningful difference in estimated blood volume would likely be smaller than this but it would require consistent use of an objective measure.

A limitation of any pairwise meta-analysis such as this, is that it does not make use of the maximum amount of available comparative data. This is because, where multiple uterotonic options exist, it is not possible to include the data from the comparisons of the uterotonic efficacy of carbetocin with agents that are not oxytocin. One solution to this is a network meta-analysis (NMA), whereby the network of comparisons of different treatment options directly and indirectly compares these options, providing estimates of effect that utilize the maximum amount of available data. A recent Cochrane NMA was performed to estimate the relative effect of numerous uterotonics including carbetocin and oxytocin.[30] Consistent with the current analysis, carbetocin was ranked ahead of oxytocin with regard to both need for additional uterotonic and incidence of PPH at CD. There is, however, good reason to be cautious in comparing the results with those of our study. The validity of NMA is dependent on the assumptions of homogeneity, transitivity, and consistency. A consequence of forming what is often a complex network of evidence is that it inevitably accumulates a substantial degree of heterogeneity because of variation in study designs and populations. Whether CD is performed in a labouring or non-labouring parturient influences uterotonic effect and bleeding risk. Failing to distinguish between the two, as was the case in this Cochrane NMA, raises concerns regarding the validity of the analysis. The results of our analysis provide a valid estimate of the uterotonic effect of carbetocin in non-elective CD and show that 4.28 patients need to be treated with carbetocin rather than oxytocin to prevent the need for additional uterotonics. Given the difference in price between carbetocin and oxytocin, this estimate can usefully inform cost-effectiveness analysis.

In conclusion, this analysis shows lower odds of needing additional uterotonics with carbetocin compared with oxytocin during non-elective CD. Trial sequential analysis confirms the statistical significance of the result and adequate power of the analysis to detect this effect. Further trials are needed to detect or reject a clinically meaningful difference in bleeding risk.

Author contributions Desire N. Onwochei contributed to all aspects of this manuscript, including study conception and design; acquisition, analysis, and interpretation of data; and drafting the article. Desire N. Onwochei, Preet Mohinder Singh, and David T. Monks contributed to the conception and design of the study and the interpretation of data. Desire N. Onwochei and Adetokunbo Owolabi contributed to the acquisition of data. Desire N. Onwochei, Adetokunbo Owolabi, Preet Mohinder Singh, and David T. Monks contributed to the analysis of data.

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References

1. *Say L*, *Chou D*, *Gemmill A*, *et al*. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014; 2: 323-33.
2. *Anderson JM*, *Etches D*. Prevention and management of postpartum hemorrhage. Am Fam Physician 2007; 75: 875-82.
3. *Salati JA*, *Leathersich SJ*, *Williams MJ*, *Cuthbert A*, *Tolosa JE*. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev 2019; DOI: https://doi.org/10.1002/14651858.CD001808.pub3.
4. *Mousa H, Blum J, El Senoun A, Shakur H, Alfirevic Z.* Treatment for primary postpartum haemorrhage (Review). Cochrane Database Syst Rev 2014; 2: CD003249.
5. *Heesen M*, *Carvalho B*, *Carvalho JC*, *et al*. International consensus statement on the use of uterotonic agents during caesarean section. Anaesthesia 2019; 74: 1305-19.
6. *Hunter DJ*, *Schulz P*, *Wassenaar W*. Effect of carbetocin, a long-acting oxytocin analog on the postpartum uterus. Clin Pharmacol Ther 1992; 52: 60-7.
7. *World Health Organization.* WHO recommendations: Uterotonics for the prevention of postpartum haemorrhage - 2018. Available from URL: https://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1 (accessed June 2020).
8. *NHS Digital.* NHS Maternity Statistics. Availble from URL: https://files.digital.nhs.uk/D0/C26F84/hosp-epis-stat-mat-summary-report-2018-19.pdf (accessed June 2020).
9. *Carvalho JC*, *Balki M*, *Kingdom J*, *Windrim R*. Oxytocin requirements at elective cesarean delivery: a dose-finding study. Obstet Gynecol 2004; 104: 1005-10.
10. *Balki M*, *Ronayne M*, *Davies S*, *et al*. Minimum oxytocin dose requirement after cesarean delivery for labor arrest. Obstet Gynecol 2006; 107: 45-50.
11. *Khan M*, *Balki M*, *Ahmed I*, *et al*. Carbetocin at elective cesarean delivery: a sequential allocation trial to determine the minimum effective dose. Can J Anesth 2014; 61: 242-8.
12. *Nguyen-Lu N*, *Carvalho JC*, *Farine D*, *Seaward G*, *Ye XY*, *Balki M*. Carbetocin at cesarean delivery for labour arrest: a sequential

allocation trial to determine the effective dose. Can J Anesth 2015; 62: 866-74.
13. *Onwochei DN*, *Van Ross J*, *Singh P*, *Salter A*, *Monks DT*. Carbetocin reduces the need for additional uterotonics in elective caesarean delivery: a systematic review, meta-analysis and trial sequential analysis of randomised controlled trials. Int J Obstet Anesth 2019; 40: 14-23.
14. *Imberger G*, *Thorlund K*, *Gluud C*, *Wetterslev J*. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. BMJ Open 2016; DOI: https://doi.org/10.1136/bmjopen-2016-011890.
15. *Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C*. User manual for Trial Sequential Analysis (TSA). Available from URL: http://www.ctu.dk/tsa/files/tsa_manual.pdf (accessed June 2020).
16. *Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group*. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. J Clin Epidemiol 2009; 62: 1006-12.
17. *Hozo SP*, *Djulbegovic B*, *Hozo I*. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; DOI: https://doi.org/10.1186/1471-2288-5-13.
18. *Thiessen Philbrook H*, *Barrowman N*, *Garg AX*. Imputing variance estimates do not alter the conclusions of a meta-analysis with continuous outcomes: a case study of changes in renal function after living kidney donation. J Clin Epidemiol 2007; 60: 228-40.
19. *Chowdhry AK*, *Dworkin RH*, *McDermott MP*. Meta-analysis with missing study-level sample variance data. Stat Med 2016; 35: 3021-32.
20. *Sterne JA*, *Savović J*, *Page MJ*, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; DOI: https://doi.org/10.1136/bmj.l4898.
21. *Guyatt GH*, *Oxman AD*, *Vist GE*, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924-6.
22. *Attilakos G*, *Psaroudakis D*, *Ash J*, *et al*. Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. BJOG 2010; 117: 929-36.
23. *El Behery MM*, *El Sayed GA*, *El Hameed AA*, *Soliman BS*, *Abdelsalam WA*, *Bahaa A*. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in obese nulliparous women undergoing emergency cesarean delivery. J Matern Fetal Neonatal Med 2016; 29: 1257-60.
24. *Razali N*, *Latar IL*, *Chan YK*, *Omar SZ*, *Tan PC*. Carbetocin compared to oxytocin in emergency cesarean section: a randomized trial. Eur J Obstet Gynecol Reprod Biol 2016; 198: 35-9.
25. *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: 2807-12.
26. *Whigham CA*, *Gorelik A*, *Loughnan TE*, *Trivedi A*. Carbetocin versus oxytocin to reduce additional uterotonic use at non-elective caesarean section: a double-blind, randomised trial. J Fetal Matern Neonatal Med 2016; 29: 3866-9.
27. *Su L*, *Chong Y*, *Samuel M*. Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2012; DOI: https://doi.org/10.1002/14651858.CD005457.pub4.
28. *Jin B*, *Du Y*, *Zhang F*, *Zhang K*, *Wang L*, *Cui L*. Carbetocin for the prevention of postpartum hemorrhage: a systematic review and meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med 2016; 29: 400-7.
29. *Monks DT*, *Palanisamy A*. Intrapartum oxytocin: time to focus on longer term consequences? Anaesthesia 2019; 74: 1219-22.
30. *Gallos ID*, *Williams H*, *Price M*, *et al*. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev 2018; DOI: https://doi.org/10.1002/14651858.CD011689.pub2.