Preventing postpartum hemorrhage after cesarean delivery: a network meta-analysis of available pharmacologic agents

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BACKGROUND: Postpartum hemorrhage causes a quarter of global maternal deaths. The World Health Organization recommends oxytocin as the first line agent to prevent hemorrhage during cesarean delivery. However, some randomized controlled trials suggest that other uterotonics are superior.

OBJECTIVE: We conducted a network meta-analysis comparing the ability of pharmacologic agents to reduce blood loss and minimize the need for additional uterotonics during cesarean delivery.

DATA SOURCES: We searched the Cochrane Central Register of Controlled Trials, Embase, and MEDLINE databases from inception to May 2020.

STUDY ELIGIBILITY CRITERIA: We included randomized controlled trials that compared oxytocin, carbetocin, misoprostol, ergometrine, carboprost, or combinations of these in the prevention of postpartum hemorrhage during cesarean delivery.

METHODS: We performed a systematic review followed by an NMA in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Quality of the evidence was assessed with the Confidence in Network Meta-Analysis approach and Grading of Recommendations, Assessment, Development and Evaluations tool within the summary of findings table. Our primary outcomes were the estimated blood loss and need for additional uterotonics. Secondary outcomes included nausea and postpartum hemorrhage of >1000 mL. We performed sensitivity analyses to explore the influence of surgical context and oxytocin administration strategy.

RESULTS: A total of 46 studies with 7368 participants were included. Of those, 21 trials (6 agents and 3665 participants) formed the "estimated blood loss" network and, considering the treatment effects, certainty in the evidence, and surface under the cumulative ranking curve scores, carbetocin was assessed to probably be superior to oxytocin, but only in reducing the estimated blood loss by a clinically insignificant volume (54.83 mL; 95% confidence interval, 26.48—143.78). Misoprostol, ergometrine, and the combination of oxytocin and ergometrine were assessed to probably be inferior, whereas the combination of oxytocin and misoprostol was assessed to definitely be inferior to oxytocin. A total of 37 trials (8 agents and 6193 participants) formed the "additional uterotonic" network and, again, carbetocin was assessed to probably be superior to oxytocin, requiring additional uterotonics 185 (95% confidence interval, 130—218) fewer times per 1000 cases. Oxytocin plus misoprostol, oxytocin plus ergometrine, and misoprostol were assessed to probably be inferior, whereas carboprost, ergometrine, and the placebo were definitely inferior to oxytocin. For both primary outcomes, oxytocin administration strategies had a higher probability of being the best uterotonic, if initiated as a bolus.

CONCLUSION: Carbetocin is probably the most effective agent in reducing blood loss and the need for additional uterotonics. Oxytocin appears to be more effective when initiated as a bolus.

Key words: carbetocin, carboprost, CD, ergometrine, misoprostol, NMA, oxytocin, PPH, prostaglandin

Introduction

Hemorrhage remains the largest direct cause of global maternal mortality with postpartum hemorrhage (PPH) contributing to almost a fifth of all maternal deaths.[1] Approximately a third of women in the United States undergo cesarean delivery (CD), which is associated with a higher risk for PPH (defined as blood loss of >1000 mL) than vaginal delivery.[2,3] Uterine atony is the most common cause of postpartum bleeding and consequently the most commonly studied agents for PPH prophylaxis are uterotonics.[4,5] The most recent World Health Organization recommendations on the subject suggest oxytocin as the drug of choice for PPH prophylaxis.[4] The

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AJOG at a Glance

Why was this study conducted?

Available systematic reviews examining the evidence of agents to prevent postpartum hemorrhage (PPH) after cesarean delivery (CD) have been limited to pairwise meta-analyses and a single network meta-analysis (NMA). Our updated NMA compared interventions in terms of additional bleeding-related outcomes and explored the influence of surgical context and oxytocin administration strategy.

Key findings

Carbetocin was the highest-ranking agent for reducing blood loss and the need for additional uterotonics during CD. Further research that focuses on intrapartum CD is warranted. Oxytocin administration is more effective if initiated as a bolus.

What does this add to what is known?

This NMA provides a probability rank order of the ability of uterotonic agents to prevent blood loss during CD that will be valuable to clinicians in a wide variety of healthcare settings.

recommendations were made broadly for both vaginal delivery and CD together and were based almost entirely on findings from a large, recent Cochrane network meta-analysis (NMA) that had limited focus on CD and did not differentiate based on whether the CD was performed pre- or intrapartum.[4,5] Evidence would suggest that interventions for the prevention of PPH may have different effects in vaginal delivery, intrapartum CD, and prepartum CD in part because of the increased risk of bleeding during operative delivery and in part because of the down-regulation and desensitization of oxytocin receptors observed during labor.[6–8] This is illustrated by a recent consensus statement that recommended larger uterotonic doses for intrapartum CD.[9]

Objective

We aimed to use an NMA to compare the efficacies of prophylactic agents in women undergoing CD and to explore the influence of surgical context.

Materials and Methods

To compare the efficacy of the many agents available to prevent PPH, we performed an NMA focusing on the dual primary outcomes of intraoperative estimated blood loss (EBL) and the need for additional uterotonics. Secondary outcomes included incidence of PPH with >1000 mL EBL and maternal nausea. We conducted 3 sensitivity analyses. The first was a single-study exclusion sensitivity analysis (SSESA) that assessed the influence of the only trial retrieved from our search that evaluated a combination of oxytocin and carbetocin. The second was intended to explore the influence of surgical context by comparing the interventions in separate networks of elective and emergent settings. The third sensitivity analysis was designed to compare the efficacies of specific oxytocin administration strategies (bolus, infusion, or combination) with other agents. Because of the authors' knowledge of the relevant literature and the variation in study definitions for "bolus" and "infusion," arbitrary definitions for these terms for the purposes of this review were decided on a priori. We defined a dosing strategy as a bolus if 3 IU was administered within the first 3 minutes.

Eligibility criteria, search strategy, and study selection

We performed a systematic review followed by an NMA in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10]. A protocol was registered with the International Prospective Register of Systematic Reviews (CRD42020171925). Following an initial scoping review of the literature using the following search terms: "postpartum hemorrhage," "cesarean," and "prevention," a search string was developed for use in the Cochrane Central Register of Controlled Trials, Embase, and MEDLINE (PubMed) databases. The searched key words included uterotonic, oxytocin, carbetocin, misoprostol, ergometrine, tranexamic, prostaglandin, carboprost, sulprostone, methylergonovine, ergonovine, syntometrine, fibrinogen, factor VII, postpartum, hemorrhage, PPH, and cesarean. The search strings are included in Supplemental Figure 1. We also manually searched meta-analyses, systematic reviews, guidelines, and reference lists of individual studies for additional publications. The searches were last updated on May 1, 2020. To be eligible for inclusion, studies had to be peer-reviewed randomized controlled trials comparing pharmacologic agents used to prevent PPH in women undergoing elective or emergent CD. Studies were assessed for eligibility by initial reference to the abstract and subsequent examination of the full-text article if further information was required. Studies were excluded if they were not peer-reviewed or randomized; exclusively studied patients undergoing vaginal delivery; assessed the ability of agents to treat instead of prevent PPH; assessed interventions that were commenced postoperatively; assessed different doses of the same agent without an alternative agent or placebo comparator; reported total EBL without clearly reporting the intraoperative contribution; involved patients with placenta accreta spectrum; or had insufficient information for data extraction. Two authors (D.J. and A.A.) applied the eligibility criteria and selected studies independently, and disagreements were resolved through discussion. When a consensus was not reached, this was resolved by a third author (D.T.M. or P.M.S.).

Data extraction

Two authors (D.J. and A.A.) independently recorded the study characteristics, methodology, and outcome data according to a data extraction form. When

data were lacking, an attempt to contact the authors for clarification was made. We collected data regarding the dose and administration strategy for each intervention. We combined the data from studies on methylergometrine, methylergonovine, ergonovine, and ergometrine under the category of ergometrine. We also combined data from groups that received a placebo and groups that received no intervention under the category of placebo treatment. For studies stating the use of gravimetry for EBL, it was confirmed that the volume in any suction canister was included in the calculation.

Assessment of quality of evidence

Risk of bias for each study was assessed independently by 2 authors (D.J. and A.A.) using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[11] The overall risk of bias was expressed as low risk, some concerns or uncertainty, or high risk. The Confidence in Network Meta-Analysis (CINeMA) approach was used to evaluate the overall evidence quality. Trials were individually assessed for the indirectness of evidence. Indirectness refers to the relevance of the included studies to the research question. It helps to establish how well the included studies address the research question for the present network meta-analysis. Included studies were scored based on uniformity across 3 parameters—study participants, interventions, and outcome characteristics reported. The more divergence noted in these parameters, the more indirectness assumed. In addition, the Grading of Recommendations, Assessment, Development and Evaluations tool was employed to assess the certainty in the evidence for the pairwise comparison of each agent with the common comparator in the summary of findings table.

Data synthesis

For each trial, the requirement for additional uterotonics was analyzed and expressed as odds ratios (ORs). For continuous variables, if a study did not report a standard deviation, according to Cochrane collaboration recommendations, the mean standard deviation from the entire data set for that measurement was used. Once all required data were extracted, a network plot was used to study the pattern of the evidence. In the network plot, the size of the node (treatment group) corresponded to the number of patients in that group. The thickness of the lines connecting any 2 nodes was related to the number of the direct comparisons available between those 2 interventions. We constructed similar networks to review our secondary outcomes.

Statistical analysis

Analysis was performed using a Bayesian hierarchical model (binomial modeling with logit link function) supplemented with a Markov chain Monte Carlo approach. We ran 5000 adaptations and 20,000 iterations with a thinning factor of 10. These parameters helped us to get a potential scale reduction factor of <1.05. The convergence diagnostics for the model are shown in the Gelman-Rubin diagrams (Supplemental Figures 2 and 3). The indirect estimates were computed by the consistency equation from the direct estimates having a common arm. The outcomes were reported as credible intervals (CrIs). Based on the distribution of CrIs, rank probabilities (preferred order of therapeutic success) were calculated for all the included treatment nodes. We calculated the cumulative probabilities for each intervention as being at each possible rank and then used the surface under the cumulative ranking curve (SUCRA) score to create a treatment hierarchy. The SUCRA scores is a commonly used method to numerically summarize the cumulative rankings so that the SUCRA score is 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst.[12] The statistical analysis was performed in R (The R Foundation for Statistical Computing, Vienna, Austria) with assistance from the "gemtc" package (version 0.8-7, Github.com, GitHub, Inc, San Francisco, CA).

Exploration of model fitness and inconsistency

We evaluated model fit using the deviance information criterion (DIC) values and overall deviance for each parameter analyzed.[13] The lower the DIC values in comparison with the estimated number of datapoints, the better the model. For all our networks, the DIC values from the random-effects model were lower and thus further reporting is from results obtained using this model. To inspect the consistency of direct and indirect estimates, we constructed a node-split model. To further explore inconsistency, we created net-heat plots to visually inspect and locate sites of high inconsistency in our network (assisted by the frequentist approach).[13] We evaluated the proportion of direct comparisons in the final outcome using the direct evidence plot. Using this approach, we were able to estimate the minimum number of independent paths in the network contributing to the effect estimate at an aggregated level. "Minimum parallelism" and the "mean path length" estimated the degree of indirectness in the reported pooled outcome (Supplemental Figures 4 and 5).

Summary of findings table

NMAs can produce valuable information regarding the relative effectiveness of different interventions, but the complexity of the results can make interpretation challenging. Summary of findings (SoF) tables summarize the data necessary to make decisions about which intervention is best. An important function of an SoF table is to aid in the evaluation of the clinical significance of differences between interventions by providing absolute effect sizes. This step requires the arbitrary identification of a common or reference comparator (often the most studied or connected intervention in the network, standard treatment, or placebo). For each intervention, a simultaneous evaluation of the effect size and certainty in the evidence for the pairwise comparison with the reference together with the probability ranking can inform an assessment of each intervention's effectiveness relative to that of the common comparator. For the primary outcomes in this NMA, an SoF table was constructed using oxytocin as the reference comparator.

Results

Study selection

Our database searches yielded 2682 records and our manual search of references lists found an additional 226 records. We excluded 1380 duplicates and 1192 articles based on the study title and abstract. After review of 336 full-text articles, a further 290 studies were excluded. A synopsis of the study selection and reasons for exclusion is provided in the PRISMA flow diagram (Figure 1).

Study characteristics and network geometry

A total of 46 studies, including 7368 participants, contributed data to the networks that were constructed in this NMA. The characteristics of the included studies are described in Table 1. A total of 42 articles were in full-text form, whereas only the abstracts were available for 4 studies. Most studies were 2-arm trials, but there were also 3-arm trials (n=4) and a 4-arm trial (n=1). Of the included studies, 24 trials studied women who underwent elective CD, 4 trials studied women who underwent emergent CD, 15 trials evaluated a mixture of elective and emergent CD, and 3 studies did not clarify the urgency of surgery. Seven trials studied women with an elevated risk for PPH, 11 trials evaluated women with a low risk for PPH, and 28 studies studied women with a mixed or unstated risk for PPH. In 3 studies, general anesthesia was used, 39 studies employed neuraxial anesthesia, 1 study used a mix of general and neuraxial anesthesia, and 3 studies did not describe the anesthetic used. Overall, 39 studies evaluated the need for additional uterotonics, 22 studies evaluated intraoperative EBL, 13 studies evaluated PPH >1000 mL, and 17 studies evaluated the incidence of nausea. Of the studies that calculated intraoperative EBL, 2 studies based the calculation on hematocrit change, 2 studies based it on colorimetry, 8 studies on gravimetry, 8 studies on visual estimation, and 2 studies did not describe their method. There were 2 studies that assessed carboprost, which was administered by a different route in each study (intramyometrial and intramuscular [IM]). All 25 studies that assessed carbetocin evaluated a single dosing regimen (100 ug, intravenous [IV]). The 3 studies that evaluated ergometrine all used the IV route with doses ranging from 200 to 500 μg. The 17 studies that evaluated misoprostol included a mix of oral, sublingual (SL), buccal, rectal, and intrauterine tablet administration routes with doses ranging from 400 to 800 μg. The 40 studies evaluating oxytocin administered doses ranging from 2.5 to 40 IU with administration times ranging from rapid boluses to IM injections and 24-hour infusions. The regimen in 1 study in which oxytocin was administered as a 2.5 IU bolus followed by 30 IU administered over 16 hours was classified as an infusion because it did not meet the criteria for bolus plus infusion administration.[26] One study evaluated an oxytocin infusion combined with a carbetocin bolus. Three studies evaluated the IM combination of oxytocin and ergometrine (5 IU with 200 μg). Two studies looked at the combination of oxytocin and SL misoprostol.

Quality of evidence of included studies

All studies were evaluated on 5 domains and an overall risk of bias was provided using the RoB 2.[11] The certainty of evidence was reported using the CINeMA approach, which illustrates how and where the network of evidence is affected by bias and the 3 domains of indirectness, namely population, intervention, and outcome.[60] The risks of bias are shown in Supplemental Figure 6, A for EBL and Supplemental Figure 6, B for additional uterotonics. For EBL, 3 trials were determined to have a low risk of bias in all domains and 8 trials were determined to have a high risk in at least 1 domain. The remaining trials were determined to have some concerns in at least 1 domain. For additional uterotonics use, 15 trials were determined to have a low risk of bias in all domains and 16 trials were determined to have a high risk in at least 1 domain. The remaining trials were determined to have some concerns in at least 1 domain. The potential for publication bias was assessed for both primary outcomes using a funnel plot and Egger's test. For intraoperative EBL (Supplemental Figure 7), the trials were symmetrically distributed and the *P* value from a regression test was .20 (nonsignificant). For additional uterotonics use (Supplemental Figure 8), the trials were also symmetrically distributed and the *P* value from a regression test was .11 (nonsignificant). Hence, publication bias was deemed to be unlikely.

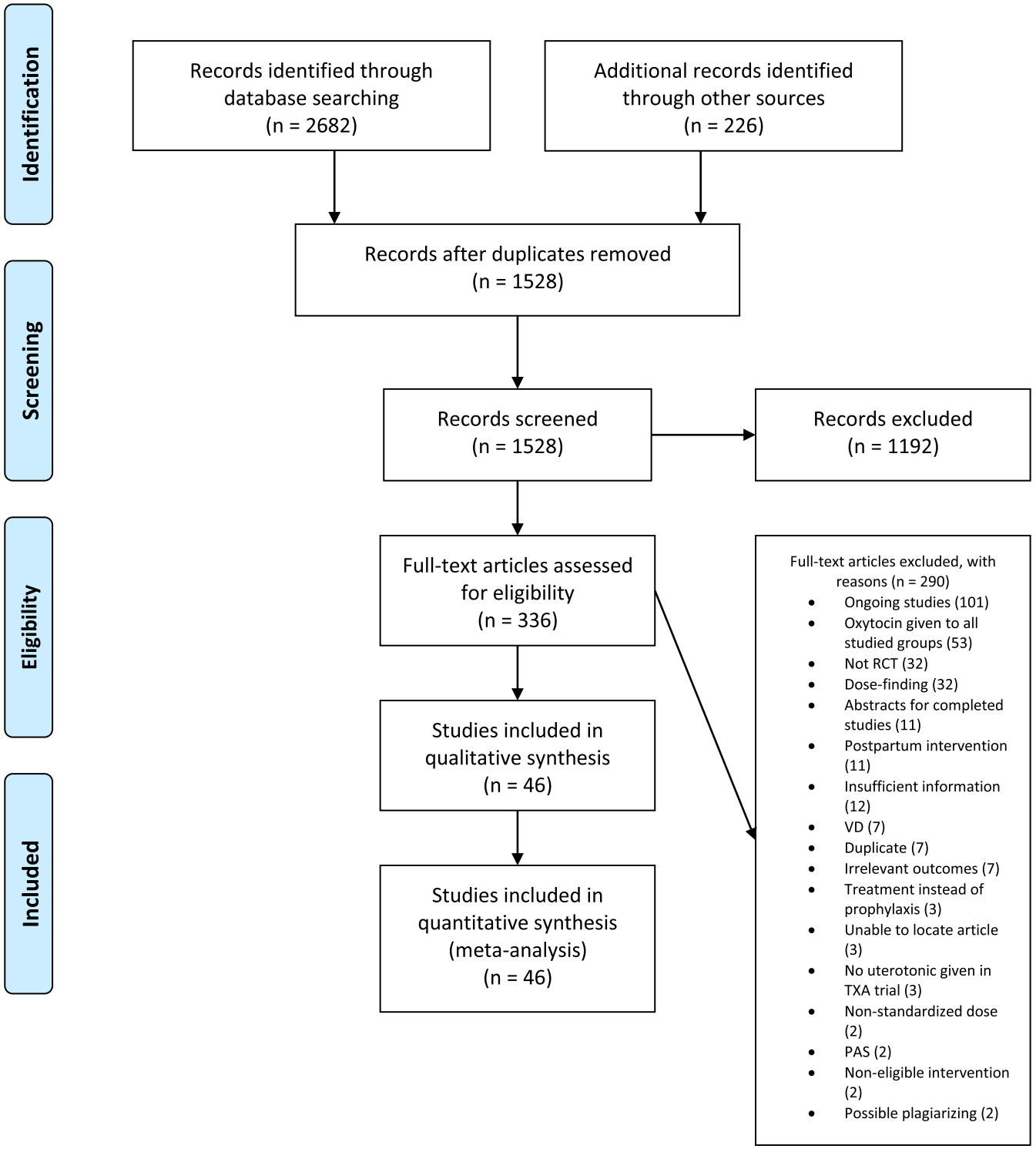
Quantitative synthesis of results

Primary outcomes

The SSESA that removed the data from the only study that evaluated a combination of oxytocin and carbetocin suggested that this study had a disproportionate impact on the output of the network as illustrated in Table 2.[33] Because of this and concerns over the validity of that study's data, the results of the sensitivity analysis in which the study was excluded are presented as the primary analysis and subsequent sensitivity analyses were performed on this data set. The original analysis is reported in Supplemental Table 1 and Supplemental Figures 9 to 11. A summary of the findings for each of the primary outcomes is provided in Table 3. The network estimates of the effect for pairwise comparisons of interventions for the primary outcomes are shown in Table 4 and the corresponding directness plots are displayed in Supplemental Figures 4 and 5.

Intraoperative estimated blood loss. A total of 21 trials were included in this analysis, which included 6 interventions and 3865 participants. The best ranking agent was carbetocin. The probability rank order (and associated SUCRA score) was carbetocin (0.76), misoprostol (0.65), oxytocin with ergometrine (0.57), oxytocin (0.38), ergometrine (0.36), and oxytocin with misoprostol (0.28). The network is shown in Table 3 and the CINeMA plot is shown in Figure 2. The DIC value for the random-effects modeling was 88.53 (with 45 data points). We were unable to construct a net-heat plot because of the small number of direct comparisons. A node-split model using a Bayesian model also suffered the same limitation.

FIGURE 1
PRISMA flow diagram of included randomized controlled trials



PAS, placenta accreta spectrum; *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; *RCT*, randomized controlled trial; *TXA*, tranexamic acid; *VD*, vaginal delivery.
Jaffer. NMA of agents to prevent PPH at cesarean delivery. Am J Obstet Gynecol 2022.

TABLE 1
Characteristics of Included Studies

Study	Country	Scheduling of Case	Group [n]	Additional Uterotonics	PPH >1000	Method of EBL	Intraoperative EBL*	Nausea
Abdeen 2018[14]	Egypt	Elective	Oxy+Ermt [100] v. Cbtn [100]	48 v. 27				
Abdelaleem 2019[15]	Egypt	Elective and emergent	Mspt [120] v. Oxy infusion [120]	79 v. 6		Gravimetric	470.9 +/- 68.43 v. 387.69 +/- 47.11	
Abdelhamid 2019[16]	Egypt	Elective and emergent	Oxy infusion [48] v. Cbtn [52]	13 v. 4	0 v. 0			
Acharya 2001[17]	UK	Elective	Oxy bolus [30] v. Mspt [30]	3 v. 2		Visual	533 +/- 283.87 v. 545 +/- 184.79	
Adefuye 2012[18]	Nigeria	Elective and Emergent	Mspt [50] v. Oxy infusion [50]			Gravimetric	489.42 +/- 15.19 v. 621.22 +/- 22.74	
Ali 2012[19]	Pakistan	Elective and emergent	Mspt [187] v. Ermt [187]					
Alwani 2014[20]	India	Unstated	Mspt [100] v. IM Oxy [100]	4 v. 9				1 v. 2
Anvaripour 2013[21]	Iran	Elective	Ermt [40] v. Oxy infusion [40]			Visual	433.25 +/- 108.44 v. 452.25 +/- 120.18	
Attilakos 2010[22]	UK	Elective and emergent	Cbtn [188] v. Oxy bolus [189]	63 v. 86	9 v. 9	Visual	533.33 +/- 224.12 v. 500 +/- 149.41	10 v. 8
Barton 1996[23]	USA	Elective	Cbtn [62] v. Placebo [57]	8 v. 41				
Begum 2015[24]	Bangladesh	Unstated	Oxy infusion [50] v. Mspt [50]	10 v. 8				
Borruto 2009[25]	Italy	Elective and emergent	Cbtn [52] v. Oxy infusion [52]	2 v. 5		Colorimetric	370.1 +/- 164.67 v. 400.5 +/- 164.67	14 v.
Boucher 1998[26]	Canada	Elective	Oxy infusion [28] v. Cbtn [29]	3 v. 0		Colorimetric	188 +/- 115 v. 159 +/- 92	6 v. 6
Chaudhuri 2010[27]	India	Elective and emergent	Mspt [96] v. Oxy infusion [94]	11 v. 14	1 v. 6	Gravimetric	502.79 +/- 178.35 v. 592.41 +/- 225.35	
Chou 1994[28]	UK	Elective	Oxy bolus+infusion [30] v. Cpst [30]	1 v. 3				
Dansereau 1999[29]	Canada	Elective	Oxy bolus+infusion [318] v. Cbtn [317]	32 v. 15				97 v. 88
Eftekhari 2009[30]	Iran	Elective	Mspt [50] v. Oxy infusion [50]	7 v. 16		Gravimetric	608.78 +/- 18.01 v. 673.86 +/- 27.03	
El Behery 2016[31]	Egypt	Emergent	Cbtn [90] v. Oxy infusion [90]	2 v. 64	2 v. 12	Visual	689 +/- 580 v. 1027 +/- 659	

Jaffer. NMA of agents to prevent PPH at cesarean delivery. Am J Obstet Gynecol 2022. *(continued)*

TABLE 1
Characteristics of Included Studies *(continued)*

Study	Country	Scheduling of Case	Group [n]	Additional Uterotonics	PPH >1000	Method of EBL	Intraoperative EBL*	Nausea
Elbohoty 2016[32]	Egypt	Elective	Cbtn [88] v. Mspt [89] v. Oxy bolus+infusion [86]	5 v. 20 v. 11	3 v. 7 v. 5			12 v. 12 v. 12
Fahmy 2015[33]	Egypt	Elective	Oxy bolus [50] v. Oxy bolus+infusion [50] v. Oxy+Cbtn [50] v. Cbtn [50]	10 v. 0 v. 0 v. 6		Calculated	449 +/- 68.96 v. 467.8 +/- 67.87 v. 359.5 +/- 63.13 v. 398.7 +/- 60.36	
Fahmy 2016[34]	Egypt	Elective	Oxy bolus [30] v. Cbtn [30]	25 v. 4				
Fazel 2013[35]	Iran	Elective	Mspt [50] v. Oxy infusion [50]			Visual	578 +/- 185 v. 620 +/- 213	5 v. 7
Gavilanes 2016[36]	Ecuador	Elective	Mspt [50] v. Oxy infusion [50]	10 v. 12		Gravimetric	837 +/- 287 v. 829 +/- 417	
Jenkumwong 2017[37]	Thailand	Unstated	Oxy infusion [61] v. Cbtn [61]	22 v. 6		Visual	500 +/- 233.93 v. 400 +/- 233.93	13 v. 19
Kikutani 2006[38]	Japan	Elective	Oxy bolus [68] v. Oxy infusion [34] v. Ermt [34]	4 v. 4 v. 15		Unstated	597.5 +/- 172.03 v. 675 +/- 607.75 v. 785 +/- 767.5	
Lamont 2001[39]	UK	Elective and emergent	Cpst [32] v. Oxy+Ermt [31]		1 v. 2			
Lokugamage 2001[40]	UK	Elective and emergent	Oxy bolus [20] v. Mspt [20]	1 v. 6	3 v. 3			
Maged 2017[41]	Egypt	Elective and emergent	Cbtn [150] v. Oxy+Ermt [150]	5 v. 26	4 v. 15	Calculated	578 +/- 178 v. 602 +/- 213	5 v. 11
Mannaerts 2018[42]	Belgium	Elective	Cbtn [32] v. Oxy bolus+infusion [26]	0 v. 2				2 v. 4
Moertl 2011[43]	Austria	Elective	Oxy bolus [28] v. Cbtn [28]					4 v. 3
Mohamed 2015[44]	Egypt	Elective	Oxy bolus [86] v. Cbtn [86]			Gravimetric	434.7 +/- 171.7 v. 366.4 +/- 165	
Ortiz-Gomez 2013[45]	Spain	Elective	Cbtn [52] v. Oxy infusion [104]	0 v. 8				8 v. 16
Othman 2016[46]	Egypt	Elective	Mspt [60] v. Oxy infusion [60]	10 v. 14		Gravimetric	160.75 +/- 85 v. 376.08 +/- 75	
Owonikoko 2011[47]	Nigeria	Elective and emergent	Mspt [50] v. Oxy infusion [50]	24 v. 21		Unstated	667 +/- 213 v. 650 +/- 251	0 v. 2

Jaffer. NMA of agents to prevent PPH at cesarean delivery. Am J Obstet Gynecol 2022. *(continued)*

TABLE 1
Characteristics of Included Studies *(continued)*

Study	Country	Scheduling of Case	Group [n]	Additional Uterotonics	PPH >1000	Method of EBL	Intraoperative EBL*	Nausea
Pakniat 2015[48]	Iran	Elective and emergent	Oxy+Mspt [50] v. Mspt [50] v. Oxy infusion [50]	7 v. 8 v. 7	0 v. 0 v. 0			6 v. 11 v. 7
Rabow 2017[49]	Sweden	Elective	Oxy bolus [30] v. Cbtn [31]	8 v. 3				
Razali 2016[50]	Malaysia	Emergent	Oxy bolus [271] v. Cbtn [276]	155 v. 107	10 v. 15	Visual	446 +/- 281 v. 458 +/- 258	
Rosseland 2013[51]	Norway	Elective	Oxy bolus [26] v. Placebo [25] v. Cbtn [25]	5 v. 23 v. 5				
Sharkwy 2013[52]	Egypt	Elective	Cbtn [190] v. Oxy+Mspt [190]	26 v. 31		Visual	706 +/- 233.93 v. 812 +/- 233.93	14 v. 17
Siddiqua 2017[53]	Bangladesh	Elective and emergent	Cbtn [100] v. IM Oxy [100]	2 v. 10				
Taheripanah 2018[54]	Iran	Emergent	Cbtn [110] v. Oxy infusion [110]	11 v. 40				17 v. 19
Uy 2013[55]	Philippines	Elective	Oxy infusion [35] v. Cbtn [35]	12 v. 2				
Vimala 2006[56]	India	Elective and emergent	Mspt [50] v. Oxy infusion [50]	16 v. 18	6 v. 10			
Whigham 2016[57]	Australia	Emergent	Oxy bolus [53] v. Cbtn [59]	7 v. 13	8 v. 7			
Yaliwal 2019[58]	India	Elective and emergent	Mspt [50] v. Oxy infusion [50]	8 v. 0	6 v. 2	Gravimetric	750.62 +/- 250.9 v. 630.25 +/- 156.17	
Yamaguchi 2011[59]	Brazil	Elective	Oxy infusion [9] v. Oxy bolus [21]	0 v. 0				1 v. 2

* Values reported as Mean +/- Standard Deviation. PPH: Postpartum Hemorrhage, EBL: Estimated Blood Loss, IV: Intravenous, IM: Intramuscular, Oxy: Oxytocin, Cbtn: Carbetocin, Mspt: Misoprostol, Cpst: Carboprost, Ermt: Ergometrine

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TABLE 2
Ranking of interventions for the primary outcomes by SUCRA score: Comparison of the original and single study exclusion sensitivity analyses

Estimated Blood Loss SUCRA Ranking [Score]			Additional Uterotonic SUCRA Ranking [Score]		
Intervention	**Original Analysis**	**SSESA Analysis**	**Intervention**	**Original Analysis**	**SSESA Analysis**
Oxytocin+Carbetocin	1st [0.79]	-	Oxytocin+Carbetocin	1st [1.0]	-
Carbetocin	2nd [0.69]	1st [0.76]	Carbetocin	2nd [0.84]	1st [0.96]
Misoprostol	3rd [0.59]	2nd [0.65]	Oxytocin+Misoprostol	3rd [0.64]	2nd [0.73]
Oxytocin+Ergometrine	4th [0.53]	3rd [0.57]	Oxytocin	4th [0.54]	4th [0.61]
Oxytocin	5th [0.33]	4th [0.38]	Oxytocin+Ergometrine	5th [0.53]	3rd [0.62]
Ergometrine	6th [0.32]	5th [0.36]	Misoprostol	6th [0.42]	5th [0.47]
Oxytocin+Misoprostol	7th [0.25]	6th [0.28]	Carboprost	7th [0.28]	6th [0.31]
			Ergometrine	8th [0.15]	7th [0.17]
			Placebo	9th [0.11]	8th [0.13]

SUCRA: surface under the cumulative ranking curves; SSESA: Single-study exclusion analysis.

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The sensitivity analysis in which the influence of the surgical context on the intraoperative EBL was evaluated failed. This was because not all involved treatments (nodes) were connected to the resulting network. For the sensitivity analysis assessing the influence of oxytocin administration strategies on the comparative performance of agents in terms of intraoperative EBL, it was possible to include data from 21 trials, including 3665 participants and 7 interventions. Oxytocin administration strategies (per the review definitions) included an IV bolus in 5 trials (644 participants, dosing ranged from 5 to 10 IU) and IV infusion in 15 trials (879 participants, dose range from 10 to 30 IU given over 15 minutes to 16 hours). Carbetocin ranked best. The probability rank order (SUCRA value) was carbetocin (0.78), oxytocin bolus (0.72), oxytocin with ergometrine (0.61), misoprostol (0.52), oxytocin with misoprostol (0.32), ergometrine (0.29), and oxytocin infusion (0.26). The network and SUCRA bar chart are shown in Figure 3.

Need for additional uterotonics. A total of 37 trials were included in this analysis, which included 8 interventions and 6393 participants. The best ranking intervention was carbetocin. The probability rank order (SUCRA value) was carbetocin (0.96), oxytocin with misoprostol (0.73), oxytocin with ergometrine (0.62), oxytocin (0.61), misoprostol (0.47), carboprost (0.31) ergometrine (0.17), and placebo (0.13). The network is shown in Table 3 and the CINeMA plot is shown in Figure 2. The DIC value for the random-effects modeling was 150.77 (with 80 data points). The net-heat plot and node-split model, shown in Supplemental Figure 12, demonstrate that the degree of inconsistency in the network can be considered insignificant.

The sensitivity analysis evaluating outcomes from trials studying emergent CD did not produce a complete network for analysis but the sensitivity analysis evaluating elective CD alone included 22 trials, 8 interventions, and 3119 participants. The best ranking intervention was carbetocin. The probability rank order (SUCRA value) is carbetocin (0.91), oxytocin with misoprostol (0.83), oxytocin with ergometrine (0.67), misoprostol (0.58), oxytocin (0.48), carboprost (0.26), placebo (0.14), and ergometrine (0.13). The network and rankogram is shown in Supplemental Figure 9. The sensitivity analysis assessing the influence of oxytocin administration strategies on the comparative performance of agents in terms of the need for additional uterotonics included 38 trials, including 6223 participants and 11 interventions. Oxytocin administration strategies (per the review definitions) included an IV bolus in 10 trials (738 participants, dosing ranged from 5 to 20 IU), an IV infusion in 20 trials (1195 participants, dosing ranged from 10 to 30 IU given over 15 minutes to 24 hours), an IV bolus followed by infusion in 4 trials (460 participants, boluses ranging from 5 to 10 IU and infusions ranging from 10 to 20 IU given over 4 to 24 hours), and an IM injection of oxytocin in 2 trials (200 participants, 10 IU in both trials). Carbetocin ranked best. The probability rank order (SUCRA value) is carbetocin (0.97), oxytocin bolus (0.77), oxytocin with misoprostol (0.69), oxytocin bolus and infusion (0.64), oxytocin with ergometrine (0.63), oxytocin infusion (0.47), misoprostol (0.4), IM oxytocin (0.34), carboprost (0.33), ergometrine (0.15), and placebo (0.13). The network and SUCRA bar chart are shown in Figure 3.

Secondary outcomes

In terms of PPH >1000 mL, a total of 13 trials were included in this analysis, which included 6 interventions and 2522 participants. The best ranking intervention was oxytocin with misoprostol. The probability rank order per the SUCRA values is oxytocin with misoprostol,

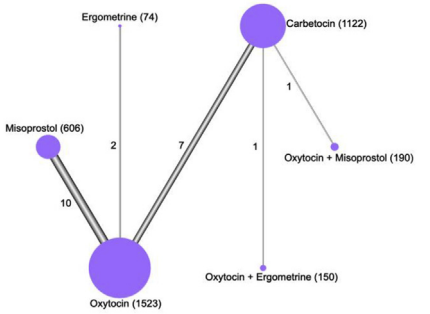
TABLE 3

NMA Summary of Findings (SoF): Estimates of effects, credible intervals, and certainty of the evidence for reducing estimated blood loss and need for additional uterotonics at Cesarean Delivery

Bayesian NMA-SoF table

Estimated blood loss

Patients or population: Pregnant women undergoing cesarean delivery
Intervention: Carbetocin, Ergometrine, Misoprostol, Oxytocin+Ergometrine, Oxytocin+Misoprostol
Comparator (reference): Oxytocin
Outcome: Estimated intraoperative blood loss in milliliters
Setting: Inpatient



Total Studies: 21 **Total Participants:** 3665 **Geometry of the Network***

Interventions	Anticipated absolute effect (95% CI) *Without* intervention	Anticipated absolute effect (95% CI) *With* intervention	Mean difference (with intervention) (95% CrI)	Certainty in the evidence	Ranking**** (SUCRA)	Interpretation of Findings*****
Carbetocin	552.54 ml	497.71 ml	-54.83 ml (-143.78, 26.48)	⊕⊕◯◯ Low a, d	1st (0.76)	**Probably superior**
Misoprostol	552.54 ml	516.14 ml	-36.4 ml (-104.86, 35.45)	⊕⊕◯◯ Low a, d	2nd (0.65)	**Probably inferior**
Oxytocin + Ergometrine	552.54 ml	521.23 ml	-31.31 ml (-265.99, 194.39)	⊕◯◯◯ Very low a, c, d	3rd (0.57)	**Probably inferior**
Oxytocin	Not estimable	Not estimable	Reference comparator	Reference comparator	4th (0.38)	**Reference comparator**
Ergometrine	552.54 ml	576.83 ml	24.29 ml (-152.2, 211)	⊕⊕◯◯ Low a, d	5th (0.36)	**Probably inferior**

(continued)

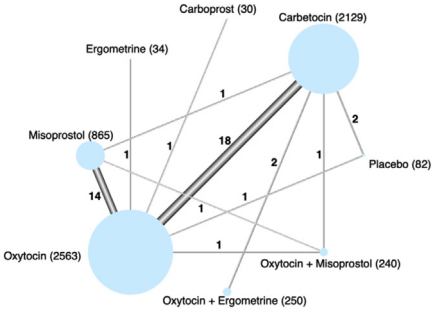
TABLE 3

NMA Summary of Findings (SoF): Estimates of effects, credible intervals, and certainty of the evidence for reducing estimated blood loss and need for additional uterotonics at Cesarean Delivery *(continued)*

Interventions	Anticipated absolute effect (95% CI) *Without* intervention	*With* intervention	Mean difference (with intervention) (95% CrI)	Certainty in the evidence	Ranking**** (SUCRA)	Interpretation of Findings*****
Oxytocin + Misoprostol	552.54 ml	604.52 ml	51.98 ml (-182.11, 278.7)	⊕◯◯◯ Very low a, c, d	6th (0.28)	**Definitely inferior**

Need for additional uterotonic therapy

Patients or population: Pregnant women undergoing cesarean delivery
Intervention: Carbetocin, Carboprost, Ergometrine, Misoprostol, Oxytocin+Ergometrine, Oxytocin+Misoprostol, placebo
Comparator (reference): Oxytocin
Outcome: Requirement for additional uterotonic therapy
Setting: Inpatient



Total Studies: 37 **Total Participants:** 6193 **Geometry of the Network***

Interventions	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CI) *Without* intervention	*With* intervention	Difference (in need of additional uterotonics)	Certainty in the evidence	Ranking**** (SUCRA)	Interpretation of Findings*****
Carbetocin	0.22 (0.11, 0.42) Network Estimate	253 of 1000	68 of 1000	185 fewer per 1000 (218 to 130 fewer)	⊕⊕◯◯ Low a, b	1st (0.96)	**Probably superior**
Oxytocin + Misoprostol	0.57 (0.09 to 3.55) Network Estimate	253 of 1000	172 of 1000	93 fewer per 1000 (224 fewer to 285 more)	⊕◯◯◯ Very low a, c, d	2nd (0.73)	**Probably inferior**

(continued)

TABLE 3

NMA Summary of Findings (SoF): Estimates of effects, credible intervals, and certainty of the evidence for reducing estimated blood loss and need for additional uterotonics at Cesarean Delivery *(continued)*

		Anticipated absolute effect*** (95% CI)					
Interventions	**Relative effect** (95% CrI)**	*Without* intervention	*With* intervention	Difference (in need of additional uterotonics)	**Certainty in the evidence**	**Ranking**** (SUCRA)**	**Interpretation of Findings*****
Oxytocin + Ergometrine	0.87 (0.11 to 6.39) Network Estimate	253 of 1000	160 of 1000	28 fewer per 1000 (218 fewer to 433 more)	⊕◯◯◯ Very low a, c, d	3rd (0.62)	**Probably inferior**
Oxytocin	Reference comparator	Not estimable	Not estimable	Not estimable	Reference comparator	4th (0.61)	**Reference comparator**
Misoprostol	1.39 (0.67 to 2.98) Network Estimate	253 of 1000	316 of 1000	64 more per 1000 (70 fewer to 245 more)	⊕⊕◯◯ Low a, d	5th (0.47)	**Probably inferior**
Carboprost	4.45 (0.13 to 292) Network Estimate	253 of 1000	600 of 1000	347 more per 1000 (211 fewer to 737 more)	⊕⊕⊕◯ Moderate a, d, x	6th (0.31)	**Definitely inferior**
Ergometrine	9.61 (0.6 to 151) Network Estimate	253 of 1000	764 of 1000	511 more per 1000 (84 fewer to 728 more)	⊕⊕⊕◯ Moderate a, d, x	7th (0.17)	**Definitely inferior**
Placebo	10.67 (1.5 to 81.48) Network Estimate	253 of 1000	780 of 1000	527 more per 1000 (72 more to 711 more)	⊕⊕◯◯ Low a, b, c, x	8th (0.13)	**Definitely inferior**

NMA SoF Table definitions:

* Size of nodes corresponds to sample size of treatment group (reported in parenthesis). The lines connecting nodes show the number of trials (in parenthesis) comparing the connected nodes and is proportional to the thickness of line; ** Estimates are reported as odds ratio (OR) with associated credible intervals (CrI) in parenthesis for likelihood of event in comparison to oxytocin; *** Anticipated absolute effect is calculated using the difference between the risks of the intervention groups and that of the control group; **** The ranking of interventions is made using the surface under the cumulative ranking curve (SUCRA) scores. The 1st ranked intervention is the most likely to be the best intervention regarding the outcome in question; ***** The interpretation of findings incorporates the effect estimate size and precision, certainty in the evidence and the SUCRA score

GRADE working group grades of evidence (or certainty in the evidence)

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

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

Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different to the estimate of the effect

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

Explanatory footnotes:

Factors lowering quality: [a]bias, [b]heterogeneity, [c]indirectness, [d]imprecision, [e]publication bias

Factors increasing quality: [x]large magnitude of effect, [y]plausible opposing bias/confounding, [z]dose-response

TABLE 4
Network estimates of effect for pairwise comparisons of interventions

Estimated blood loss (ml)	Carbetocin	0.05 (0, 1.69)	0.02 (0, 0.38)	0.16 (0.06, 0.41)	0.22 (0.11, 0.42)	0.25 (0.04, 1.7)	0.38 (0.06, 2.36)	0.02 (0, 0.14)	Additional Uterotonics (odds ratio)
-	**Carboprost**	0.46 (0.01, 66.26)	3.18 (0.09, 217.71)	4.45 (0.13 to 292)	5.18 (0.09, 528.15)	7.89 (0.15, 719.1)	0.42 (0.01, 41)		
-78.06 (-290.46, 112.22)	-	**Ergometrine**	6.95 (0.39, 120.24)	9.61 (0.6 to 151)	11.21 (0.36, 338.97)	17.15 (0.61, 471.25)	0.9 (0.03, 26.93)		
-18.62 (-134.41, 86.61)	-	59.25 (-129.33, 259.13)	**Misoprostol**	1.39 (0.67 to 2.98)	1.6 (0.19, 14.14)	2.45 (0.38, 16.31)	0.13 (0.02, 1.07)		
-54.83 (-143.78, 26.48)	-	24.29 ml (-152.2, 211)	-36.4 (-104.86, 35.45)	**Oxytocin**	1.15 (0.16, 8.88)	1.76 (0.28, 10.93)	0.09 (0.01, 0.67)		
-23.68 (-236.44, 191.57)	-	54.31 (-230.98, 358.12)	-5.11 (-240.12, 240.59)	31.31 (-194.39, 265.99)	**Oxytocin + Ergometrine**	1.53 (0.11, 21.45)	0.08 (0.01, 1.21)		
-106.42 (-320.53, 108.06)	-	-28.31 (-310.69, 274.26)	-88.07 (-323.43, 157.87)	-51.98 (-278.7, 182.11)	-83.04 (-383.84, 219.75)	**Oxytocin + Misoprostol**	0.05 (0, 0.74)		
-	-	-	-	-	-	-	**Placebo**		

League table of network estimates of pairwise comparisons between interventions for estimated blood loss (bottom left cells) and need of additional uterotonic (top right cells). The estimate in each cell is for the effect of the column intervention compared to that of the row. Estimated blood loss values reported as mean difference (standard deviation). Need for additional uterotonic comparisons reported as odds ratios (95% credible interval).

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carbetocin, misoprostol, carboprost, oxytocin, and oxytocin with ergometrine. The network is shown in Supplemental Figure 11. The SUCRA values for the interventions are shown in Supplemental Tables 2 and 3.

In terms of nausea, a total of 16 trials were included in this analysis, which included 5 interventions and 3226 participants. The best ranking intervention was oxytocin with misoprostol. The probability rank order per SUCRA values is oxytocin with misoprostol, carbetocin, misoprostol, oxytocin, and oxytocin with ergometrine. The SUCRA values for the interventions are shown Supplemental Tables 2 and 3. We extracted data for adverse effects other than nausea (eg, headache, flushing, fever, shivering, diarrhea, dyspnea, thrombosis, death). The incidences are shown in Supplemental Table 4. Because of significant heterogeneity in their measurements among the studies and their low incidence overall, we were unable to complete a statistical analysis comparing the association of these adverse effects with the interventions.

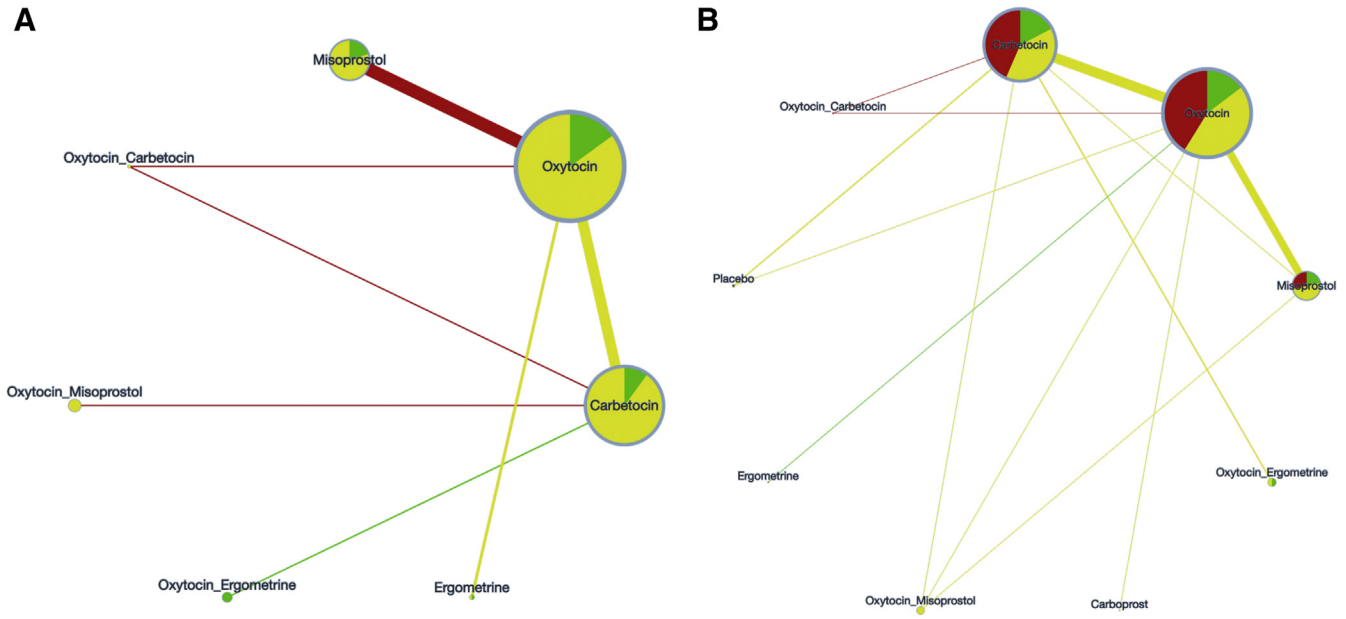
Comment

This NMA provides evidence for the relative efficacies of prophylactic agents for PPH during CD. A large amount of evidence was pooled to allow the estimation of the relative effects of prophylactic agents to allow for their comparison.

Principal findings

Our analysis suggests that carbetocin is probably the most effective agent in reducing blood loss and the need for additional uterotonics during CD. It is worth noting, however, that the overall quality of the evidence was poor for both primary outcomes, and the estimates of effect size were small and imprecise. It is also important to be cautious of interpreting the rank order of interventions in an NMA without reference to effect estimates. When the network estimates were utilized to provide anticipated effect sizes for each intervention compared with oxytocin (Table 3), carbetocin was found to reduce the EBL (95% confidence interval [CI]), 54.83 mL

FIGURE 2
Confidence in Network Meta-Analysis (CINeMA) diagrams (SSESA)



CINeMA diagrams showing the quality of evidence. **A,** Estimated blood loss. **B,** Additional uterotonic use. The colors in the diagram represent the degree of uncertainty or bias. Red indicates high risk, yellow indicates that there are some concerns, and green indicates a low risk for bias. The node color in the diagram shows the percentage of the sample size of that treatment group that fall into high, moderate, and low risk of bias (evaluated based on the Cochrane criterion). The color of lines connecting the nodes represents the degree of the indirectness in the evidence (evaluated based on the CINeMA) criterion.

SSESA, single-study exclusion sensitivity analysis.

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(26.48−143.78 mL blood loss). This does not provide clinicians with any confidence that it will reduce blood loss by a clinically meaningful amount. Carbetocin was also found to require additional uterotonics (185; 95% CI, 130−218) less frequently per 1000 cases. Although we can be more confident of the benefit of carbetocin in terms of this outcome, neither this outcome nor EBL are indicators of hemorrhage-related morbidity.

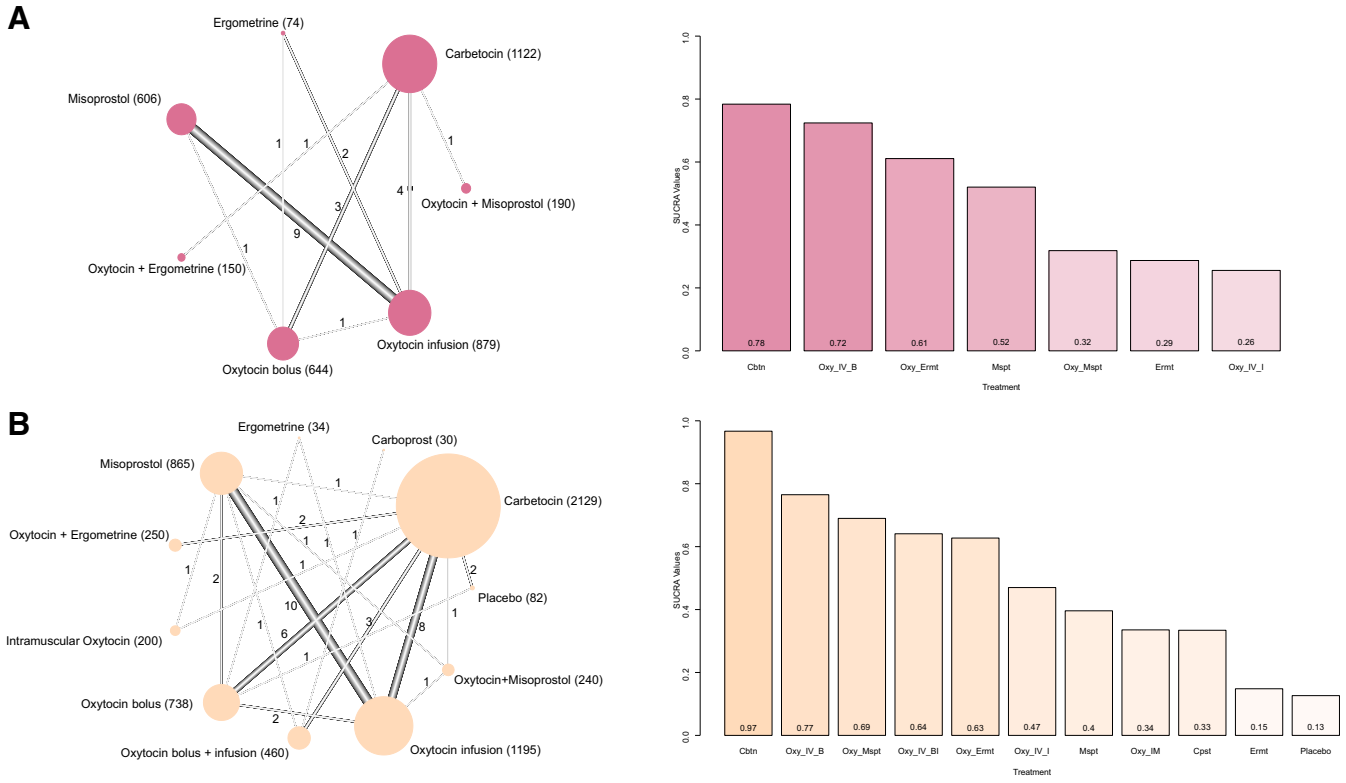
The decision to exclude the study by Fahmy et al[33] was made on the basis of it being the only study in which a combination of oxytocin and carbetocin was evaluated and because of concerns over the adequacy of peer review for their analysis. Furthermore, from a pharmacodynamic standpoint, the combination of 2 oxytocin receptor agonist is arguably only of value if the dose or duration of one agent is inadequate. Selecting an adequate dose of the longer acting carbetocin or optimizing oxytocin administration with the aim of maintaining effective plasma concentrations, might be considered more appropriate. One finding of this review was the wide variation in oxytocin administration protocols selected by investigators. This will undoubtedly contribute to heterogeneity in the pooled estimate of the effect of oxytocin. Further evidence for this is provided by our sensitivity analysis, which suggests that oxytocin administration strategies that incorporate an initiating bolus perform better than those that do not and in which administration strategies such as single fixed-rate infusions or IM injections are used. From a pharmacokinetic perspective, an initiating bolus (or a brief high-rate infusion) of oxytocin is desirable to efficiently achieve effective plasma concentrations of oxytocin especially given the commonly employed time frames of assessment of the need for second-line agents. The dose and rate of administration, however, must be carefully selected if acute adverse effects are to be avoided. Further pharmacokinetic data to guide the precise administration of oxytocin and carbetocin in patients of varying body habitus is much more likely to be of value to clinicians than further evaluation of any combination of these 2 oxytocin receptor agonists.

Despite the higher risk of uterotonic failure and bleeding seen during intrapartum CD, a paucity of good quality data limited our ability to compare agents in this context and this represents a significant knowledge gap.

Comparison with existing literature

Numerous systematic reviews on PPH prophylactic agents for CD have been performed but, with the exclusion of 1, these have been limited to pairwise meta-analyses. The only NMA (Gallos

FIGURE 3
Network geometry and SUCRA scores of sensitivity analysis assessing oxytocin administration strategies



A, Estimated blood loss network. Left, network geometry. The size of the nodes corresponds to sample size of the treatment group (*parentheses*). The lines connecting the nodes show the number of trials (*parentheses*) comparing the connected nodes and is proportional to the thickness of the line. Right, SUCRA ranking chart. Plot showing the surface under the cumulative ranking curves (SUCRA). The higher the SUCRA value, the higher the likelihood that the treatment is superior. **B,** Additional uterotonic network. Left, network geometry. Right, SUCRA ranking chart.

Cbtn, carbetocin; *Cpst*, carboprost; *Ermt*, ergometrine; *Mspt*, misoprostol; *Oxy*, oxytocin; *Oxy_IV_B*, oxytocin intravenous bolus; *Oxy_IV_BI*, oxytocin intravenous bolus followed by infusion; *Oxy_IM*, intramuscular oxytocin; *Oxy_IV_I*, oxytocin intravenous infusion; *SSESA*, single-study exclusion sensitivity analysis.

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et al[5]) in this context was able to compare uterotonics used for PPH prophylaxis for PPH >500 mL and >1000 mL during CD as part of a subgroup analyses. For both outcomes, it concluded that carbetocin ranked highest, however, it did not assess other important outcomes including EBL and the need for additional uterotonics. Among the bleeding-related outcomes, a continuous measure such as EBL is arguably preferred over the arbitrary dichotomization necessary to measure incidence of PPH at any given threshold.[61] However, methods employed in the literature to measure EBL vary considerably. These methods include visual estimation, gravimetric tools, or change in hematocrit and each of these methods under- or overestimate EBL relative to another. For example, visual estimation has been found to estimate a value 30% lower than gravimetric estimations and visual estimation and gravimetric estimation both overestimate compared with colorimetric methods.[62,63] Indeed, the domain that provided the predominant source of bias for our EBL network was "measurement of the outcome," with 7 and 11, respectively, out of the 22 included studies judged to be at "high risk" of bias or "some concerns" for bias. This highlights the need for researchers to employ a core set of outcomes and establish a consensus on the optimal measurement tool for this important outcome. In contrast to our analysis, Gallos et al[5] did not provide an analysis for the 2 very different surgical contexts. Differentiating between intra- and prelabor CD is important for 2 reasons. First, because intrapartum CD is known to be associated with a higher risk of bleeding and second, because uterotonic effect has been shown to differ substantially between the 2 contexts.[64–67] The literature supporting this differential uterotonic effect comes from studies examining oxytocin receptor agonists and is likely to be, at least in part, because of the down-regulation of oxytocin receptors seen after prolonged exposure to oxytocin, whether

endogenously secreted or exogenously administered.[6–8] In the sensitivity analyses for our primary outcomes, we attempted to perform an NMA for each of the surgical contexts but were unable to form complete networks for emergent CD because of the small number of trials that evaluated this scenario. We were, however, able to form a network to compare the need for additional uterotonics among the available agents for elective CD but this demonstrated only a minimal change in probability rank order. A greater research focus on the performance of agents to prevent PPH after intrapartum CD is required.

A recent analysis attempted to perform an NMA of uterotonic agents for first-line treatment of PPH but was unable to construct a network because of the small number of studies evaluating different uterotonic interventions for this indication.[68] The results of 2 pairwise meta-analyses (2 and 4 trials, respectively) suggested that oxytocin is probably more effective than misoprostol with less side-effects and that the combination of oxytocin and misoprostol probably makes little or no difference to the effectiveness outcomes and is also associated with more side effects when compared with oxytocin alone. In our analysis, it should be noted that although a combination of uterotonic agents may require fewer treatments with additional uterotonics, a strategy that only administers a second uterotonic to those who need it may produce fewer side effects overall.

Strengths and limitations

By using a thorough and inclusive search strategy, we were able to pool data from a large number of trials in our review. Our analysis compared the ability of multiple PPH prophylactic agents to reduce EBL during cesarean delivery. It is also unique in its assessment of the influence of surgical context and different strategies for oxytocin administration. The shared focus on 2 important efficacy outcomes also meant that we arguably incorporated the most important bleeding-related outcome and the measure of uterotonic effect most commonly assessed in the literature. Including these as co-primary outcomes ensured that they were subject to equal scrutiny including a thorough assessment of the quality of the contributing evidence. The adoption of the CINeMA approach to evaluating the quality of evidence in NMAs also provides the reader with a greater appreciation of the how bias and indirectness of estimates affect the network of evidence.

There are important limitations to this analysis that should be considered when interpreting the results. Although NMAs provide an important method of including a large amount of direct and indirect evidence from comparisons of many different interventions, this very often comes at the cost of the incorporation of a considerable amount of heterogeneity in the pooled estimates of effect. This can be because of variable baseline risks for the outcome among the different study populations, differences in the study conditions, and important variations in administration of the interventions. Consequently, credible intervals frequently overlap and only provide the probability rank order for each outcome. As with any data synthesis, this analysis was limited by biased estimates from the included trials. Across both outcomes, the majority of trials had at least 1 domain with at least some concerns for bias. As can be seen when referencing the CINeMA graphics provided in Figure 2, bias and indirectness of evidence were problems for both primary outcomes but seem to have particularly affected the evidence for EBL. We believe that this provides further confirmation of the value of including both outcomes as primary outcomes. It should also be noted that the large majority of included studies examined oxytocin in comparison with 1 other agent, most commonly carbetocin or misoprostol. This means that most of the network evidence for other interventions would have been sourced form indirect comparisons, a problem emphasized by the inability for the statistical software to construct the node-split model for EBL.

The dose, duration, and profile of administration of most therapeutic agents will influence effect-site concentrations and have important consequences for either safety, efficacy, or both. The substantial variation in these pharmacokinetic parameters for oxytocin is problematic for our networks given this agent's dominance over them. Outcome estimates are likely to have varied considerably within those interventions under the oxytocin umbrella. We attempted to address this issue via an arbitrary subcategorization of oxytocin administration. The nomenclature can be misleading but from a pharmacokinetic perspective, all parenteral administration strategies can be considered to be infusions. A bolus and infusion can be modeled as fixed-rate infusions with a faster rate followed by a slower one. Even an IM injection can be considered an infusion, but this time with a rate that varies as a function of intramuscular drug concentration and blood flow. We chose to define a dosing strategy as a bolus if it administered 3 IU within 3 minutes. We used this arbitrary definition because it is consistent with a commonly-quoted protocol, "rule of threes" in which 3 IU of oxytocin is given and the need for additional uterotonics is assessed at 3-minute intervals.[69] There are, of course, many options for categorizing the oxytocin administration strategy and none would be ideal. Considering the broad spectrum of strategies, some may even question the validity of any categorization. However, even with these caveats in mind, this exploratory analysis highlights the need for a greater understanding of the pharmacokinetics of oxytocin in parturient women and suggests that optimization of its administration could lead to greater efficacy. In addition, because most studies only assessed tone in the intraoperative period, we were unable to determine the uterotonic agents' ability to maintain uterine tone in the first few hours after initiation.

An important additional limitation related to this review's primary outcomes is the heterogeneity of assessment of both EBL and uterine tone and the often subjective criteria used in the decision to administer a second-line

uterotonic. Because of the lack of relevant granular study-level data, we were also unable to perform a meta-regression to explore the impact of important effect modifiers such as body mass index or baseline risk for PPH.

This review was very limited in its ability to compare agents based on important safety outcomes. We would have liked to assessed the hemodynamic effects but there was too much variation in the definitions for hypotension or tachycardia. Similarly, low incidences prevented meaningful analyses of headaches, flushing, fever, shivering, diarrhea, dyspnea, thrombosis, and death. The low incidence of misoprostol-associated fever also raises concerns for underreporting of this adverse effect.

Conclusions and implications

This NMA provides a comparison of the available therapeutic agents for the prevention of PPH. It suggests that carbetocin may be the most effective, but larger high-quality randomized controlled trials are required to confirm this, and further research is also warranted to confirm the optimal administration strategy for oxytocin. Not all of the agents included in our analysis are universally available, whether this is because of the financial constraints and inconsistent supply experienced by many of the world's healthcare systems or because of international variation in licensing of medicines. Consequently, this NMA provides an evaluation of the comparative effectiveness of available uterotonic agents for a number of important outcomes that will be valuable to clinicians in a wide variety of healthcare settings. ■

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