Intravenous oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery: a systematic review and meta-analysis

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OBJECTIVE: To compare the available evidence on intravenous oxytocin dosing regimens for the prevention of postpartum hemorrhage following cesarean delivery.

DATA SOURCES: We searched Ovid MEDLINE, Embase, Global Index Medicus, Cumulative Index of Nursing and Allied Health Literature, Cochrane Controlled Register of Trials, ClinicalTrials.gov, and the International Clinical Trials Registry Platform for eligible studies published until February 2020.

STUDY ELIGIBILITY CRITERIA: We included any randomized or nonrandomized study published in peer-reviewed journals that compared at least 2 different dosing regimens of intravenous oxytocin for postpartum hemorrhage prevention in women undergoing cesarean delivery.

METHODS: Two authors independently assessed the eligibility of studies, extracted the data, and assessed the risk of bias. The primary outcome was incidence of postpartum hemorrhage ≥1000 mL. Other review outcomes included use of additional uterotonics, blood loss, and adverse maternal events. Data were analyzed according to the type of intravenous administration (bolus only, infusion only, or bolus plus infusion) and total oxytocin dose. A meta-analysis was performed on randomized trials and the results were reported as risk ratios or mean differences with 95% confidence intervals. The Grading of Recommendations, Assessment, Development, and Evaluations scale was used to rate the certainty of evidence. Findings from dose-finding trials and nonrandomized studies were reported narratively.

RESULTS: A total of 35 studies (7333 women) met our inclusion criteria and included 30 randomized trials and 5 nonrandomized studies. There were limited data available from the trials for most outcomes, and the results were not conclusive. Compared with bolus plus infusion regimens, bolus only regimens probably result in slightly higher mean blood loss (mean difference, 52 mL; 95% confidence interval, 0.4—104 mL; moderate certainty). Among the bolus plus infusion regimens, initial bolus doses <5 IU may reduce nausea (risk ratio, 0.26; 95% confidence interval, 0.11—0.63; low certainty) when compared with doses of 5—9 IU. Total oxytocin doses of 5—9 IU vs total doses of 10—19 IU may increase the use of additional uterotonics (risk ratio, 13.00; 95% confidence interval, 1.75—96.37; low certainty). Effects on other outcomes were generally inconclusive.

CONCLUSION: There are limited data available for comparisons of IV oxytocin regimens for postpartum hemorrhage prevention following cesarean delivery. Bolus plus infusion regimens may lead to minor reductions in mean blood loss and initial bolus doses of <5 IU may minimize nausea. Bolus only regimens of 10 IU vs bolus only regimens of 5 IU may decrease the need for additional uterotonics, however, further comparative trials are required to understand the effects on other key outcomes, particularly hypotension.

Key words: abdominal delivery, birth, blood loss, dosing, drug administration, pregnancy, uterine atony, uterotonics

Introduction

Postpartum hemorrhage (PPH) is one of the leading causes of maternal mortality, accounting for nearly 20%[1] of the 295,000 maternal deaths that occur worldwide.[2] The most common cause of PPH is uterine atony,[3] hence increasing the use of uteronics for all women during delivery has been a key component of

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AJOG at a Glance

Why was this study conducted?

The World Health Organization guidelines state that there is insufficient evidence to recommend a specific oxytocin dosing regimen to prevent women from experiencing postpartum hemorrhage following a cesarean delivery. This systematic review was conducted to identify and compare intravenous oxytocin dosing regimens administered during cesarean deliveries and to determine whether any regimens are superior.

Key findings

We found limited and generally low-quality data for most outcomes and further research is required. Bolus plus infusion regimens, with an initial bolus dose of <5 international units (IU), may have minor benefits. Bolus only regimens of 10 IU vs 5 IU may decrease the use of additional uterotonics, although the effects on adverse events (particularly hypotension) is unknown.

What does this add to what is known?

This study compared data on all oxytocin regimens administered during cesarean delivery for postpartum hemorrhage prevention. It provides valuable information for clinical guidelines and future research.

global efforts to reduce PPH-associated morbidity and mortality.[4]

In 2018, the World Health Organization (WHO) recommended that 10 international units (IU) of oxytocin should be administered to all women during delivery, irrespective of the mode of delivery (vaginal or cesarean delivery [CD]).[4] This recommendation was informed by a Cochrane network meta-analysis of uterotonic agents for PPH prevention by Gallos et al.[5] Based on further evidence from observational studies suggesting dose-dependent adverse effects,[4] the WHO recommendations specified that when used for PPH prevention during CD, 10 IU oxytocin should be administered as a divided dose using a smaller initial intravenous (IV) bolus followed by infusion.[4] However, the WHO Guideline Development Group acknowledged that there was insufficient evidence from randomized controlled trials and specified that identifying an optimal IV oxygocin regimen for PPH prophylaxis during CD was a high research priority.[4]

Previous reports have synthesized evidence on oxytocin dosing regimens for PPH prevention during CD, however, none of these were systematic reviews or were published nearly a decade ago.[6–8] An up-to-date review and comparison of studies are important to help guide clinical practice and address the priority identified by the WHO Guideline Development Group. The aim of this systematic review was, therefore, to identify and compare IV oxytocin dosing regimens during CD and determine whether any regimens are superior.

Methods

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance[9] (Appendix A). We followed a prespecified protocol registered with the International Prospective Register of Systematic Reviews (CRD42020175544),[10] and outlined any deviations in Appendix B. Ethics approval was not required because this was a systematic review of publicly available data.

Eligibility criteria

Randomized controlled trials (RCTs) and nonrandomized studies of interventions (NRSIs) published in peer-reviewed journals were eligible for inclusion without date restrictions. Conference abstracts were not included. We included studies written in English and those written in other languages if we were able to obtain adequate translations.

Eligible studies were those that included women who gave birth at any gestational age to a live or stillborn baby via CD and included both planned and intrapartum CDs. Women were eligible if they received IV oxytocin for PPH prevention either at or around the third stage of labor, recognizing that administration of oxytocin during the third stage may not be possible or practical during a CD, particularly during an emergency CD.

Studies comparing at least 2 different IV dosing regimens of oxytocin during CD were eligible. Trials with coadministered interventions were eligible, provided that the use of cointerventions was identical in all trial arms.

Outcomes of interest

We prespecified 25 outcomes based on those used in the WHO recommendations on uterotonics for PPH prevention,[4] the PPH core outcome set,[11] and the 2019 Cochrane network meta-analysis on uterotonics for PPH prevention.[5] The primary review outcome was incidence of PPH ≥1000 mL, with secondary outcomes including PPH ≥500 mL, maternal death, severe maternal morbidity (intensive care unit [ICU] admissions), severe maternal morbidity (shock), use of additional uterotonics, satisfactory uterine tone, use of surgical or invasive nonsurgical interventions, blood transfusion, mean volumes of blood loss, change in hemoglobin measurements before vs after birth, any adverse maternal events (including nausea, vomiting, headache, hypotension, chest pain, myocardial ischemia, cardiac arrythmia, dyspnea, bradycardia, tachycardia, or water intoxication), breastfeeding at hospital discharge, maternal sense of well-being, and maternal satisfaction.

Information sources, search strategy, and study selection

A search strategy was developed in consultation with an information specialist (Supplemental Table 1). Between February 14, 2020, and February 19, 2020, we searched the following 7 electronic databases: Ovid MEDLINE, Embase, Global Index Medicus,

Cumulative Index of Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform. Recovered citations were de-duplicated using Endnote (Clarivate Analytics, Philadelphia, PA)[12] and imported into Covidence (Covidence, Melbourne, Australia)[13] for screening. Each unique citation was reviewed and independently assessed by 2 review authors (L.C.P., E.K.F., and M.C.) for inclusion, initially based on titles and abstracts and then on the full-text articles of potentially eligible citations. Disagreements were resolved through discussion or consultation with another reviewer (J.P.V.). We also screened the reference lists of all included studies, in addition to the reference list of the Gallos et al[5] network meta-analysis for additional eligible studies.

Data extraction and assessment of risk of bias

For each study, 2 reviewers (L.C.P., E.K.F., M.C.) double-extracted data using a predesigned and pretested electronic spreadsheet (Google Sheets). Data about the study design, year of publication, period of recruitment, number of participants, maternal age, gestational age, primary and secondary review outcomes, and potential effect modifiers (type of CD, previous oxytocin administration during childbirth, and previous risk for PPH) were extracted. Disagreements between the reviewers at the title and abstract, and full-text stages were 4% and 9%, respectively, and were resolved through discussion or consultation with another reviewer (J.P.V.). We attempted to contact the study authors for all studies for which further information was required.

Each included study was assessed for risk of bias by at least 2 review authors (L.C.P., E.K.F., M.C.). RCTs were assessed using the Cochrane Risk Of Bias 2.0 (ROB 2.0, Cochrane, London, United Kingdom) tool,[14] and NRSIs were assessed using the Risk Of Bias In Nonrandomized Studies of Interventions (ROBINS-I, Cochrane) tool.[15] We made an explicit judgment about the overall risk of bias for each included study. In addition, we assessed the risk of bias of blood loss measurements using a similar approach to Gallos et al[5] (Supplemental Table 2). Extracted data about the review outcomes from RCTs were entered into the Review Manager 5 software (Cochrane)[16] for the meta-analysis. Data from NRSIs were reported narratively.

Data synthesis

We identified the following 3 types of studies: comparative RCTs with ≥2 arms, dose-finding RCTs, and NRSIs.

Comparative randomized controlled trials.

For comparative RCTs, we first assessed trial populations and methods used between trials to judge whether they were sufficiently similar to warrant a meta-analysis. A random-effects model was used to assess all outcomes with >1 trial. Results from dichotomous data were presented as a summary risk ratio (RR) with 95% confidence intervals (CI) and as mean differences (MDs) for continuous data. For all meta-analyses we used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[17] to rate the certainty of evidence as very low, low, moderate, or high using GRADEpro software (Evidence Prime, Inc, Ontario, Canada).[18] We planned to assess publication bias using funnel plots if there were 10 or more studies included in the meta-analysis, however, this was not done because of the limited number of studies.

We conducted separate meta-analyses for (1) type of IV administration (bolus only, infusion only, or bolus plus infusion) and (2) total oxytocin dose administered. We calculated the total oxytocin dose for each trial arm by adding all preplanned doses of oxytocin described in the study methods, including any doses used in a bolus, short infusion, and maintenance infusion (studies were not included for analysis of total oxytocin dose if there was insufficient information to determine the total dose). Considering the available evidence (and to standardize the analyses), trial arms were grouped into 5 total oxytocin dose categories (<5 IU, 5−9 IU, 10−19 IU, 20−49 IU, and ≥50 IU) for comparison in pairwise analyses. In addition, among trials using bolus plus infusion regimens, we identified trials that studied the effects of using different initial bolus doses by varying the initial bolus dose while keeping the infusion component identical between trial arms. Hence, we also analyzed (3) the effects of different initial bolus doses among trials using bolus plus infusion regimens. To accomplish this, we grouped the initial bolus doses as <5 IU, 5 IU, or 10 IU for comparison in pairwise analyses.

In line with the 2019 international consensus statement recommendation of a 2- to 4-hour maintenance infusion,[8] we performed a subgroup analysis on studies that used a maintenance infusion between 2 and 4 hours only. Owing to limited available data, we were only able to perform this for the analysis of initial bolus doses in a bolus plus infusion regimen.

We planned to conduct subgroup analyses by type of CD (planned vs intrapartum), previous oxytocin administration, and previous risk of PPH, however, these were not possible because of limited available data. We performed sensitivity analyses for risk of bias (only including studies with an overall low risk of bias) and method of blood loss estimation (only including studies that used calculated or volumetric assessment of blood loss). When making statements on the effects of an intervention, we adopted standardized language derived from Santesso et al.[19]

Dose-finding trials and nonrandomized studies.

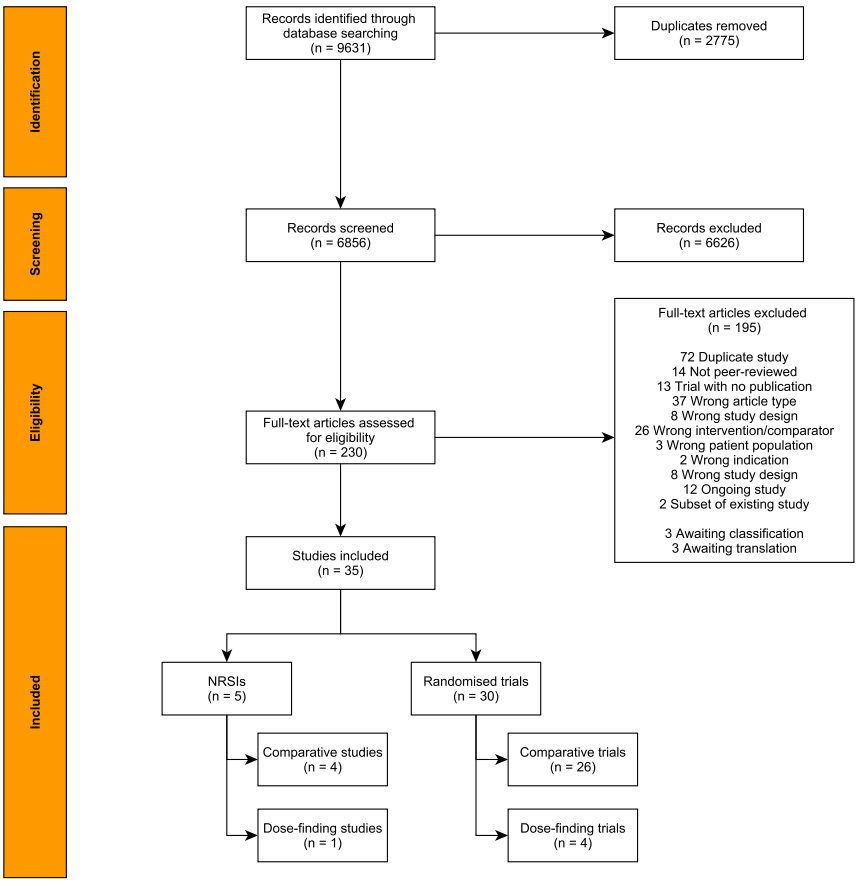
The dose-finding RCTs used a 1-arm up-and-down sequential allocation method in which the oxytocin dose for the next participant was adjusted according to the response of the preceding participant.[20] For example, if the first participant had a satisfactory response, the next participant was allocated either an equal or lower dose using a biased-coin technique. Dose-finding trials did not make explicit, pairwise comparisons between dosing regimens, hence findings from these trials were reported narratively. Eligible NRSIs were also reported narratively.

Results

Study selection and characteristics

The results of the search are summarized in the PRISMA flow diagram (Figure 1). We identified 9631 records of which 6626 records were excluded at the title and abstract screening stage and 195 at the full-text review stage. The most common reasons for exclusion were duplicate study (n=72) and wrong article type (n=37). No further articles were identified through screening of the reference lists. In total, 35 studies of 7333 women were included. We found 30 RCTs of which 26 were comparative RCTs and 4 were dose-finding RCTs. We found 5 NRSIs of which 4 were comparative and 1 was a dose-finding study. A summary of the study characteristics and an overview of study comparisons are provided in Tables 1 to 4 and Supplemental Table 3. Among the 26 comparative RCTs included, 9 were at an overall high risk for bias and 15 were at low risk for bias (Supplemental Figures 1 and 2); the 4 dose-finding RCTs were assessed to be at an overall high risk for bias. Of the 5 NRSIs, 2 were assessed to be at an overall critical risk of bias and the remaining 3 as at moderate risk (Supplemental Figures 3 and 4).

FIGURE 1
Flow diagram



PRISMA flow diagram.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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Comparative randomized controlled trials

We identified 26 comparative RCTs (64 trial arms) that included 5271 women. Of these, 19 RCTs were 2-arm trials, and 7 RCTs were multi-arm trials (ranging from 3–6 arms). Sample sizes ranged from 28–2069 women, and 23 trials included women undergoing planned CD only. The types of IV administrations used were bolus only (14 arms), infusion only (23 arms), and bolus plus infusion (27 arms). There were 26 different total doses of oxytocin used ranging from 1 IU–260 IU. The most common total doses were 5 IU (11 arms) and 10 IU (8 arms). We could not calculate the total dose for 3 of the studies.[25,27,35] Among those trial arms that used an infusion component, the total infusion duration ranged from 5 minutes to 24 hours, and the rate of oxytocin administration varied from 0.7 IU per hour to 120 IU per hour. Among the 5 trials that compared different initial bolus doses within a bolus plus infusion regimen, the initial bolus doses ranged from 0.5–10 IU.

Dose-finding trials and nonrandomized studies

We identified 4 dose-finding RCTs (180 women). The sample sizes ranged from 30–70 women. Two trials included women undergoing planned CD only and 1 trial included women undergoing intrapartum CD only. All studies used either an initial bolus or infusion followed by a maintenance infusion. We found 5 NRSIs that included 1840 women with sample sizes ranging from 41–1122 women. Of these, 4 were comparative studies (3 2-arm studies, 1 3-arm study) and 1 was a dose-finding study. The most common type of IV administration was bolus only (4 arms). Doses ranged from 3–80 IU with the most common dose being 5 IU (2 arms).

Outcomes

The most commonly reported outcomes were the use of additional uterotonics (28 studies) and mean blood loss (20 studies). No data were available for 7 outcomes (maternal deaths, ICU admissions, shock, water intoxication, breastfeeding after discharge, maternal sense of well-being, and maternal sense of satisfaction (Supplemental Table 4).

TABLE 1
Characteristics of included studies

First author, year	Study design	n	Country	CD type	Oxytocin dosing regimens						
Comparative randomized controlled trials					**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**All arms**
Bhattacharya et al,[21] 2013	2-arm RCT	80	India	Planned	Bolus 3 IU	Infusion 3 IU	—	—	—	—	Infusion (0.16 IU/min) after study period
Butwick et al,[22] 2010	5-arm RCT	75	United States	Planned	No bolus	Bolus 0.5 IU	Bolus 1 IU	Bolus 3 IU	Bolus 5 IU	—	Infusion of 10 IU over 2 h once adequate UT plus infusion (0.16 IU/min) after study period
Cecilia et al,[23] 2018	2-arm RCT	271	India	Both	Infusion 2.5 IU/h over 2–4 h	Infusion 10 IU/h over 8–12 h	—	—	—	—	—
Derbel et al,[24] 2016	2-arm RCT	87	Tunisia	Planned	Bolus 10 IU	Bolus 5 IU	—	—	—	—	Infusion of 25 IU over 3 h
Duffield et al,[25] 2017	2-arm RCT	51	United States	Planned	Infusion of 10 IU until discharge	Infusion of 60 IU until discharge	—	—	—	—	Bolus 1 IU
Ghulmiyyah et al,[26] 2017	3-arm RCT	189	Lebanon	Planned	20 IU over 30 min	30 IU over 30 min	40 IU over 30 min	—	—	—	Infusion of 30 IU then 20 IU then 10 IU for 24 h total
Golparvar et al,[27] 2014	2-arm RCT	84	Iran	Planned	Infusion 15 IU/h	Infusion 30 IU/h	—	—	—	—	—
Güngördük et al,[28] 2010	2-arm RCT	720	Turkey	Planned	Placebo infusion	Infusion of 30 IU over 4 h	—	—	—	—	Bolus 5 IU
Jonsson et al,[29] 2010	2-arm RCT	103	Sweden	Planned	Bolus 5 IU	Bolus 10 IU	—	—	—	—	—
Kajendran et al,[30] 2017	2-arm RCT	92	Sri Lanka	Planned	Infusion of 20 IU over 4 h	Placebo infusion	—	—	—	—	Bolus 5 IU
Kikutani et al,[31] 2003	2-arm RCT	90	Japan	Planned	Bolus 10 IU over 30 s	Infusion 10 IU over 5 min	—	—	—	—	—
Kim et al,[32] 2011	3-arm RCT	60	Korea	Planned	Infusion of 20 IU over 40 min	Bolus 2 IU plus infusion of 10 IU over 40 min	Bolus 5 IU plus infusion of 10 IU over 40 min	—	—	—	—

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TABLE 1
Characteristics of included studies *(continued)*

First author, year	Study design	n	Country	CD type	Oxytocin dosing regimens						
Comparative randomized controlled trials					**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**All arms**
King et al,[33] 2010	2-arm RCT	143	Canada	Both	Bolus 5 IU	Placebo bolus	—	—	—	—	Infusion of 40 IU over 30 min then infusion of 20 IU over 4 h
Kiran et al,[34] 2013	3-arm RCT	90	India	Planned	Bolus 0.5 IU	Bolus 1 IU	Bolus 2 IU	—	—	—	Infusion 20 IU over 2 h
Kovacheva et al,[35] 2015	2-arm RCT	60	United States	Planned	Bolus 3 IU every 3 min until adequate UT or maximum 3 boluses	Infusion of 30 IU until adequate UT	—	—	—	—	Infusion of 30 IU over 6 h
Munn et al,[36] 2001	2-arm RCT	321	United States	Intra	Infusion of 10 IU over 30 min	Infusion of 80 IU over 30 min	—	—	—	—	Infusion of 20 IU over 8 h
Murphy et al,[37] 2009	2-arm RCT	115	Scotland	Planned	Placebo infusion	Infusion of 30 IU over 4 h	—	—	—	—	Bolus 5 IU
Palacio et al,[38] 2011	2-arm RCT	104	Spain	Planned	Bolus 1 IU plus infusion of 2.5 IU/h for 24 h	Infusion of 20 IU at 700 mIU/min plus 10 IU/h for 24 h	—	—	—	—	—
Pinder et al,[39] 2002	2-arm RCT	34	United Kingdom	Planned	Bolus 5 IU	Bolus 10 IU	—	—	—	—	—
Qian et al,[40] 2019	6-arm RCT	145	China	Planned	No infusion	Infusion of 1 IU/h for 1 h	Infusion of 2 IU/h for 1 h	Infusion of 3 IU/h for 1 h	Infusion of 5 IU/h for 1 h	Infusion of 8 IU/h for 1 h	Bolus 1 IU
Sarna et al,[41] 1997	4-arm RCT	40	United States	Planned	Infusion of 5 IU at 1 IU/min	Infusion of 10 IU at 1 IU/min	Infusion of 15 IU at 1 IU/min	Infusion of 20 IU at 1 IU/min	—	—	—
Sartain et al,[42] 2008	2-arm RCT	80	Australia	Planned	Bolus 2 IU	Bolus 5 IU	—	—	—	—	Infusion of 40 IU over 4 h
Sheehan et al,[43] 2011	2-arm RCT	2069	Ireland	Planned	Placebo infusion	Infusion of 40 IU over 4 h	—	—	—	—	Bolus 5 IU
Taj and Ommid,[44] 2014	2-arm RCT	50	India	Planned	Bolus 10 IU over 15 s	Infusion of 10 IU over 5 min	—	—	—	—	—

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(continued)

TABLE 1
Characteristics of included studies *(continued)*

First author, year	Study design	n	Country	CD type	Oxytocin dosing regimens						
Comparative randomized controlled trials					**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**All arms**
Tariq and Syed,[45] 2018	2-arm RCT	90	Pakistan	Planned	Bolus 5 IU over 10 s	Infusion of 5 IU over 5 min	—	—	—	—	—
Thomas et al,[46] 2007	2-arm RCT	28	United Kingdom	Planned	Bolus 5 IU over 1 s	Infusion of 5 IU over 5 min	—	—	—	—	—

Dose-finding randomized trials					Initial dose	Maintenance infusion to all patients
Balki et al,[47] 2006	1-arm DF RCT	30	Canada	Intra	Starting bolus 0.5 IU Subsequently up or down by 0.5 IU (based on response of preceding patient)	Infusion of 40 mIU/min for up to 8 h
Carvalho et al,[48] 2004	1-arm DF RCT	40	USA	Planned	Starting bolus 0.5 IU Subsequently up or down by 0.5 IU (based on response of preceding patient)	Infusion of 40 mIU/min until discharge
George et al,[49] 2010	1-arm DF RCT	40	Canada	Planned	Starting infusion at 0.4 IU/min Subsequently up or down by 0.1 IU for 1 h (based on response of preceding patient)	Infusion of 30 IU until discharge
Lavoie et al,[50] 2015	2-arm DF RCT	70	—	Arm 1: intra; arm 2: planned	Starting infusion of 18 IU/h until end of CD Subsequently up or down by 3 IU/h (based on response of preceding patient)	Infusion of 3.6 IU/h until discharge

Nonrandomized studies of interventions					Arm 1	Arm 2	Arm 3	All arms
Ahmadi et al,[51] 2018	2-arm NRSI	150	Iran	—	Infusion of 80 IU	Infusion of 30 IU	—	—
Holleboom et al,[52] 2013	3-arm NRSI	1122	Netherlands	Planned	Bolus 5 IU	Bolus 10 IU	Bolus 5 IU plus infusion of 10 IU over 2 h	—
Pursche et al,[53] 2012	2-arm NRSI	454	Germany	Both	Bolus 3 IU plus infusion at 100 mL/h	Infusion with at least 120 mL/h	—	—
Terblanche et al,[54] 2017	2-arm NRSI	73	Australia	Planned	Bolus 3 IU	Bolus 5 IU	—	—
Beiranvand et al,[55] 2019	2-arm DF NRSI	41	Iran	Arm 1: intra; arm 2: planned	Bolus 1 IU bolus, plus 0.5 IU every min until adequate UT	—	—	Infusion 30 mU/min

CD, cesarean delivery; *DF*, dose-finding; *GA*, gestational age; *intra*, intrapartum; *IU*, international units; *NRSI*, nonrandomized studies of interventions; *RCT*, randomized controlled trial; *UT*, uterine tone.

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TABLE 2
Overview of study comparisons: type of intravenous administration

Type of IV administration	Bolus only	Infusion	Bolus plus infusion
Bolus only	No studies	5 RCTs (338 women, all 2-arm trials)[21,31,44–46]	5 RCTs (3141 women) • Four 2-arm trials[28,30,37,43] • One 6-arm trial[a,40] 1 NRSI (1122 women, 2-arm study)[b,52]
Infusion	—	No studies	5 RCTs (442 women) • Three 2-arm trials[32,35,38] • One 3-arm trial[c,32] • One 4-arm trial[d,22] 1 NRSI (454 women, 2-arm study)[53]
Bolus plus infusion	—	—	No studies

Dose-finding studies (4 RCTs, 1 NRSI) are not included in this table.

IV, intravenous; *NRSI*, nonradomized studies of intervention; *RCT*, randomized controlled trial.

[a] Six-arm study comparing bolus only with bolus plus infusion (B+I) vs B+I vs B+I vs B+I vs B+I; [b] Three-arm study comparing bolus only with bolus and B+I; [c] Three-arm study comparing infusion with B+I and B+I; [d] 4-arm study comparing infusion with B+I and B+I and B+I.

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TABLE 3
Overview of study comparisons: total oxytocin dose

Dose	<5 IU	5–9 IU	10–19 IU	20–49 IU	≥50 IU
<5 IU	No studies	1 RCT (145 women) • 1 IU vs 2 IU vs 3 IU vs 4 IU vs 6 IU vs 9 IU[40] 1 NRSI (73 women) • 3 IU vs 5 IU[54]	No studies	No studies	No studies
5–9 IU	—	No studies	3 RCTs (177 women) • 5 IU vs 10 IU[29,39] • 5 IU vs 10 IU vs 15 IU[41] 3 NRSI (1122 women) • 5 IU vs 10 IU vs 15 IU[52]	4 RCTs (2996 women) • 5 IU vs 35 IU[28,37] • 5 IU vs 45 IU[43] • 5 IU vs 25 IU[30]	No studies
10–19 IU	—	—	No studies	2 RCTs (331 women) • 10 IU vs 30 IU[23] • 12 IU vs 15 IU vs 20 IU[32]	No studies
20–49 IU	—	—	—	3 RCTs (257 women)[a] • 42 IU vs 45 IU[42] • 30 IU vs 35 IU[24] • 20.5 IU vs 21 vs 22 IU[34]	1 RCT (321 women) • 30 IU vs 100 IU[36] 1 NRSI (150 women) • 30 IU vs 80 IU[51]
≥50 IU	—	—	—	—	3 RCTs (436 women)[a] • 80 IU vs 90 IU vs 100 IU[26] • 60 IU vs 65 IU[33] • 61 IU vs 260 IU[38]

Four dose-finding studies (4 RCTs, 1 NRSI) and 3 RCTs were not included because the total oxytocin dose could not be calculated.

IU, international unit; *NRSI*, nonrandomized studies of intervention; *RCT*, randomized controlled trial.

[a] Studies compared outcomes within the same total oxytocin dose category and were not analyzed.

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TABLE 4
Overview of study comparisons: initial bolus dose in a bolus plus infusion regimen

Dose	<5 IU	5 IU	10 IU
<5 IU	1 RCT (90 women) • 0.5 IU vs 1 IU vs 2 IU[34]	3 RCTs (180 women) • 0.5 IU vs 1 IU vs 3 IU vs 5 IU[22] • 2 IU vs 5 IU[32] • 2 IU vs 5 IU[42]	No studies
5 IU	—	No studies	1 RCT (87 women) • 5 IU vs 10 IU[24]
10 IU	—	—	No studies

Dose-finding studies (4 RCTs, 1 NRSI) are not included in this table.

IU, international unit; *NRSI*, nonrandomized studies of intervention; *RCT*, randomized controlled trial.

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Synthesis of results

Meta-analysis.

Type of intravenous administration. A total of 15 RCTs (3921 women) compared different types of IV administration regimens (Table 2, Supplemental Table 5). The incidence of PPH ≥1000 mL was only reported for 1 comparison (bolus only vs bolus plus infusion).

Bolus only vs infusion only. In 5 RCTs (338 women), bolus only regimens were compared with infusion only regimens. No study reported on the outcome of incidence of PPH ≥1000 mL. The effects of either dosing regimen on the use of additional uterotonics, mean blood loss, or maternal adverse effects (nausea, vomiting, chest pain, and myocardial ischemia) are inconclusive because the certainty of evidence was very low. No other outcomes were reported.

Bolus only vs bolus plus infusion. In 5 RCTs (4580 women), bolus only regimens were compared with bolus plus infusion regimens. The effect of either dosing regimen on the outcome of incidence of PPH ≥1000 mL was inconclusive because the certainty of evidence was very low (4 trials of 2976 women; RR, 1.44; 95% CI, 0.75−2.76; very low certainty), although bolus only regimens slightly increased the mean blood loss (5 trials of 3068 women; MD, 52 mL; 95% CI, 0.4−104 mL; moderate certainty) (Figure 2) and decreased the incidence of satisfactory uterine tone (1 trial of 145 women; RR, 0.63; 95% CI, 0.41−0.95; low certainty) (Figure 3). There were no clear differences in the mean change in hemoglobin (3 trials of 2260 women; MD, −0.05 g/dL; 95% CI, −0.27 to 0.17 g/dL; high certainty) or incidence of blood transfusion (3 trials of 2870 women; RR, 1.55; 95% CI, 0.47−5.13; low certainty). The effects of either dosing regimen on the outcomes of incidence of PPH ≥500 mL, use of additional uterotonics, and maternal adverse effects (hypotension, nausea, and chest pain) were inconclusive because the certainty of evidence was very low. There were zero events reported for surgical or nonsurgical interventions, vomiting, bradycardia, tachycardia, and dyspnea. A sensitivity analysis on risk of bias (including only studies at an overall low risk of bias) suggested no clear difference in mean blood loss.

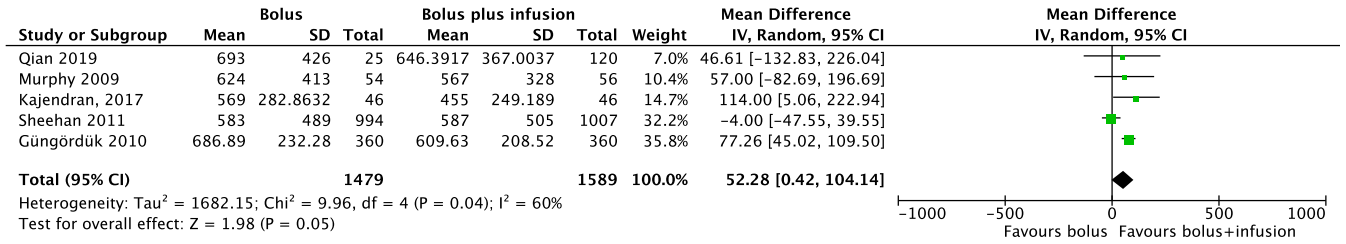
Infusion only vs bolus plus infusion. In 5 RCTs (442 women), infusion only regimens were compared with bolus plus infusion regimens. No study reported on the outcome of incidence of PPH ≥1000 mL. There were no clear differences in the incidence of satisfactory uterine tone (2 trials of 164 women; RR, 0.98; 95% CI, 0.90−1.06; low certainty), blood transfusion (1 trial of 145 women; RR, 0.35; 95% CI, 0.04−3.26; low certainty), or maternal adverse events (vomiting [1 trial of 60 women; RR, 0.50; 95% CI, 0.06−4.18; low certainty], headache [1 trial of 152 women; RR, 0.36; 95% CI, 0.01−8.71; low certainty], hypotension [2 trials of 263 women; RR, 0.60; 95% CI, 0.34−1.05; moderate certainty], cardiac arrythmia [1 trial of 60 women; RR, 1.50; 95% CI, 0.27−8.34; low certainty], and tachycardia [1 trial of 143 women; RR, 0.96; 95% CI, 0.06−15.04; low certainty]). The effects on use of additional uterotonics, mean blood loss, and nausea were inconclusive because the certainty of evidence was very low. There were zero events reported for surgical interventions, chest pain, and dyspnea.

Total oxytocin dose. A total of 17 RCTs (4663 women) compared different total oxytocin doses (Table 3, Supplemental Table 6). The outcome of the incidence of PPH ≥1000 mL was reported for 2 comparisons (<5 IU vs 5−9 IU and 5−9 IU vs 20−49 IU).

Total oxytocin dose of <5 IU vs 5−9 IU. One RCT[40] (145 women) compared a total oxytocin dose of <5 IU with 5−9 IU. It reported zero incidences of PPH ≥1000 mL with either dosing regimen. The effects on the use of additional uterotonics, satisfactory uterine tone, mean blood loss, or maternal adverse events (nausea, hypotension, chest pain) were inconclusive because the certainty of evidence was very low. There were zero events reported for blood transfusions, vomiting, bradycardia, tachycardia, and dyspnea.

Total oxytocin dose of 5−9 IU vs 10−19 IU. Three RCTs (177 women) compared a total oxytocin dose of 5−9 IU with 10−19 IU. No study reported on the incidence of PPH ≥1000 mL. The use of a total dose of 5−9 IU vs 10−19 IU may result in a large increase in the use of additional uterotonics (2 trials of 137 women; RR, 13.00; 95% CI, 1.75−96.37;

FIGURE 2
Bolus only vs bolus plus infusion: mean blood loss



CI, confidence interval; *IV*, intravenous; *SD*, standard deviation.

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low certainty) (Figure 4). There was no clear difference in myocardial ischemia (1 trial of 103 women; RR, 0.98; 95% CI, 0.14−6.70; low certainty). The effect on mean blood loss was inconclusive because the certainty of evidence was very low. There were zero events reported for hypotension.

Total oxytocin dose of 5−9 IU vs 20−49 IU. Four RCTs (2996 women), compared a total oxytocin dose of 5−9 IU with 20−49 IU. The effects of either dosing regimen on the outcomes of incidence of PPH ≥1000 mL, PPH ≥500 mL, use of additional uterotonics or blood transfusion, or mean blood loss were inconclusive because the certainty of evidence was very low. There was no clear difference in the change in hemoglobin (3 trials of 2260 women; MD, −0.05 g/dL; 95% CI, −0.27 to 0.17 g/dL; low certainty).

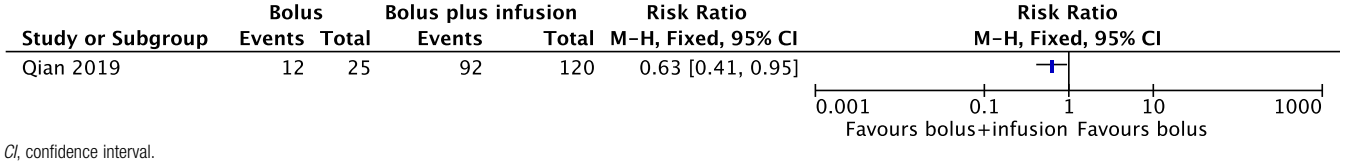
Total oxytocin dose of 10−19 IU vs 20−49 IU. Two RCTs (331 women) compared a total oxytocin dose of 10−19 IU with 20−49 IU. Neither study reported on the incidence of PPH ≥1000 mL. The use of a total dose of 10−19 IU compared with of 20−49 IU probably reduces chest pain (1 trial of 271 women; RR, 0.05; 95% CI, 0.00−0.81; moderate certainty) (Supplemental Figure 5). There were no clear differences in the incidence of blood transfusion (1 trial of 271 women; RR, 0.86; 95% CI, 0.28−2.62; low certainty), satisfactory uterine tone (1 trial of 271 women; RR, 1.05; 95% CI, 1.00−1.09; moderate certainty), or tachycardia (1 trial of 271 women; RR, 0.84; 95% CI, 0.26−2.69). The effects on the use of additional uterotonics, mean blood loss, nausea, or vomiting were inconclusive because the certainty of evidence was very low.

Total oxytocin dose of 20−49 IU vs ≥50 IU. One RCT[36] (321 women) compared a total oxytocin dose of 20−49 IU with ≥50 IU. It did not report on the incidence of PPH ≥1000 mL. The use of doses of 20−49 IU compared with ≥50 IU may increase the use of additional uterotonics (RR, 2.07; 95% CI, 1.42−3.01; low certainty) (Supplemental Figure 6). There were no clear differences in mean blood loss (MD, 20 mL; 95% CI, −14 to 54 mL; low certainty) or hypotension (RR, 1.05; 95% CI, 0.71−1.53; low certainty).

Different bolus doses in bolus plus infusion regimens. A total of 5 RCTs using oxytocin regimens of bolus plus infusion (357 women) compared different initial bolus doses while keeping the infusion component identical for both trial arms (Table 4, Supplemental Table 7).

Initial bolus dose of <5 IU vs 5 IU in a bolus plus infusion regimen. In 3 RCTs (180 women) in which a bolus plus infusion regimen was used, an initial bolus dose of <5 IU was compared with that of 5 IU. No study reported on the incidence of PPH ≥1000 mL. Data from all 3 trials showed that initial bolus doses of <5 IU may reduce nausea (RR, 0.29; 95% CI, 0.10−0.81; low certainty) (Supplemental Figure 7), but there were no clear differences in the use of additional uterotonics (RR, 1.08; 95% CI, 0.51−2.31; low certainty) or vomiting (RR, 0.23; 95% CI, 0.05−1.04; low certainty). The effect on mean blood loss was very uncertain owing to very low certainty about the evidence. There were zero events reported for surgical or nonsurgical interventions, blood transfusions, and maternal adverse events (chest pain, cardiac arrythmia, dyspnea, hypotension).

FIGURE 3
Bolus only vs bolus plus infusion: satisfactory uterine tone



CI, confidence interval.

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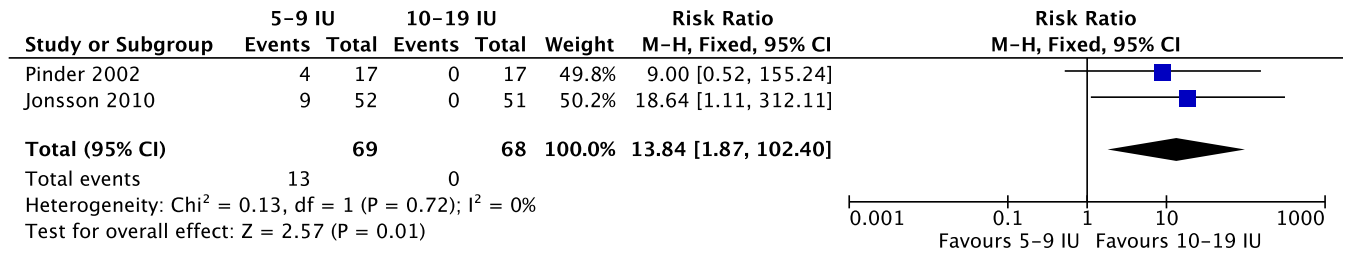
FIGURE 4
Total oxytocin dose of 5–9 IU vs 10–19 IU: use of additional uterotonics



CI, confidence interval.

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Initial bolus dose of 5 IU vs 10 IU in a bolus plus infusion regimen. One RCT[24] (87 women) that employed a bolus plus infusion regimen compared an initial bolus dose of 5 IU with 10 IU. It did not report on the incidence of PPH ≥1000 mL and there were no clear differences in mean blood loss (MD, 2 mL; 95% CI, −135 to 138 mL; low certainty), cardiac arrythmia (RR, 0.34; 95% CI, 0.01−8.14; low certainty), or chest pain (RR, 0.41; 95% CI, 0.08−2.00; low certainty). There were zero events reported for surgical or nonsurgical interventions and dyspnea.

We were largely unable to perform sensitivity and subgroup analyses owing to limited available data. However, where data permitted these analyses, no significant effects were found except where otherwise described.

Narrative synthesis.

We reviewed dose-finding RCTs and NRSIs separately. Findings from these studies are inconclusive, however, we report the main findings below. The results were not reported as statistically significant unless otherwise noted.

Dose-finding studies. A total of 4 dose-finding RCTs (180 women) studied the different initial doses required to initiate uterine contraction when followed by a maintenance infusion. No study reported on the incidence of PPH ≥1000 mL. The studies found that small doses (0.3 IU as a bolus or 0.27−0.29 IU/min as a short infusion) may be adequate to prevent uterine atony during planned CD[48–50] and that higher doses of oxytocin may be required during intrapartum CD regardless of the type of administration.[47,50] One dose-finding NRSI[55] (83 women) reported that small doses (1 IU as a bolus) may be adequate to prevent uterine atony, with higher doses needed during intrapartum CD. Hypotension, secondary to oxytocin administration, was noted in all studies, however, was not explored in relation to specific doses or types of IV administration regimens.

Nonrandomized studies.

Type of intravenous administration. One study[52] (1122 women, critical risk of bias) compared bolus only with bolus plus infusion regimens. It suggested that more women who received bolus only regimens experienced PPH ≥1000 mL than women who received bolus plus infusion regimens, greater use of additional uterotonics, and increased incidence in blood transfusions. There were no significant differences reported for any other outcomes.[52] Another study[53] (454 women, moderate risk of bias) compared infusion only with bolus plus infusion regimens. It did not report on the incidence of PPH ≥1000 mL but suggested that women who received infusion only regimens experienced a greater overall decrease in hemoglobin levels.

Total oxytocin dose. One study[54] (73 women, moderate risk of bias) compared a total oxytocin dose of 3 IU with that of 5 IU. It did not report on the incidence of PPH ≥1000 mL but suggested more women who received 5 IU experienced vomiting when compared with women who received 3 IU. One study[52] (1122 women, critical risk of bias) compared a total oxytocin dose of 5 IU with that of 10 IU and 15 IU. It suggested that increased doses of oxytocin may result in less PPH ≥1000 mL, the use of additional uterotonics and blood transfusions, and may lead to more satisfactory uterine tone.[52] One study[51] (150 women, critical risk of bias) compared a total oxytocin dose of 30 IU with that of 80 IU. It did not report on the incidence of PPH ≥1000 mL but suggested that 30 IU may lead to a statistically significant increase in the use of additional uterotonics and a decrease in satisfactory uterine tone. No significant differences were reported for any other outcomes including hypotension.

Comment

Main findings

We identified 35 studies of 7333 women comparing different IV oxytocin regimens for PPH prevention following CD. The evidence in general was limited and data were lacking for most of the review outcomes, with the data from 11 studies at high or critical risk of bias. We did not find any clear differences in the incidence of PPH ≥1000 mL, although data were sparse for this outcome. Bolus plus infusion regimens are possibly superior to bolus only regimens in terms of a small reduction in mean blood loss (around 52 mL) and increased uterine

tone, although these findings were based on a few trials. In general, we found no clear indication of a superior total oxytocin dose (largely because of insufficient evidence). Although we found doses of 10−19 IU is possibly better than doses of 5−9 IU in terms of decreasing the use of additional uterotonics, there were limited data on adverse maternal events (particularly hypotension). Of interest, both studies used in the meta-analysis of this outcome exclusively compared 5 IU with 10 IU in a bolus only regimen.

Oxytocin regimens were described using varying time intervals, which complicated meaningful comparison. However, available evidence suggests that when administering oxytocin in a bolus plus infusion regimen, initial bolus doses of <5 IU may lead to less nausea, but the effects of lower vs higher initial bolus doses on blood loss are not known. The infusion component of bolus plus infusion regimens most commonly continued for 2−4 hours.

Findings from nonrandomized studies, although not conclusive owing to a greater susceptibility to bias, were broadly consistent with the findings of meta-analyses on RCTs. These generally indicated that bolus plus infusion regimens may be superior to bolus only regimens and that higher oxytocin doses may be more effective but can increase adverse maternal events. Among the bolus plus infusion regimens, 4 dose-finding RCTs reported that small initial doses (0.3 IU as a bolus or 0.27−0.29 IU/min as a short infusion) may be adequate to prevent uterine atony during planned CD,[48−50] with higher doses required at intrapartum CD,[47,50] but the evidence was not conclusive and should be interpreted with caution.

Comparison with existing literature

Our findings are broadly consistent with previous work on IV oxytocin dosing regimens for PPH prevention following at CD, including a 2012 systematic review[7] of 7 RCTs (626 women) and a 2011 literature review.[6] Both reviews recommended the use of a small initial bolus dose (ranging between 0.3 and 3 IU)[6,7] with 1 review further recommending a bolus plus infusion regimen.[7] Both reviews further reported more adverse hemodynamic events with higher doses of oxytocin, which is consistent with our findings. Our findings are compatible with a 2019 international consensus statement,[8] which recommends using a 1 IU bolus followed by a 2.5−7.5 IU/h infusion over 2−4 hours and the WHO recommendation of 10 IU oxytocin administered IV or intramuscular during all births with doses divided into a small initial IV bolus with subsequent infusion during CD.[4] However, it is evident that good-quality trials comparing different oxytocin dosing regimens are needed to guide practice. It is noteworthy to mention that national guidelines vary (Supplemental Table 8), probably reflecting the lack of clear evidence to guide practice. The 2017 American College of Obstetricians and Gynecologists guidelines recommend using a dilute IV infusion (bolus dose of 10 IU) for PPH prevention without specification for mode of delivery.[57] Australian guidelines only recommend prophylactic oxytocin for all births without specifying a dosing regimen.[61] Carbetocin is recommended in Canada during planned CD,[60] and a bolus only oxytocin regimen is recommended in the United Kingdom.[58] French guidelines recommend a oxytocin bolus plus infusion regimen during CD, however, suggest an initial bolus dose of 5−10 IU.[59]

Strengths and limitations

We used a systematic and methodologically robust approach to searching and analyzing literature without date or language restrictions. We included both randomized and nonrandomized studies, which allowed for a more thorough and nuanced investigation of oxytocin dosing regimens. We also prespecified outcomes that aligned with WHO priority outcomes[4] and the PPH core outcome set[11] and used the latest and more sophisticated iterations of the Cochrane risk of bias tools (ROB 2.0 and ROBINS-I).[14,15]

Despite this, evidence was generally limited for most outcomes. In a network meta-analysis by Gallos et al[5] in which different uterotonic options were compared, the authors similarly described inadequate reporting of adverse events in trials of uterotonics for PPH prevention.[5] The international consensus statement by Heesen et al[8] also called for further large studies on this topic.[8] Any such trials should be sufficiently powered for important health-related outcomes and should clearly specify the dosing regimen. Specifically, trials comparing different oxytocin doses of bolus plus infusion regimens should be conducted. We consider it particularly important that future trials should report on the outcome of PPH ≥1000 mL, an important outcome for clinical guideline decision making.

We also found hypotension to be a poorly studied outcome, despite dose-dependent hypotension being well described.[21,29,42,46,62] Among RCTs, the effects of different dosing regimens on hypotension were generally either inconclusive or equivocal. No NRSI reported significant differences in the incidence of hypotension. However, it would not seem unreasonable to expect an increased incidence of hypotension with higher doses (particularly with bolus regimens), and it is likely that the combination of a bolus plus infusion regimen allows doses to exceed 5 IU while avoiding significant hemodynamic instability. Indeed, we consider it particularly important to prioritize research in this area.

We also did not find any clear evidence of diminishing returns from increasing doses and/or longer time periods of infusion despite it also being well described.[22,26] Again, this was largely because of lack of good-quality data and is an area for which further research is required.

We identified a wide range of dosing regimens that added to the complexity of this analysis and likely contributed to high heterogeneity. Although we aimed to standardize comparisons by using total oxytocin dose, we were not able to account for other factors such as rate of oxytocin administration or total infusion time. We acknowledge that our dose categories are somewhat arbitrary, although necessary to standardize and

interpret comparisons. We also tried to minimize the effect of subjective judgments on blood loss by including this in our risk of bias assessment and performing sensitivity analyses.

Finally, the majority of studies included only women undergoing planned CD with low risk of PPH. Hence, these findings may not be generalizable to other, higher-risk groups of women who may require a different oxytocin regimen.

Conclusions and implications

Based on current evidence, the most appropriate oxytocin regimen may be bolus plus infusion and an initial bolus of <5 IU, although further trials are needed to confirm these conclusions. Bolus only regimens of 10 IU vs 5 IU may decrease the use of additional uterotonics, however, further research is required to understand the implications on adverse events, particularly hypotension. In the absence of more robust evidence, many current guidelines on PPH prevention following CD may warrant reconsideration. Further research is required, particularly in women at high risk for PPH, for other important outcomes such as adverse maternal events, breastfeeding, and maternal well-being and satisfaction.

Final conclusion

This systematic review and meta-analysis of IV oxytocin dosing regimens for PPH prevention during CDs identified a lack of data for several important outcomes. Future well-designed studies are required to identify an optimal oxytocin dosing regimen for women undergoing CD. Nevertheless, available data suggest that an IV bolus plus infusion regimen, with an initial bolus dose of <5 IU, may be preferable. However, the degree of certainty for the evidence was generally low, and further research is required to identify the optimal oxytocin regimen for PPH prevention during CDs. ■

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APPENDIX A
PRISMA checklist

Section/topic	R	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2–3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2–3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021. *(continued)*

APPENDIX A
PRISMA checklist *(continued)*

Section/topic	R	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3–4 & Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4, Supplemental Figures 1–4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplemental Tables 5–7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	4, 9–11, Supplemental Tables 5–7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplemental Figures 1–4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	4, 9–11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11–13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12–13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

For more information, visit: www.prisma-statement.org.

Supplemental Reference

Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

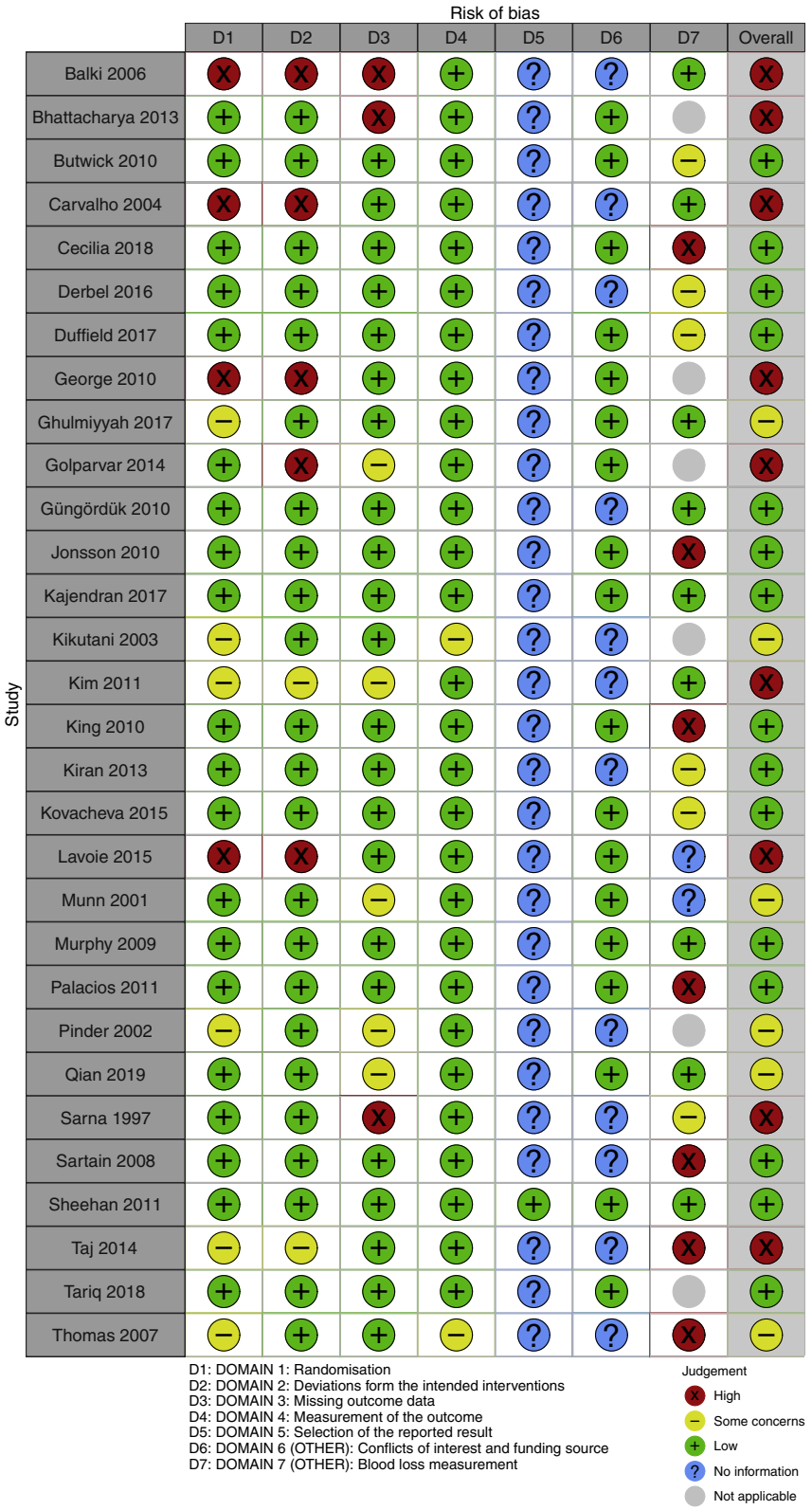
APPENDIX B
Deviations from protocol

Protocol	Deviation	Justification
Primary outcomes: PPH ≥500 mL and PPH ≥1000 mL	PPH ≥500 mL downgraded from primary outcome to secondary outcome	We opted to downgrade PPH ≥500 mL from a primary to a secondary outcome, considering that the definition of PPH after CD is PPH ≥1000 mL (as distinct from PPH after vaginal birth).
	Included dyspnea and chest pain as additional secondary outcomes	Additional adverse events reported in some trials.
Include only third stage administration of oxytocin	Included administration of oxytocin at or around third stage	Practicality considerations means oxytocin not always able to be delivered at third stage during CD.
Random-effects model if I^2 >30%	Random-effects model for all analyses with >1 trial	Given large heterogeneity of trials and as per Cochrane handbook, random-effects model provided a more conservative estimate.
Specific comparisons made between high dose vs low dose bolus, and high dose vs low dose infusion	We further divided the comparison of studies into (1) type of IV administration and (2) total oxytocin dose using the categories of <5 IU, 5–9 IU, 10–19 IU, 20–49 IU, ≥50 IU. Among studies comparing a bolus plus infusion regimen, we further compared various initial bolus doses when followed by an infusion.	The wide range of oxytocin regimens identified meant that our original approach of high and low dose was not practical nor informative.
	GRADE approach used to rate certainty of evidence.	More accurately report study findings and draw conclusions from the data.
	Subgroup analysis for studies with maintenance infusions lasting 2–4 h included	Explore hypothesis proposed by Heesen et al[8] that maintenance infusion should be run for 2–4 h.

CD, cesarean delivery; *GRADE*, Grading of Recommendations, Assessment, Development, and Evaluations; *PPH*, postpartum hemorrhage.

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

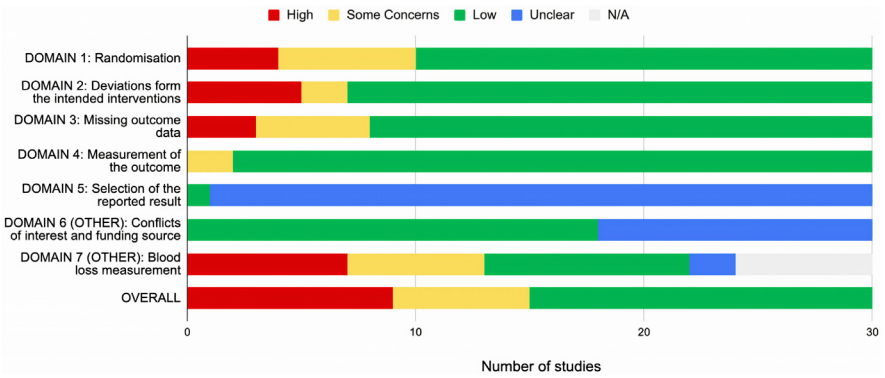
SUPPLEMENTAL FIGURE 1
Randomized trials: risk of bias assessment by study



Generated using robvis.[56]

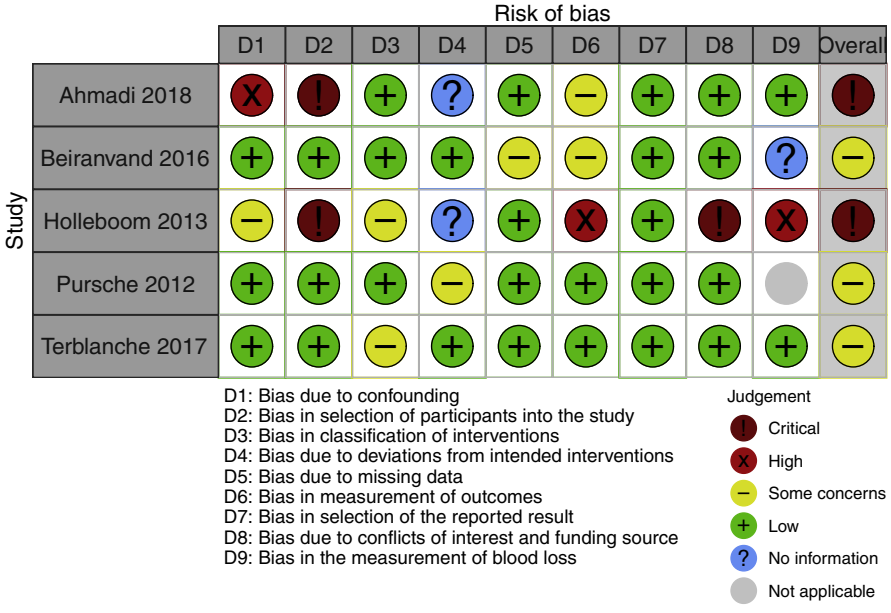
Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

SUPPLEMENTAL FIGURE 2
Comparative randomized trials: risk of bias by domain



Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

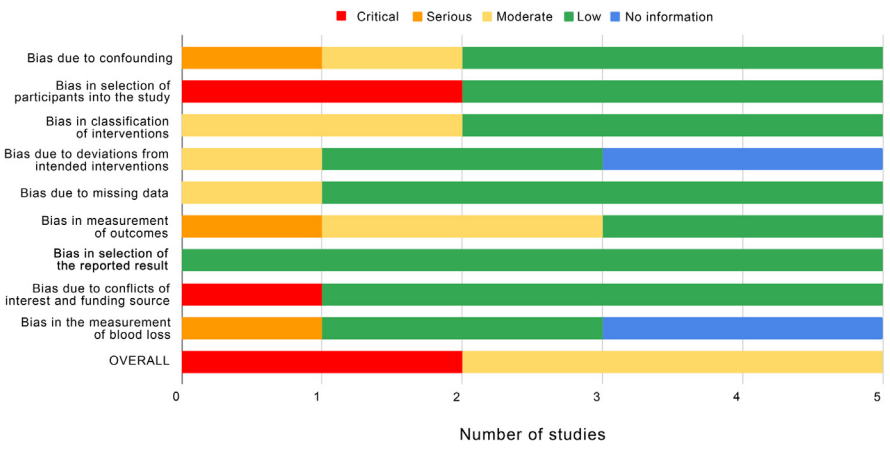
SUPPLEMENTAL FIGURE 3
Nonrandomised studies of interventions: risk of bias by study



Generated using robvis.[56]

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

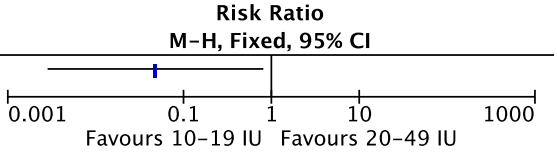
SUPPLEMENTAL FIGURE 4
Nonrandomized studies of interventions: risk of bias by domain



Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

SUPPLEMENTAL FIGURE 5
Total oxytocin dose of 10–19 IU vs 20–49 IU: chest pain

Study or Subgroup	10–19 IU Events	10–19 IU Total	20–49 IU Events	20–49 IU Total	Risk Ratio M–H, Fixed, 95% CI
Cecilia 2018	0	135	10	136	0.05 [0.00, 0.81]

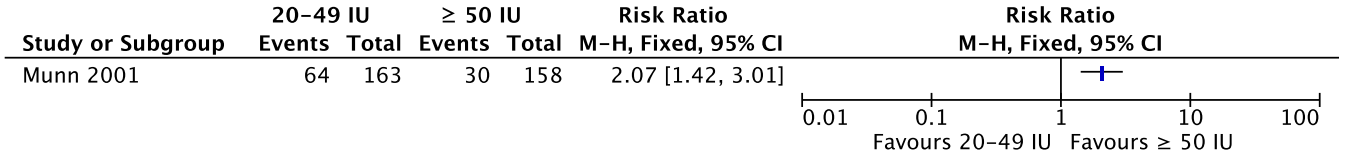


CI, confidence interval; *IU*, international unit.

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

SUPPLEMENTAL FIGURE 6

Total oxytocin dose of 20–49 IU vs ≥50 IU: use of additional uterotonics

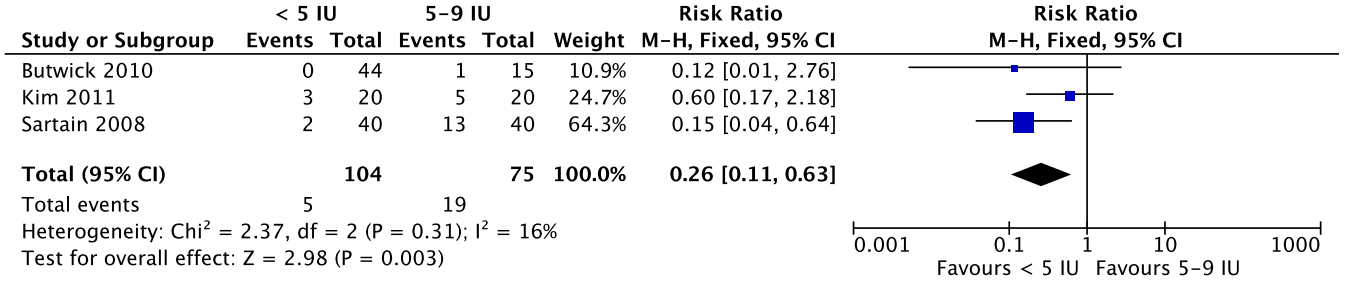


CI, confidence interval; *IU*, international unit.

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

SUPPLEMENTAL FIGURE 7

Initial bolus dose of <5 IU vs 5–9 IU: nausea



CI, confidence interval; *IU*, international unit.

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 1
Search strategy

Database(s): Ovid MEDLINE(R) and Epub ahead of print, in-process, and other nonindexed citations and daily 1946 to February 14, 2020

Number	Searches	Results
1	exp Oxytocin/ or (oxytocin or ocytocin or syntocinon or pitocin or oxytocic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	28,066
2	exp Cesarean Section/ or (c?esarean or csection* or c section* or abdominal delivery or elective delivery or CS).mp.	129,383
3	exp Postpartum Hemorrhage/	6910
4	(h?em?or?hag* or pph or (blood adj2 loss) or bleed* or uterine atony or atonic uterus).mp.	538,153
5	3 or 4	538,153
6	exp drug administration routes/	603,411
7	((oxytocin or oxytocic or syntocinon or pitocin or drug or drugs) adj5 (administ* or delivery or route or routes or dose or doses or dosing or dosage or dosages or intravenous or bolus or infusion or iv)).mp.	876,861
8	6 or 7	1,338,847
9	1 and 2 and (5 or 8)	1565
Database(s): Embase Classic+Embase 1947 to February 14, 2020		
1	exp Oxytocin/ or (oxytocin or ocytocin or syntocinon or pitocin or oxytocic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	44,929
2	exp Cesarean Section/ or (c?esarean or csection* or c section* or abdominal delivery or elective delivery or CS).mp.	204,077
3	exp Postpartum Hemorrhage/	14,406
4	(h?em?or?hag* or pph or (blood adj2 loss) or bleed* or uterine atony or atonic uterus).mp.	968,513
5	3 or 4	968,513
6	exp drug administration routes/	1,222,962
7	((oxytocin or oxytocic or syntocinon or pitocin or drug or drugs) adj5 (administ* or delivery or route or routes or dose or doses or dosing or dosage or dosages or intravenous or bolus or infusion or iv)).mp.	3,561,354
8	6 or 7	3,569,315
9	1 and 2 and (5 or 8)	4631

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021. *(continued)*

SUPPLEMENTAL TABLE 1
Search strategy *(continued)*

Database(s): Ovid MEDLINE(R) and Epub ahead of print, in-process, and other nonindexed citations and daily 1946 to February 14, 2020

Number	Searches	Results
1	exp Oxytocin/ or (oxytocin or ocytocin or syntocinon or pitocin or oxytocic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	44,929
2	exp Cesarean Section/ or (c?esarean or csection* or c section* or abdominal delivery or elective delivery or CS).mp.	204,077
3	exp Postpartum Hemorrhage/	14,406
Database: CINAHL Complete		
Interface: EBSCOhost Research Databases		
Search Screen: Advanced Search		
Date: February 14, 2020		
(MM "Oxytocin") or (oxytocin or ocytocin or syntocinon or pitocin or oxytocic) AND		
(MH "Cesarean Section+") or (c#esarean or csection* or c section* or abdominal delivery or elective delivery or CS) AND		
((MH "Postpartum Hemorrhage") or (h#em#or#hag* or pph or (blood N2 loss) or bleed* or uterine atony or atonic uterus)) or ((MH "Drug Administration+") or (oxytocin or oxytocic or syntocinon or pitocin or drug or drugs) N5 (administ* or delivery or route or routes or dose or doses or dosing or dosage or dosages or intravenous or bolus or infusion or iv))		
(797 results)		
Global Index Medicus, February 14, 2020		
tw:((tw:(oxytocin OR ocytocin OR syntocinon OR pitocin OR oxytocic)) AND (tw:(c?esarean OR csection* OR c section* OR abdominal delivery OR elective delivery OR cs)) AND (tw:(h?em?or?hag* OR pph OR blood loss OR loss of blood OR bleed* OR uterine atony OR atonic uterus OR administ* OR delivery OR route OR routes OR dose OR doses OR dosing OR dosage OR dosages OR intravenous OR bolus OR infusion OR iv)))		
(686 results)		
CENTRAL		
Search Name: MDRP (19 Feb)		
Date Run: February 19, 2020, 02:16:59 PM		
ID	**Search**	**Hits**
#1	MeSH descriptor: [Oxytocin] explode all trees	1802
#2	((oxytocin or ocytocin or syntocinon or pitocin or oxytocic)):ti,ab,kw	4706
#3	MeSH descriptor: [Cesarean Section] explode all trees	2989
#4	((c?esarean or csection* or "c section*" or "abdominal delivery" or "elective delivery" or CS)):ti,ab,kw	18,468
#5	MeSH descriptor: [Postpartum Hemorrhage] explode all trees	621
#6	((h*em*or*hag* or pph or "blood NEAR/2 loss" or bleed* or "uterine atony" or "atonic uterus")):ti,ab,kw	63,385
#7	MeSH descriptor: [Administration, Intravenous] explode all trees	18,229
#8	(((oxytocin or oxytocic or syntocinon or pitocin or drug or drugs) NEXT/5 (administ* or delivery or route or routes or dose or doses or dosing or dosage or dosages or intravenous or bolus or infusion or iv))):ti,ab,kw	149,407

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021. *(continued)*

SUPPLEMENTAL TABLE 1
Search strategy *(continued)*

ID	Search	Hits
#9	#1 or #2	4706
#10	#3 or #4	18,468
#11	#5 or #6	63,385
#12	#7 or #8	162,486
#13	#9 and #10 and (#11 or #12)	1048
ICTRP, February 19, 2020		
Oxytocin AND hemorrhage (207)		
Oxytocin AND dose (163)		
Oxytocin AND bleed (191)		
ClinicalTrials.gov, February 19, 2020		
oxytocin (other terms) | Post Partum Hemorrhage (condition) (151)		
oxytocin (other terms) | Bleed (condition) (178)		
oxytocin (other terms) | Caesarean (condition) | Dose (intervention) (41)		

ICTRP, International Clinical Trials Registry Platform; *MeSH*, medical subject headings.

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 2
Assessment of risk of bias of methods of measuring blood loss

ROB assessment (RCTs)	ROB assessment (NRSIs)	Description
Low	Low	Objective measurements such as calculated blood loss, weighing sponges or volumetric assessment
High	Critical	Subjective measurement such as clinical or visual estimates
Medium	Moderate	Mixture of objective and subjective measurements
Unclear	Unclear	Unspecified methods of measurement

NRSI, nonrandomized studies of intervention; *RCT*, randomized controlled trial.

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 3

Dosing regimens of all included studies

Author, year	n	Oxytocin dosing regimens												
		Arm 1		Arm 2		Arm 3		Arm 4		Arm 5		Arm 6		
Comparative RCTs		Study dose	30 min[a]	Study dose	30 min[a]	Study dose	30 min[a]	Study dose	30 min[a]	Study dose	30 min[a]	Study dose	30 min[a]	All arms
Bhattacharya et al,[21] 2013	80	Bolus 3 IU		Infusion of 3 IU		—		—		—		—		Infusion (0.16 IU/min) after study period
Butwick et al,[22] 2010	75	Bolus 0 IU		Bolus 0.5 IU		Bolus 1 IU		Bolus 3 IU		Bolus 5 IU		—		Infusion 10 IU over 2 h once adequate UT plus infusion (0.16 IU/min) after study period
Cecilia et al,[23] 2018	271	2.5 IU/h over 2–4 h	1.25 IU	10 IU/h over 8–12 h	5 IU	—		—		—		—		—
Derbel et al,[24] 2016	87	10 IU	14 IU	5 IU	9 IU	—		—		—		—		Infusion of 25 IU over 3 h
Duffield et al,[25] 2017	51	Infusion 10 IU until d/c	NE[b]	Infusion of 60 IU until d/c	NE[b]	—		—		—		—		Bolus 1 IU
Ghulmiyyah et al,[26] 2017	189	20 IU over 30 min		30 IU over 30 min		40 IU over 30 min		—		—		—		Infusion of 30 IU then 20 IU then 10 IU for 24 h total
Golparvar et al,[27] 2014	84	15 IU/h	7.5 IU	30 IU/h	15 IU	—		—		—		—		—
Güngördük et al,[28] 2010	720	Placebo infusion	5 IU	30 IU over 4 h	12.5 IU	—		—		—		—		Bolus 5 IU
Jonsson et al,[29] 2010	103	5 IU		10 IU		—		—		—		—		—
Kajendran et al,[30] 2017	92	20 IU over 4 h	10 IU	Placebo infusion	5 IU	—		—		—		—		Bolus 5 IU
Kikutani et al,[31] 2003	90	Bolus 10 IU		Infusion 10 IU		—		—		—		—		—
Kim et al,[32] 2011	60	20 IU over 40 min	15 IU	Bolus 2 IU plus infusion of 10 IU over 40 min	9.5 IU	Bolus 5 IU plus infusion of 10 IU over 40 min	12.5 IU	—		—		—		—

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

(continued)

SUPPLEMENTAL TABLE 3

Dosing regimens of all included studies *(continued)*

Author, year	n	Oxytocin dosing regimens												
		Arm 1		Arm 2		Arm 3		Arm 4		Arm 5		Arm 6		
Comparative RCTs		Study dose	30 min[a]	Study dose	30 min[a]	Study dose	30 min[a]	Study dose	30 min[a]	Study dose	30 min[a]	Study dose	30 min[a]	All arms
King et al,[33] 2010	143	Bolus 5 IU	45 IU	Placebo bolus	40 IU	—		—		—		—		Infusion of 40 IU over 30 min then infusion of 20 IU over 4 h
Kiran et al,[34] 2013	90	Bolus 0.5	5.5 IU	Bolus 1 IU	6 IU	Bolus 2 IU	7 IU	—		—		—		Infusion of 20 IU over 2 h
Kovacheva et al,[35] 2015	60	Bolus 3 IU every 3 min until adequate UT or max of 3 boluses	NE[b]	Infusion of 30 IU until adequate UT	NE[b]	—		—		—		—		Infusion of 30 IU over 6 h
Munn et al,[36] 2001	321	Infusion of 10 IU over 30 min		Infusion of 80 IU over 30 min		—		—		—		—		Infusion of 20 IU over 8 h
Murphy et al,[37] 2009	115	Placebo infusion	5 IU	Infusion of 30 IU over 4 h	8.75 IU	—		—		—		—		Bolus 5 IU
Palacio et al,[38] 2011	104	Bolus 1 IU plus infusion at 2.5 IU/h for 24 h	2.125 IU	Infusion of 20 IU at 700 mIU/min plus 10 IU/h for 24 h	21 IU	—		—		—		—		—
Pinder et al,[39] 2002	34	Bolus 5 IU		Bolus 10 IU		—		—		—		—		—
Qian et al,[40] 2019	145	No infusion	1 IU	Infusion of 1 IU/h for 1 h	1.5 IU	Infusion of 2 IU/h for 1 h	2 IU	Infusion of 3 IU/h for 1 h	2.5 IU	Infusion of 5 IU/h for 1 h	3.5 IU	Infusion of 8 IU/h for 1 h	5 IU	Bolus 1 IU
Sarna et al,[41] 1997	40	Infusion of 5 IU at 1 IU/min		Infusion of 10 IU at 1 IU/min		Infusion of 15 IU at 1 IU/min		Infusion of 20 IU at 1 IU/min		—		—		—
Sartain et al,[42] 2008	80	Bolus 2 IU	7 IU	Bolus 5 IU	10 IU	—		—		—		—		Infusion of 40 IU over 4 h
Sheehan et al,[43] 2011	2069	Placebo infusion	5 IU	Infusion of 40 IU over 4 h	10 IU	—		—		—		—		Bolus 5 IU

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

(continued)

SUPPLEMENTAL TABLE 3

Dosing regimens of all included studies *(continued)*

Author, year	n	Oxytocin dosing regimens												
		Arm 1		Arm 2		Arm 3		Arm 4		Arm 5		Arm 6		
Comparative RCTs		**Study dose**	**30 min[a]**	**Study dose**	**30 min[a]**	**Study dose**	**30 min[a]**	**Study dose**	**30 min[a]**	**Study dose**	**30 min[a]**	**Study dose**	**30 min[a]**	**All arms**
Taj and Ommid,[44] 2014	50	Bolus 10 IU over 15 s		Infusion of 10 IU over 5 min		—		—		—		—		—
Tariq and Syed,[45] 2018	90	Bolus 5 IU over 10 s		Infusion of 5 IU over 5 min		—		—		—		—		—
Thomas et al,[46] 2007	28	Bolus 5 IU over 1 s		Infusion of 5 IU over 5 min		—		—		—		—		—

Dose-finding randomized trials		**Initial dose (Dose in 30 min not estimable for all studies in this category)**	**Maintenance infusion to all patients**
Balki et al,[47] 2006	30	Starting bolus 0.5 IU Subsequently up or down by 0.5 IU (based on response of preceding patient)	Infusion 40 mU/min for up to 8 h
Carvalho et al,[48] 2004	40	Starting bolus 0.5 IU Subsequently up or down by 0.5 IU (based on response of preceding patient)	Infusion 40 mU/min until discharge
George et al,[49] 2010	40	Starting infusion at 0.4 IU/min Subsequently up or down by 0.1 IU for 1 h (based on response of preceding patient)	Infusion 30 IU until discharge
Lavoie et al,[50] 2015	70	Starting infusion 18 IU/h until end CD Subsequently up or down by 3 IU/h (based on response of preceding patient)	Infusion 3.6 IU/h until discharge

Nonrandomized studies of interventions		**Arm 1**		**Arm 2**		**Arm 3**		
		Study dose	**30 min[a]**	**Study dose**	**30 min[a]**	**Study dose**	**30 min[a]**	**All arms**
Ahmadi et al,[51] 2018	150	Infusion 80 IU	NE[b]	Infusion 30 IU	NE[b]	—		—
Holleboom et al,[52] 2013	1122	Bolus 5 IU		Bolus 10 IU		Bolus 5 IU plus infusion of 10 IU over 2 h	7.5 IU	—
Pursche et al,[53] 2012	454	Bolus 3 IU plus infusion of 3 IU in 500 mL at 100 mL/h	3.3 IU	Infusion with at least 120 mL/h	NE[b]	—		—
Terblanche et al,[54] 2017	73	Bolus 3 IU		Bolus 5 IU		—		—
Beiranvand et al,[55] 2019	41	Bolus 1 IU bolus, plus 0.5 IU every min until adequate UT	NE[b]	—		—		Infusion at 30 mU/min

CD, cesarean delivery; *d/c*, discharge; *IU*, international unit; *NE*, not estimable; *UT*, uterine tone.

[a] Total oxytocin dose received by each arm within first 30 minutes; [b] Not estimable because the study does provide enough information to reasonably estimate total dose received in 30 minutes.

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 4
Available data by outcome

Outcome	RCTs, number of trials (women)[a]	NRSIs, number of trials (women)[a]	Total, number of trials (women)[a]
PPH ≥1000 mL	8 (3324)	1 (1100)	9 (4424)
PPH ≥500 mL	1 (115)	1 (1100)	2 (1215)
Additional uterotonics	25 (5053)	3 (1323)	28 (6376)
Uterine tone	10 (1177)	3 (479)	13 (1656)
Surgical or nonsurgical interventions	5 (385)	1 (1100)	6 (1485)
Blood transfusion	12 (3994)	1 (1100)	13 (5094)
Mean blood loss	18 (4329)	2 (1173)	20 (5502)
Change in hemoglobin	4 (2400)	2 (1096)	6 (3496)
Nausea	9 (727)	3 (162)	12 (889)
Vomiting	10 (778)	2 (156)	12 (934)
Headache	6 (477)	3 (162)	9 (639)
Hypotension	10 (1048)	3 (162)	13 (1210)
Chest pain	7 (687)	3 (1278)	10 (1965)
Myocardial ischemia[b]	2 (173)	0 (0)	2 (173)
Arrythmia[c]	5 (416)	0 (0)	5 (416)
Bradycardia	3 (236)	0 (0)	3 (236)
Tachycardia	7 (794)	0 (0)	7 (794)
Maternal deaths	0 (0)	0 (0)	0 (0)
ICU admissions	0 (0)	0 (0)	0 (0)
Shock	0 (0)	0 (0)	0 (0)
Water intoxication	0 (0)	0 (0)	0 (0)
Breastfeeding after discharge	0 (0)	0 (0)	0 (0)
Maternal sense of well-being	0 (0)	0 (0)	0 (0)
Maternal satisfaction	0 (0)	0 (0)	0 (0)

Studies were not included if there were zero events in both arms or if standard deviations were not provided with mean values.

ICU, intensive care unit; *NRSI*, nonrandomized studies of intervention; *PPH*, postpartum hemorrhage; *RCT*, randomized controlled trial.

[a] Includes extra doses of oxytocin, prostaglandins (carboprost, misoprostol), and ergometrine; [b] Includes troponin I rise and ST segment changes; [c] Includes electrocardiogram changes.

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 5

Summary of funding from randomized studies: type of IV administration

Patient or population: women undergoing cesarean delivery

Outcomes	Anticipated absolute effects (95% CI)[a]		Relative effect (95% CI)	Number of women (studies)	Certainty of evidence (GRADE)	Comments	Sensitivity analyses (risk of bias, method of blood loss measurement)	Subgroup analyses (maintenance infusion for 2–4 h)
Type of IV administration: bolus only vs infusion only								
	Risk with infusion only	Risk with bolus only						
Use of additional uterotonics	359 per 1000	327 per 1000 (187–578)	RR, 0.91 (0.52–1.61)	78 (2 RCTs)	⊕◯◯◯ Very low[b,c]	Effect is inconclusive	ROB: RR, 0.88 (0.44–1.75)	Not estimable[i]
Mean blood loss	The mean blood loss was 600 mL in both arms	MD, 0 mL (−309 to 309)	—	28 (1 RCT)	⊕◯◯◯ Very low[b,c]	Effect is inconclusive	Not estimable[j]	Not estimable[i]
Nausea	80 per 1000	200 per 1000 (42–936)	RR, 2.50 (0.53–11.70)	50 (1 RCT)	⊕◯◯◯ Very low[b,c]	Effect is inconclusive	Not estimable[j]	Not estimable[i]
Vomiting	40 per 1000	120 per 1000 (13–1000)	RR, 3.00 (0.33–26.92)	50 (1 RCT)	⊕◯◯◯ Very low[b,c]	Effect is inconclusive	Not estimable[j]	Not estimable[i]
Chest pain	Unable to calculate because there were zero events in infusion arm		RR, 7.00 (0.37–131.28)	80 (1 RCT)	⊕◯◯◯ Very low[b,c]	Effect is inconclusive	Not estimable[j]	Not estimable[i]
Myocardial ischemia	Unable to calculate because there were zero events in infusion arm		RR, 11.00 (0.63–192.56)	80 (1 RCT)	⊕◯◯◯ Very low[b–d]	Effect is inconclusive	Not estimable[j]	Not estimable[i]
Type of IV administration: bolus only vs bolus plus infusion only								
	Risk with bolus plus infusion	Risk with bolus only						
PPH ≥1000 mL	119 per 1000	172 per 1000 (89–329)	RR, 1.44 (0.75–2.76)	2976 (4 RCTs)	⊕◯◯◯ Very low[e,f]	Effect is inconclusive	Not required[k]	Not estimable[i]
Use of additional uterotonics	120 per 1000	209 per 1000 (145–304)	RR, 1.75 (1.21–2.54)	3125 (5 RCTs)	⊕◯◯◯ Very low[e,f]	Effect is inconclusive	ROB: RR, 1.60 (0.99–2.58)	Not estimablei
PPH ≥500 mL	179 per 1000	259 per 1000 (127–532)	RR, 1.45 (0.71–2.98)	110 (1 RCT)	⊕◯◯◯ Very low[c,g]	Effect is inconclusive	Not estimable[j]	Not estimable[i]
Blood transfusion	9 per 1000	14 per 1000 (4–46)	RR, 1.55 (0.47–5.13)	2870 (3 RCTs)	⊕⊕◯◯ Low[f,h]	May make no clear difference	Not required[k]	Not estimable[i]
Blood loss	The mean blood loss ranged from 569–693 mL	MD, 52 mL more (0.4 more to 104 more)	—	3068 (5 RCTs)	⊕⊕⊕◯ Moderate[h]	Bolus only regimens probably slightly increases blood loss	ROB: MD, 53 mL (−4 to 111 mL) Blood loss: not required[j]	Not estimable[i]
Change in hemoglobin	The mean change in hemoglobin ranged 0.88–11.9 g/dL	MD, 0.05 g/dL less (0.27 less to 0.17 more)	—	2260 (3 RCTs)	⊕⊕⊕⊕ High	Makes no clear difference	Not required[k]	Not estimable[i]

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

(continued)

SUPPLEMENTAL TABLE 5

Summary of funding from randomized studies: type of IV administration *(continued)*

Patient or population: women undergoing cesarean delivery

Outcomes	Anticipated absolute effects (95% CI)[a]		Relative effect (95% CI)	Number of women (studies)	Certainty of evidence (GRADE)	Comments	Sensitivity analyses (risk of bias, method of blood loss measurement)	Subgroup analyses (maintenance infusion for 2–4 h)
Nausea	92 per 1000	200 per 1000 (76–525)	RR, 2.18 (0.83–5.73)	145 (1 RCT)	⊕◯◯◯ Very low[c,g]	Effect is inconclusive	Not estimable[j]	Not estimable[j]
Hypotension	142 per 1000	200 per 1000 (81–492)	RR, 1.41 (0.57–3.47)	145 (1 RCT)	⊕◯◯◯ Very low[c,g]	Effect is inconclusive	Not estimable[j]	Not estimable[j]
Chest pain	50 per 1000	137 per 1000 (44–434)	RR, 2.74 (0.87–8.67)	145 (1 RCT)	⊕◯◯◯ Very low[c,g]	Effect is inconclusive	Not estimable[j]	Not estimable[j]
Satisfactory uterine tone	767 per 1000	483 per 1000 (314–728)	RR, 0.63 (0.41–0.95)	145 (1 RCT)	⊕⊕◯◯ Low[f,g]	Bolus only regimens may decrease incidence	Not estimable[j]	Not estimable[j]
Surgical or nonsurgical interventions	Unable to calculate because zero events occurred in either arms			92 (1 RCT)	—	—	—	—
Vomiting	Unable to calculate because zero events occurred in either arms			145 (1 RCT)	—	—	—	—
Bradycardia	Unable to calculate because zero events occurred in either arms			145 (1 RCT)	—	—	—	—
Tachycardia	Unable to calculate because zero events occurred in either arms			145 (1 RCT)	—	—	—	—
Dyspnea	Unable to calculate because zero events occurred in either arms			145 (1 RCT)	—	—	—	—
Type of IV administration: infusion only vs bolus plus infusion								
	Risk with bolus plus infusion	Risk with infusion only						
Use of additional uterotonics	143 per 1000	270 per 1000 (132–551)	RR, 1.88 (0.92–3.84)	441 (5 RCTs)	⊕◯◯◯ Very low[f–h]	Effect is inconclusive	ROB: RR, 1.59 (0.71–3.54)	RR, 1.39 (0.87–2.22)
Mean blood loss	The mean blood loss ranged between 455–693 mL	MD, 20 mL more (13 less to 53 more)	—	283 (3 RCTs)	⊕◯◯◯ Very low[b,f]	Effect is inconclusive	ROB: MD, 43 mL (−12 to 97 mL) Blood loss: MD, 9 mL (2–17 mL)	MD, 90 mL (−2 to 182 mL)
Nausea	53 per 1000	49 per 1000 (17–145)	RR, 1.05 (0.28–3.97)	277 (3 RCTs)	⊕◯◯◯ Very low[b,c]	Effect is inconclusive	ROB: RR, 3.45 (0.44–27.20)	RR, 2.88 (0.12–69.49)

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021. *(continued)*

SUPPLEMENTAL TABLE 5

Summary of funding from randomized studies: type of IV administration *(continued)*

Patient or population: women undergoing cesarean delivery

Outcomes	Anticipated absolute effects (95% CI)[a]		Relative effect (95% CI)	Number of women (studies)	Certainty of evidence (GRADE)	Comments	Sensitivity analyses (risk of bias, method of blood loss measurement)	Subgroup analyses (maintenance infusion for 2–4 h)
Hypotension	186 per 1000	111 per 1000 (63–195)	RR, 0.60 (0.34–1.05)	263 (2 RCTs)	⊕⊕⊕◯ Moderate[f]	Probably makes no clear difference	Not required[k]	Not estimable[i]
Satisfactory uterine tone	927 per 1000	918 per 1000 (834–1000)	RR, 0.98 (0.90–1.06)	164 (2 RCTs)	⊕⊕◯◯ Low[d,f]	May make no clear difference	Not required[k]	Not estimable[j]
Blood transfusion	41 per 1000	14 per 1000 (2–134)	RR, 0.35 (0.04–3.26)	143 (1 RCT)	⊕⊕◯◯ Low[c]	May make no clear difference	Not estimable[j]	Not required[l]
Vomiting	100 per 1000	50 per 1000 (6–418)	RR, 0.50 (0.06–4.18)	60 (1 RCT)	⊕⊕◯◯ Low[c]	May make no clear difference	Not estimable[j]	Not estimable[i]
Headache	13 per 1000	5 per 1000 (0–110)	RR, 0.36 (0.01–8.71)	152 (1 RCT)	⊕⊕◯◯ Low[c]	May make no clear difference	Not estimable[j]	Not required[l]
Cardiac arrythmia	67 per 1000	100 per 1000 (18–556)	RR, 1.50 (0.27–8.34)	60 (1 RCT)	⊕⊕◯◯ Low[c]	May make no clear difference	Not estimable[j]	Not estimable[i]
Tachycardia	14 per 1000	14 per 1000 (1–215)	RR, 0.96 (0.06–15.04)	143 (1 RCT)	⊕⊕◯◯ Low[c]	May make no clear difference	Not estimable[j]	Not required[l]
Surgical interventions	Unable to calculate as zero events in both arms			75 (1 RCT)	—	—	—	—
Chest pain	Unable to calculate as zero events in both arms			75 (1 RCT)	—	—	—	—
Dyspnea	Unable to calculate as zero events in both arms			75 (1 RCT)	—	—	—	—

Sensitivity analysis of risk of bias included studies only at overall low risk of bias.

Sensitivity analysis of method of blood loss measurement included studies only at low risk of bias for that domain.

Subgroup analysis included only studies using a bolus plus infusion regimen, for which the infusion duration ranged between 2 to 4 hours.

GRADE working group grades of evidence were as follows:

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.

CI, confidence interval; *IV*, intravenous; *MD*, mean difference; *PPH*, postpartum hemorrhage; *RCT*, randomized controlled trial; *ROB*, risk of bias; *RR*, risk ratio.

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); [b] Downgraded for very serious risk of bias; [c] Downgraded for very serious imprecision; [d] Downgraded for serious indirectness; [e] Downgraded for very serious inconsistency; [f] Downgraded for serious imprecision; [g] Downgraded for serious risk of bias; [h] Downgraded for serious inconsistency; [i] Not estimable because no studies used maintenance infusion for 2 to 4 hours in both arms; [j] Not estimable because it was a single study; [k] Not required as all studies at low risk of bias; [l] Not required because all studies used maintenance infusion for 2 to 4 hours in both arms.

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 6

Summary of findings from randomized studies: total oxytocin dose

Patient or population: women undergoing cesarean delivery

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	Number of women (studies)	Certainty of evidence (GRADE)	Comments	Sensitivity analyses (risk of bias, method of blood loss measurement)	Subgroup analyses (maintenance of infusion for 2–4 h)
Total oxytocin dose: <5 IU vs 5–9 IU								
	Risk with 5–9 IU	Risk with <5 IU						
PPH ≥1000	Unable to calculate because zero events were recorded in either arm			145 (1 RCT)	—	—	—	—
Use of additional uterotonics	120 per 1000	379 per 1000 (172–838)	RR, 3.16 (1.43–6.98)	145 (1 RCT)	⊕◯◯◯ Very low[b–d]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Mean blood loss	The mean blood loss ranged from 642–661 mL	MD, 20 mL more (116 less to 156 more)	—	145 (1 RCT)	⊕◯◯◯ Very low[b–d]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Nausea	100 per 1000	116 per 1000 (43–315)	RR, 1.16 (0.43–3.15)	145 (1 RCT)	⊕◯◯◯ Very low[b,c,e]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Hypotension	100 per 1000	221 per 1000 (89–551)	RR, 2.21 (0.89–5.51)	145 (1 RCT)	⊕◯◯◯ Very low[b,c,e]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Chest pain	60 per 1000	84 per 1000 (23–304)	RR, 1.40 (0.39–5.06)	145 (1 RCT)	⊕◯◯◯ Very low[b,c,e]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Satisfactory uterine tone	900 per 1000	621 per 1000 (522–747)	RR, 0.69 (0.58–0.83)	145 (1 RCT)	⊕◯◯◯ Very low[b–d]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Blood transfusion	Unable to calculate because zero events were recorded in either arm			145 (1 RCT)	—	—	—	—
Vomiting	Unable to calculate because zero events were recorded in either arm			145 (1 RCT)	—	—	—	—
Bradycardia	Unable to calculate because zero events were recorded in either arm			145 (1 RCT)	—	—	—	—
Tachycardia	Unable to calculate because zero events were recorded in either arm			145 (1 RCT)	—	—	—	—
Dyspnea	Unable to calculate because zero events were recorded in either arm			145 (1 RCT)	—	—	—	—

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

(continued)

SUPPLEMENTAL TABLE 6

Summary of findings from randomized studies: total oxytocin dose *(continued)*

Patient or population: women undergoing cesarean delivery

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	Number of women (studies)	Certainty of evidence (GRADE)	Comments	Sensitivity analyses (risk of bias, method of blood loss measurement)	Subgroup analyses (maintenance of infusion for 2–4 h)
Total oxytocin dose: 5–9 IU vs 10–19 IU								
	Risk with 10–19 IU	Risk with 5–9 IU						
Use of additional uterotonics	Unable to calculate because zero events were recorded in the 10–19 IU arm		RR, 13.00 (1.75–96.37)	137 (2 RCTs)	⊕⊕◯◯ Low[b,d]	5–9 IU may increase incidence		
							ROB: RR, 18.64 (1.11–312.11)	Not estimable[j]
Mean blood loss	The mean blood loss ranged 540–578 mL	MD, 58 mL more (9 mL less to 124 mL more)	—	133 (2 RCTs)	⊕◯◯◯ Very low[d,f]	Effect is inconclusive	ROB: MD, 45 mL (−109 to 199 mL)	Not estimable[j]
							Blood loss: not required[k]	Not estimable[j]
Myocardial ischemia	39 per 1000	38 per 1000 (5–263)	RR 0.98 (0.14–6.70)	103 (1 RCT)	⊕⊕◯◯ LOW[e]	May make no clear difference.	Not estimable[i]	Not estimable[j]
Hypotension	Unable to calculate as zero events in both arms			60 (1 RCT)	—	—	—	—
Total oxytocin dose: 5–9 IU vs 20–49 IU								
	Risk with 20–49 IU	Risk with 5–9 IU						
PPH ≥1000 mL	129 per 1000	186 per 1000 (97–357)	RR, 1.44 (0.75–2.76)	2831 (4 RCTs)	⊕◯◯◯ Very low[c,d,g]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Use of additional uterotonics	110 per 1000	177 per 1000 (109–285)	RR, 1.60 (0.99–2.58)	2980 (4 RCTs)	⊕◯◯◯ Very low[c,d,h]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
PPH ≥500 mL	179 per 1000	259 per 1000 (127–532)	RR, 1.45 (0.71–2.98)	110 (1 RCT)	⊕◯◯◯ Very low[b,e]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Blood transfusion	9 per 1000	13 per 1000 (4–45)	RR, 1.55 (0.47–5.13)	2980 (4 RCTs)	⊕◯◯◯ Very low[c,d,h]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Mean blood loss	The mean blood loss ranged from 455–610 mL	MD, 53 mL more (4 less to 111 more)	—	2923 (4 RCTs)	⊕◯◯◯ Very low[c,g]	Effect is inconclusive	Not estimable[i]	Not estimable[j]

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

(continued)

SUPPLEMENTAL TABLE 6

Summary of findings from randomized studies: total oxytocin dose *(continued)*

Patient or population: women undergoing cesarean delivery

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	Number of women (studies)	Certainty of evidence (GRADE)	Comments	Sensitivity analyses (risk of bias, method of blood loss measurement)	Subgroup analyses (maintenance of infusion for 2–4 h)
Change in hemoglobin	The mean change in hemoglobin ranged from 0.88–12.1 g/dL	MD, 0.05 g/dL less (0.27 less to 0.17 more)	—	2260 (3 RCTs)	⊕⊕◯◯ Low[c,d]	Makes no clear difference	Not estimable[i]	Not estimable[j]
Total oxytocin dose: 10–19 IU vs 20–49 IU								
	Risk with 20–49 IU	Risk with 10–19 IU						
Use of additional uterotonics	45 per 1000	15 per 1000 (5–46)	RR, 0.32 (0.10–1.02)	331 (2 RCTs)	⊕◯◯◯ Very low[c,d,f]	Effect is inconclusive	RR, 1.01 (0.06–15.94)	Not estimable[j]
Blood transfusion	51 per 1000	44 per 1000 (14–135)	RR, 0.86 (0.28–2.62)	271 (1 RCT)	⊕⊕◯◯ Low[e]	May make no clear difference	Not estimable[i]	Not estimable[j]
Nausea	100 per 1000	200 per 1000 (47–856)	RR, 2.00 (0.47–8.56)	60 (1 RCT)	⊕◯◯◯ Very low[c,e,f]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Vomiting	150 per 1000	50 per 1000 (9–276)	RR, 0.33 (0.06–1.84)	60 (1 RCT)	⊕◯◯◯ Very low[c,e,f]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Chest pain	74 per 1000	4 per 1000 (0–60)	RR, 0.05 (0.00–0.81)	271 (1 RCT)	⊕⊕⊕◯ Moderate[d]	10–19 IU may reduce incidence	Not estimable[i]	Not estimable[j]
Tachycardia	44 per 1000	37 per 1000 (11–119)	RR, 0.84 (0.26–2.69)	271 (1 RCT)	⊕⊕◯◯ Low[e]	May make no clear difference	Not estimable[i]	Not estimable[j]
Mean blood loss	The mean blood ranged from 448–457 mL	MD, 9 mL less (17 less to 0.7 less)	—	60 (1 RCT)	⊕◯◯◯ Very low[c,d,f]	Effect is inconclusive	Not estimable[i]	Not estimable[j]
Satisfactory uterine tone	949 per 1000	996 per 1000 (949–1000)	RR, 1.05 (1.00–1.09)	271 (1 RCT)	⊕⊕⊕◯ Moderate[d]	Probably makes no clear difference	Not estimable[i]	Not estimable[j]

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021. *(continued)*

SUPPLEMENTAL TABLE 6

Summary of findings from randomized studies: total oxytocin dose *(continued)*

Patient or population: women undergoing cesarean delivery

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	Number of women (studies)	Certainty of evidence (GRADE)	Comments	Sensitivity analyses (risk of bias, method of blood loss measurement)	Subgroup analyses (maintenance of infusion for 2–4 h)
Total oxytocin dose: 20–49 IU vs ≥50 IU								
	Risk with ≥50 IU	Risk with 20–49 IU						
Use of additional uterotonics	190 per 1000	393 per 1000 (270–572)	RR, 2.07 (1.42–3.01)	321 (1 RCT)	⊕⊕◯◯ Low[b,d]	20–49 IU may increase incidence	Not estimable[i]	Not estimable[j]
Mean blood loss	The mean blood ranged from 937–957 mL	MD, 20 mL more (14 less to 54 more)	—	321 (1 RCT)	⊕⊕◯◯ Low[f]	May make no clear difference	Not estimable[i]	Not estimable[j]
Hypotension	241 per 1000	253 per 1000 (171–368)	RR, 1.05 (0.71–1.53)	321 (1 RCT)	⊕⊕◯◯ Low[b,d]	May make no clear difference	Not estimable[i]	Not estimable[j]

Sensitivity analysis of risk of bias included studies only at overall low risk of bias.

Sensitivity analysis of method of blood loss measurement included studies only at low risk of bias for that domain.

Subgroup analysis included only studies using a bolus plus infusion regimen for which the infusion duration ranged between 2 and 4 hours.

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.

CI, confidence interval; *MD*, mean difference; *PPH*, postpartum hemorrhage; *RCT*, randomized controlled trial; *ROB*, risk of bias; *RR*, risk ratio.

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); [b] Downgraded for serious risk of bias; [c] Downgraded for serious indirectness; [d] Downgraded for serious imprecision; [e] Downgraded for very serious imprecision; [f] Downgraded for very serious risk of bias; [g] Downgraded for very serious inconsistency; [h] Downgraded for serious inconsistency; [i] Not estimable because it was a single study; [j] Not estimable because no studies used maintenance infusion for 2 to 4 hours in both arms

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 7

Summary of findings from randomized studies: initial bolus dose in a bolus plus infusion regimen

Patient or population: women undergoing cesarean delivery

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	Number of women (studies)	Certainty of evidence (GRADE)	Comments	Sensitivity analyses (risk of bias, method of blood loss measurement)	Subgroup analyses (maintenance infusion for 2–4 h)
Initial bolus dose in a bolus plus infusion regimen: <5 IU vs 5 IU								
	Risk with <5 IU	Risk with 5 IU						
Use of additional uterotonics	133 per 1000	147 per 1000 (69–311)	RR, 1.08 (0.51–2.31)	179 (3 RCTs)	⊕⊕◯◯ Low[b]	May make no clear difference	ROB: RR– 1.01 (0.45-2.24)	RR, 1.01 (0.45–2.24)
Nausea	253 per 1000	66 per 1000 (28–160)	RR, 0.29 (0.10–0.81)	179 (3 RCTs)	⊕⊕◯◯ Low[c,d]	<5 IU may reduce incidence	ROB: RR, 0.15 (0.04–0.54)	RR, 0.15 (0.04–0.54)
Vomiting	120 per 1000	26 per 1000 (6–119)	RR, 0.23 (0.05–1.04)	179 (3 RCTs)	⊕⊕◯◯ Low[c,d]	May make no clear difference	ROB: RR, 0.17 (0.02–1.32)	RR, 0.17 (0.02–1.32)
Mean blood loss	The mean blood loss ranged from 446–451 mL	MD, 4 mL more (4 less to 13 more)	—	40 (1 RCT)	⊕◯◯◯ Very low[d,e]	Effect is inconclusive	Not estimable[f]	Not estimable[g]
Surgical or nonsurgical interventions	Unable to calculate because zero events were recorded in either arm			59 (1 RCT)	—	—	—	—
Blood transfusion	Unable to calculate because zero events were recorded in either arm			59 (1 RCT)	—	—	—	—
Chest pain	Unable to calculate because zero events were recorded in either arm			59 (1 RCT)	—	—	—	—
Cardiac arrythmia	Unable to calculate because zero events were recorded in either arm			59 (1 RCT)	—	—	—	—
Dyspnea	Unable to calculate because zero events were recorded in either arm			59 (1 RCT)	—	—	—	—
Hypotension	Unable to calculate because zero events were recorded in either arm			40 (1 RCT)	—	—	—	—
Initial bolus dose in a bolus plus infusion regimen: 5 IU vs 10 IU								
	Risk with 10 IU	Risk with 5 IU						
Mean blood loss	The mean blood loss ranged from 875–877 mL	MD, 2 mL more (135 less to 138 more)	—	87 (1 RCT)	⊕⊕◯◯ Low[c,d]	May make no clear difference	Not estimable[f]	Not required[h]
Chest pain	114 per 1000	47 per 1000 (9–227)	RR, 0.41 (0.08–2.00)	87 (1 RCT)	⊕⊕◯◯ Low[b]	Effect is inconclusive	Not estimable[f]	Not required[h]

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.

(continued)

SUPPLEMENTAL TABLE 7

Summary of findings from randomized studies: initial bolus dose in a bolus plus infusion regimen *(continued)*

Patient or population: women undergoing cesarean delivery

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	Number of women (studies)	Certainty of evidence (GRADE)	Comments	Sensitivity analyses (risk of bias, method of blood loss measurement)	Subgroup analyses (maintenance infusion for 2–4 h)
Cardiac arrythmia	23 per 1000	8 per 1000 (0–185)	RR, 0.34 (0.01–8.14)	87 (1 RCT)	⊕⊕◯◯ Low[b]	May make no clear difference	Not estimable[f]	Not required[h]
Surgical or nonsurgical interventions	Unable to calculate because zero events were recorded in either arm			87 (1 RCT)	—	—	—	—
Dyspnea	Unable to calculate because zero events were recorded in either arm			87 (1 RCT)	—	—	—	—

Sensitivity analysis of risk of bias included studies only at an overall low risk of bias.

Sensitivity analysis of method of blood loss measurement included studies only at low risk of bias for that domain.

Subgroup analysis included only studies using a bolus plus infusion regimen, for which the infusion duration ranged between 2–4 hours.

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.

CI, confidence interval; *MD*, mean difference; *RCT*, randomized controlled trial; *ROB*, risk of bias; *RR*, risk ratio.

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); [b] Downgraded for very serious imprecision; [c] Downgraded for serious risk of bias; [d] Downgraded for serious imprecision; [e] Downgraded for very serious risk of bias; [f] Not estimable because it was a single study; [g] Not estimable because no studies used maintenance infusion for 2 to 4 hours in both arms; [h] Not required because all studies used maintenance infusion for 2 to 4 hours in both arms.

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SUPPLEMENTAL TABLE 8

Guidelines on oxytocin dosing recommendations with cesarean deliveries

Country	Governing body	Recommendation
International	WHO (2018)	10 IU IV or IM during all births, with doses to be divided as a small IV bolus and an infusion at CD.[4]
International	International consensus statement (2019)	1 IU bolus followed by 2.5—7.5 IU/h infusion for around 2—4 h during planned CD.[8]
United States	ACOG (2017)	Dilute IV infusion (bolus dose of 10 IU). No specification for CD.[57]
United Kingdom	RCOG (2016)	Oxytocin 5 IU IV by slow injection during CD.[58]
France	CNGOF (2016)	Oxytocin at 5—10 IU IV by slow injection during CD plus maintenance infusion not exceeding 10 IU/h which can be stopped after 2 h based on clinical judgment.[59]
Canada	SOCG (2018)	Carbetocin 100 μg as IV bolus over 1 min during elective CD.[60]
Australia and New Zealand	RANZCOG (2017)	Prophylactic oxytocin recommended for all births. No recommendation on dose or dosing regimen provided. No specification for CD.[61]

ACOG, American College of Obstetricians and Gynecologists; *CD*, cesarean delivery; *CNGOF*, French National College of Obstetricians and Gynecologists; *IV*, intravenous; *IM*, intramuscular; *IU*, international units; *RANZCOG*, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; *RCOG*, Royal College of Obstetricians and Gynaecologists; *SOGC*, Society of Obstetricians and Gynaecologists of Canada; *WHO*, World Health Organization.

Phung. Oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery. Am J Obstet Gynecol 2021.