

Oxytocin dosing during trial of labor after cesarean to minimize the risk of uterine rupture: a systematic review and meta-analysis



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Introduction

Although with sizeable variations in rates depending on the area of the

Cite this article as: Nicoli P, Gulersen M, Beacham J, et al. Oxytocin dosing during trial of labor after cesarean to minimize the risk of uterine rupture: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM* 2026;8:101846.

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Received June 14, 2025; revised October 10, 2025; accepted October 24, 2025.

The authors report no conflict of interest.

Tweetable statement: During TOLAC, oxytocin-related uterine rupture risk appears influenced by dosing pattern: shorter escalation intervals (<30 minutes) and higher maximum doses (>20 mU/min) are associated with greater risk.

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2589-9333/\$36.00

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<http://dx.doi.org/10.1016/j.ajogmf.2025.101846>

OBJECTIVE: Oxytocin remains the mainstay for induction and for the management of labor arrest during trial of labor after cesarean (TOLAC). Therefore, the clinical question should be not whether to use oxytocin, but how to optimize its administration. This meta-analysis aimed to assess which oxytocin protocol, in terms of initial dose, amount of increase, timing to next increase, and maximum dose, may minimize the risk of uterine rupture (UR) during TOLAC.

DATA SOURCES: PubMed, Embase and Clinicaltrials.gov were searched up to September 21, 2024.

STUDY ELIGIBILITY CRITERIA: Randomized and nonrandomized studies evaluating the association between induction and/or augmentation with oxytocin and UR during TOLAC versus spontaneous TOLAC were eligible. To be included, studies had to report at least one parameter of the oxytocin protocol used (ie, initial dose, amount of increase, timing to next increase, or maximum dose). The primary outcome was UR.

METHODS: Effect measures were expressed as odds ratios (ORs) with 95% confidence intervals (CIs) and pooled using the Mantel-Haenszel method under a random-effects model. Oxytocin exposure was categorized to perform three separate meta-analyses, ie, any use (for induction and/or augmentation), for induction only, and for augmentation only. In all three comparisons, subgroup analyses assessed differences based on oxytocin initial dose (≤ 2 vs > 2 mU/min), amount of increase (≤ 2 vs > 2 mU/min), timing to next increase (< 30 vs ≥ 30 minutes), and maximum dose (≤ 20 vs > 20 mU/min).

RESULTS: Twenty-one observational studies with 51,511 patients undergoing TOLAC were included. Oxytocin use during TOLAC was consistently associated with a significantly higher risk of UR across all analyses (any use: OR 1.94, 95% CI 1.36–2.77, $P=.0003$; induction only: OR 2.07, 95% CI, 1.28–3.36, $P=.003$; augmentation only: OR 2.03, 95% CI 1.22–3.38; $P=.007$). Among oxytocin protocol parameters, the initial oxytocin dose showed no relationship with UR risk. A significant association was found in some analyses only for increments ≤ 2 mU/min, though the > 2 mU/min subgroup was consistently underpowered. A higher risk of UR was uniformly observed when dose escalations were performed at intervals < 30 minutes. Both moderate (≤ 20 mU/min) and high (> 20 mU/min) maximum doses were significantly associated with increased odds, with a greater risk at higher doses.

CONCLUSIONS: These findings showed an association between oxytocin dosing during TOLAC and an increased risk of UR. Specifically, they suggest that both the timing and cumulative exposure of oxytocin, rather than the initial or incremental dose alone, may critically influence UR risk during TOLAC. Protocols adopting longer escalation intervals (≥ 30 minutes) and limiting maximum doses (≤ 20 mU/min) may enhance safety during TOLAC. Reliable evidence, such as that from randomized trials, is required to confirm these results and define the optimal oxytocin regimen in TOLAC management.

El resumen está disponible en Español al final del artículo.

KEY WORDS: oxytocin dosing, uterine rupture, trial of labor after cesarean, TOLAC induction, labor induction, cesarean delivery

AJOG MFM at a Glance

Why was this study conducted?

To assess which oxytocin protocol, in terms of initial dose, amount of increase, timing to next increase, and maximum dose, may minimize the risk of uterine rupture (UR) during trial of labor after cesarean (TOLAC).

Key findings

Induction and/or augmentation with oxytocin during TOLAC was associated with a significantly higher risk of UR compared with spontaneous TOLAC. Among oxytocin protocol parameters, the initial dose showed no association with UR risk. A significant association was observed in some analyses for smaller dose increments (≤ 2 mU/min), while shorter escalation intervals (<30 minutes) and higher maximum doses (>20 mU/min) were consistently associated with greater risk.

What does this add to what is known?

To our knowledge, this is the first systematic review and meta-analysis to assess UR risk during TOLAC in relation to specific oxytocin dosing parameters. If oxytocin is needed during TOLAC, consideration should be given to keeping dose escalation intervals longer than 30 minutes and the maximum dose below 20 mU/min.

world considered,¹ globally the use of cesarean delivery (CD) has increased steadily over the last 30 years, from approximately 7% to 21%,² and it currently represents the most common major surgical procedure in many countries. As a consequence, trial of labor after cesarean (TOLAC) has become increasingly common.³ Compared with labor in patients without a history of CD, however, TOLAC is associated with a higher risk of life-threatening complications for both mother and fetus, primarily uterine rupture (UR) at the scar site. Although UR occurs in fewer than 1% of TOLAC attempts,^{4–6} it is strongly associated with severe maternal and perinatal morbidity and mortality.⁷

Labor induction and/or augmentation may be necessary in patients undergoing TOLAC. Early studies demonstrated that the use of misoprostol (prostaglandin E1) increases substantially the risk of UR,⁷ and current American College of Obstetricians and Gynecologists (ACOG) guidelines therefore discourage its use for cervical ripening or labor induction at term in patients with a prior CD or major uterine surgery.⁷ In contrast, the role of oxytocin in this setting remains less clear. Evidence on whether induction and/or augmentation with oxytocin during TOLAC increases the risk of UR is

EDITOR'S CHOICE

inconsistent: some studies have reported an elevated risk,^{5,8,9} while others have highlighted no significant association.^{6,10} The 2019 ACOG guideline on TOLAC⁷ does not provide specific guidance with regard to the induction with oxytocin during TOLAC, while stating that “oxytocin augmentation may be used” in such patients.

Nevertheless, when TOLAC does not occur spontaneously, oxytocin remains the principal option for induction, beyond the rupture of membranes,¹¹ and it is indispensable for the management of labor arrest. Thus, the clinical question should not be *whether* to use oxytocin during TOLAC, but rather *how* to optimize its administration to minimize the risk of UR. To our knowledge, no systematic review has specifically evaluated the association between induction and/or augmentation with oxytocin and UR during TOLAC in relation to key protocol parameters such as initial dose, amount of increase, timing to next increase, and maximum dose.

Objective

To assess which oxytocin protocol, in terms of initial dose, amount of increase, timing to next increase, and

maximum dose, may minimize the risk of UR during TOLAC.

Methods**Study design**

This is a systematic review and meta-analysis of all the available published studies investigating the association between induction and/or augmentation with oxytocin during TOLAC and the risk of UR, as compared with spontaneous TOLAC. The review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹² and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statements.¹³ The review protocol was registered in PROSPERO prior to commencing the data extraction (CRD42024556695). As this review included only published studies, it was not subject to institutional board approval.

Search strategy

Electronic databases (PubMed, Embase and Clinicaltrials.gov) were searched from inception of each until September 21, 2024. The search strategy adopted is available in [Supplementary File 1](#). No language restrictions were placed on any of the searches. Additionally, the reference lists of relevant retrieved studies were examined to identify cited articles not detected by the electronic database search. Finally, an effort was made to contact the corresponding authors to obtain missing or complete data from eligible studies.

Study eligibility criteria

Both randomized controlled trials (RCTs) and nonrandomized studies were eligible for inclusion in this systematic review. Case reports, case series (with fewer than 20 cases in the oxytocin group), conference abstracts and reviews were excluded. Studies were included for full-text evaluation when this was in English and when the following PICO criteria were met, respectively: (P) pregnant patients undergoing TOLAC after one or more CDs; (I) induction and/or augmentation with

oxytocin; (C) pregnant patients undergoing TOLAC not receiving the intervention (spontaneous TOLAC); (O) UR reported in the intervention and control groups. Finally, studies meeting these criteria were included in the current systematic review if at least one of the parameters of the oxytocin protocol used was reported, including initial dose, amount of increase, timing to next increase, or maximum dose.

Study outcomes

The study outcomes considered include UR as the primary outcome, and vaginal birth after cesarean (VBAC) and emergency CD (eCD) as secondary outcomes.

Study selection and data extraction

Two authors (P.N., A.V.) independently reviewed the titles and abstracts of studies identified from the search and evaluated them for inclusion. The same authors then evaluated the reference lists of the studies retrieved for full-text examination. The results of the study selection process were finally discussed with a third reviewer (V.B.) and disagreements were resolved.

Two authors (P.N., J.B.) extracted data related to the major general features of the included studies, including location and recruitment period, study design, population size (total and for each group - intervention/control), main inclusion criteria, outcomes of interest, definition of UR adopted, and confounders for which the analyses for the primary outcome were adjusted within the original papers. The following data were also extracted and summarized in tables: intervention type (induction and/or augmentation) and mode (oxytocin protocol used); number of URs in the intervention and control groups; number of VBACs and eCDs in each group. Finally, the entire data extraction process was reviewed by another author (V.B.).

Quality assessment

Two authors (P.N., A.V.) independently assessed the methodological quality of the included (observational) studies by using the modified Newcastle-Ottawa

Scale (m-NOS) (available in [Supplementary File 2](#)). The m-NOS evaluated the following six domains, awarding 1 point to each if satisfied: “sample representativeness”; “sampling technique”; “ascertainment of UR”; “quality of description of enrolled patients”; “quality of description of intervention”; “completeness of outcome data.” Based on the total grouped score, studies were judged to be at low (≥ 5 points), moderate ($= 3$ to 4 points) or high (≤ 2 points) risk of bias (RoB). Any discrepancies in assessments were resolved through discussion with a third reviewer (V.B.).

Data synthesis

Statistical analysis was independently performed by two investigators (P.N., A.V.) using Review Manager version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Any discrepancies in the results were discussed, and consensus was reached to resolve any differences.

All analyses were conducted using a Mantel-Haenszel method, suitable for rare events, under a random-effects model with between-study variance estimated through the DerSimonian and Laird approach,^{14,15} which accounts for expected clinical and methodological heterogeneity across studies. The effect measures of comparisons were expressed as odds ratios (ORs) with 95% confidence intervals (95% CI). Although some studies reported adjusted ORs, these were based on different sets of confounders; therefore, to ensure comparability, we extracted raw event data and pooled unadjusted ORs. For studies in which one treatment arm reported zero events, a continuity correction of 0.5 was applied to all cells of the 2×2 table, while studies with zero events in both arms were excluded from the analysis. A P value of $< .05$ was considered statistically significant. Because RevMan reports P -values rounded to two decimal places, analyses yielding borderline statistical significance ($P = .05$) were re-examined by deriving the exact P -value from the confidence interval reported by RevMan, using the log-transformed OR and its standard error. Heterogeneity was assessed using

the Higgins I^2 statistic. The results were graphically displayed with forest plots.

To assess the OR for UR (primary outcome), oxytocin exposure was categorized to perform three separate primary meta-analyses, ie, oxytocin used (a) for induction and/or augmentation (any use), (b) for induction only, and (c) augmentation only. Specifically, for the “induction only” analysis, we included patients who received oxytocin solely for induction of labor, defined as the initiation of uterine contractions in the absence of spontaneous labor. For the “augmentation only” analysis, we included patients who received oxytocin solely to augment labor, defined as the stimulation of uterine activity to enhance an already ongoing spontaneous labor. Finally, in the “induction and/or augmentation (any use)” analysis, we included all patients from the induction-only and augmentation-only groups, as well as those from studies in which it was not possible to distinguish between induction and augmentation. In each of the three analyses, the comparison group involved patients who did not receive oxytocin (controls undergoing spontaneous TOLAC). In all three comparisons, subgroup analyses were conducted to assess any differences based on initial dose of oxytocin used (≤ 2 vs > 2 mU/min), amount of increase (≤ 2 vs > 2 mU/min), timing to next increase (< 30 vs ≥ 30 min), and maximum dose (≤ 20 vs > 20 mU/min). Cut-offs were selected to reflect thresholds most frequently reported in the literature and widely adopted in clinical protocols, thereby ensuring methodological consistency, cross-study comparability, and clinical interpretability. Due to the retrospective design of almost all included studies and the small number of studies in each subgroup considered, the analysis of each subgroup was conducted separately. Finally, considering that the incidence of UR is about $\leq 1\%$ in TOLAC,⁴⁻⁶ a sensitivity analysis was performed in all cases by excluding studies with less than 1000 patients enrolled, to test the robustness of the main results obtained, to highlight a significant association

between intervention and outcome, and to mitigate the role of chance.

As the TOLAC outcome is dichotomous, possibly resulting in VBAC or eCD, the same analyses were also performed to estimate the OR for eCD (secondary outcome) when administering oxytocin during labor.

Studies that did not report the number of UR events in the oxytocin and/or no-oxytocin groups were not included in the primary quantitative analyses. When studies reported only the UR incidence rates, these were converted into absolute event counts, and such studies were included in sensitivity analyses presented in the [supplementary material](#). While this conversion is not methodologically inappropriate, it provides only an approximate estimate of the true number of events. This is generally acceptable for more frequent outcomes (as eCD), but it becomes problematic in the case of rare events, where even a single misclassified or rounded event can meaningfully influence pooled estimates and compromise the methodological rigor of the primary analysis.

Studies that reported no information on the oxytocin protocol parameter under investigation (ie, initial dose, amount of increase, etc.) or reported it in units that could not be converted to mU/min were excluded from the related subgroup analyses. When a single study reported multiple subgroups for the same subgroup analysis (eg, patient groups exposed to different initial oxytocin doses), it was excluded from the subgroup analysis to avoid double-counting and overrepresentation.

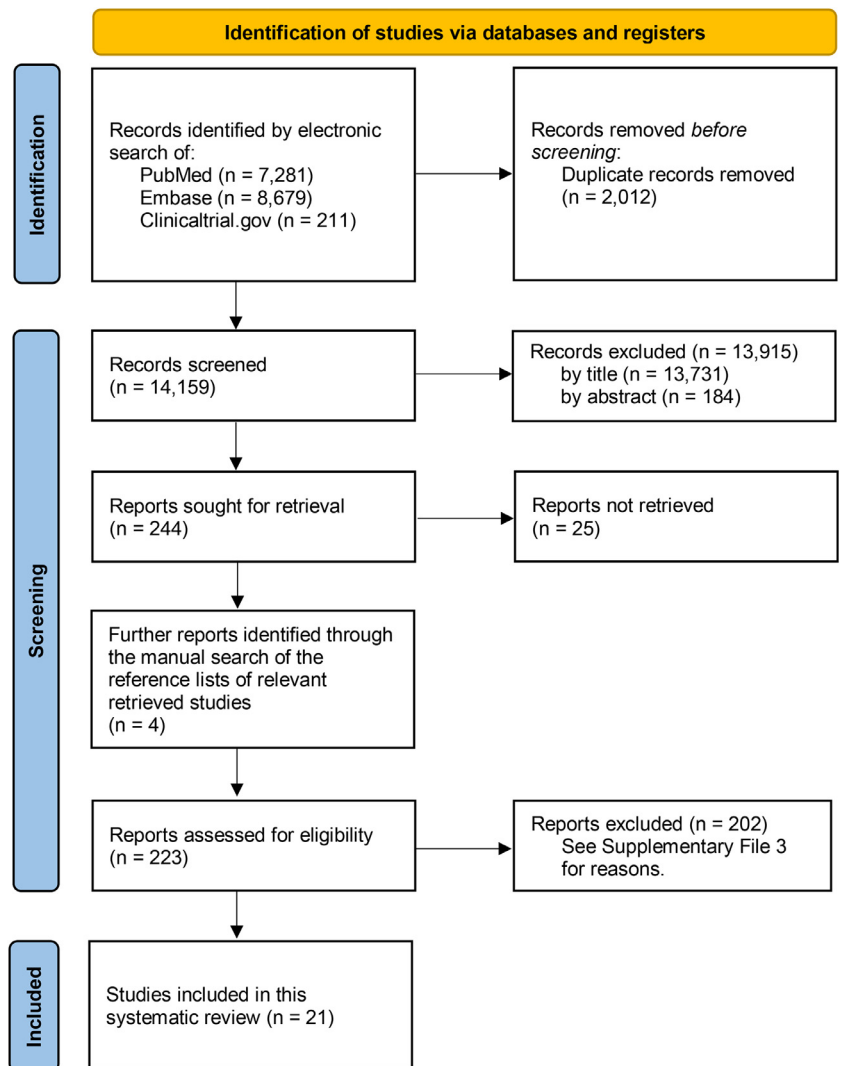
Finally, quantitative analyses including more than 10 studies were subjected to publication bias assessment, as per Cochrane Handbook recommendations.¹⁵ Publication bias was displayed graphically as a funnel plot.

Results

Study selection

The study selection process is displayed in [Figure 1](#). After screening titles and abstracts, 223 studies were assessed for eligibility. Two hundred and two of them were then excluded after the

FIGURE 1
PRISMA flowchart showing the study selection process



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evaluation of the full texts (the list of excluded studies with reasons is available in [Supplementary File 3](#)). Twenty-one studies were finally included in the current systematic review.^{9,16–35}

Study characteristics

The major general features of the included studies are summarized in [Table 1](#). The studies were published over a period of more than 30 years, from 1985¹⁶ to 2022,^{34,35} worldwide. The study design was retrospective in most cases, single-center^{9,17–24,27,29–31,34,35} or multicenter.^{25,28,32,33} A

population-based registry study²⁶ and a prospective study¹⁶ were also included. No RCT was found.

In 10 articles, the study population involved more than 1000 patients.^{9,21,22,24–29,33}

The main inclusion criteria across the studies were reported as follows. Only singleton pregnancies were included in most studies,^{16,20,22,24,27,28,30–35} multiple pregnancies were included in 2 articles,^{23,25} while the number of fetuses was not specified in 7 studies.^{9,17–19,21,26,29} Gestational age (GA) at delivery was term in 7 studies,^{9,17,29,30,32,34,35}

TABLE 1
Major general features of the included studies

Study (first author, year)	Country and recruitment period	Study design	Total population size (oxytocin group/control group)	Main inclusion criteria							Variables for adjustment for primary outcome
				Number of fetuses	GA at delivery	Prior VDs	Prior CSs, n	Type of prior uterine incision	Outcomes of interest	Definition of UR	
Horestein, 1985	USA 1 July 1982 to 30 June 1983	Prospective Single center	732 (289/443)	SP	NR	Yes	1	All but known vertical incision	Uterine dehiscence or rupture, VBAC, eCD	NR	NR
Lao, 1987	China 1980 to 1983	Retrospective Single center	631 (102/529) ^a	NR	Term	NR	1	Low transverse	UR, VBAC, eCD	NR	NR
Chua, 1989	Singapore October 1985 to April 1988	Retrospective Single center	207 (97/110) ^b	NR	NR	NR	1	Low transverse	UR, VBAC, eCD	NR	NR
Meehan, 1989	Ireland April 1st, 1982 and ended on March 31st, 1987	Prospective Single center	209 (47/162)	NR	NR	NR	≥ 1	NR	True UR	Rupture of the uterine scar accompanied by intraabdominal or vaginal bleeding	NR
McNally, 1999	Ireland 1993 to 1994	Retrospective Single center	663 (103/560) ^c	SP	NR	Yes	1	Low transverse	UR, VBAC, eCD	NR	NR
Zelop, 1999	USA July 1984 to June 1996	Retrospective Single center	2672 (1530/1142)	NR	Term	No	1	Low transverse, low-vertical or unknown	Symptomatic UR	Complete disruption of the prior uterine scar with at least 1 of the following: laparotomy for hemorrhage or hemoperitoneum, excessive injury to the bladder or extrusion into the peritoneal cavity of any portion of the fetal-placental unit, CD for not reassuring FHR tracing, suspected UR for acute onset of incisional pain	Duration of labor, birth weight, use of epidural anesthesia, maternal age, year of delivery, years since last birth
Ravasia, 2000	Canada 1992 to 1998	Retrospective Single center	1758 (274/1544) ^d	NR	NR	Yes	≥ 1	NR	UR, VBAC, eCD	Full-thickness separation of the uterine wall associated with at least 1 of the following: laparotomy for uterine repair, hysterectomy, extrusion of fetal parts, and severe FHR abnormalities	NR
Locatelli, 2004	Italy January 1992 to December 2001	Retrospective Single center	1105 (263/842) ^e	SP	≥ 24	Yes	≥ 1	Low transverse	UR, VBAC, eCD	Full-thickness separation of the uterine wall associated with at least one of the following: hemorrhage, defined as presence of any amount of intraperitoneal blood at laparotomy; extrusion of placenta	NR

(continued)

TABLE 1
Major general features of the included studies (continued)

Study (first author, year)	Country and recruitment period	Study design	Total population size (oxytocin group/control group)	Main inclusion criteria						Outcomes of interest	Definition of UR	Variables for adjustment for primary outcome
				Number of fetuses	GA at delivery	Prior VDs	Prior CSs, n	Type of prior uterine incision				
Hoffman, 2004	USA September 1996 to December 1999	Prospective Single center	604 (68/536)	SP and MP	Preterm and term	Yes	NR	NR	Symptomatic UR	Through-and-through disruption of the uterine incision associated with one or more of the following: acute onset of pain localized to the site of the uterine incision, CD for nonreassuring FHR, extrusion of the fetus or fetal parts into the peritoneal cavity, and/or the need for laparotomy for hemorrhage or hemoperitoneum	NR	
Grossetti, 2007	France 1995 to 2003	Retrospective Single center	1212 (138/1074)	SP	≥ 24	NR	1	Low transverse	UR	NR	NR	
Cahill, 2007	USA 1996 to 2000	Retrospective, 17 centers	13430 (5225/8205)	SP and DP	Preterm and term	Yes	≥ 1	Low transverse	Symptomatic UR	Full-thickness separation of the uterine scar that was diagnosed at laparotomy and clinical evidence of UR: nonreassuring FHR tracing immediately preceding laparotomy or signs/symptoms of acute maternal hemorrhage, which included SBP of <70 mm Hg, DBP of <40 mm Hg, HR of >120 beats/min, or presence of blood in the peritoneal cavity at the time of surgical entry	Maternal age, gestational age, labor induction or augmentation, previous vaginal delivery, university hospital, and residency program	
Al-Zirqi, 2010	Norway 1 January 1999 to 30 June 2005	Population-based registry study (MBRN)	9794 (555/9239) ^f	NR	≥ 28	NR	1	All	UR	NR	GA	
Ashwal, 2014	Israel 1 June 2007 to 31 December 2012	Retrospective Single center	1639 (1418/221) ^g	SP	NR	Yes	1	Low transverse	UR	Clinical rupture involving the full thickness of the uterine wall and requiring surgical repair	Parity, previous VDs, diabetes, neuro-axial analgesia, GA at delivery, oxytocin augmentation and birthweight, induction of labor	
Hochler, 2014	Israel 1999 to 2009	Retrospective Three centers	1922 (498/1424)	SP	≥ 24	≥ 6	1	Low transverse	UR	Clinical rupture involving the full thickness of the uterine wall diagnosed during laparotomy	NR	

(continued)

TABLE 1

Major general features of the included studies (continued)

Study (first author, year)	Country and recruitment period	Study design	Total population size (oxytocin group/control group)	Main inclusion criteria							Variables for adjustment for primary outcome
				Number of fetuses	GA at delivery	Prior VDs	Prior CSs, n	Type of prior uterine incision	Outcomes of interest	Definition of UR	
Hehir, 2016	Ireland 1 January 2001 - 31 December 2011	Retrospective Single center	2222 (485/1737)	NR	Term	No	1	NR	UR, VBAC, eCD	NR	NR
Abraham, 2017	USA 2011 to 2015	Retrospective Single center	159 (81/78) ^h	SP	Term	No	1	Low transverse	UR, VBAC, eCD	NR	NR
Fishel Bartal, 2019	USA January 2011 to March 2017	Retrospective Single center	830 (107/723) ⁱ	SP	≥ 34	Yes	1	Low transverse	UR, VBAC, eCD	NR	NR
Familiari, 2020	Italy January 2015 to January 2017	Retrospective Two centers	300 (123/177)	SP	Term	Yes	≥ 1	Low transverse	UR, VBAC	UR was defined with imaging or intraoperative confirmation	NR
Hochler, 2020	Israel 2003 to 2015	Retrospective 4 centers	10400 (2706/7694)	SP	≥ 24	≥ 6	1	Low transverse	UR	Separation of all uterine wall layers	NR
Dick, 2022	Israel January 2015 and October 2020	Retrospective Single center	665 (173/492) ^j	SP	Term	Yes	1	NR	UR, VBAC, eCD	NR	NR
Ji, 2022	China January 2020 to January 2021	Retrospective, case control Single center	160 (80/80) ^m	SP	Term	NR	NR	Low transverse	UR, VBAC, eCD	NR	NR

CD = cesarean delivery; DP = double pregnancy; eCD = emergency cesarean delivery; FHR = fetal heart rate; GA = gestational age; MP = multiple pregnancy; NR = not reported; SP = single pregnancy; UR = uterine rupture; VBAC = vaginal birth after cesarean; VD = vaginal delivery

^a Lao, 1987 = Induction was performed with amniotomy (35 cases) or oxytocin plus amniotomy (102 cases, including 3 given prostaglandins vaginally for cervical ripening); ^b Chua, 1989 = Induction was performed with amniotomy plus oxytocin; ^c McNally, 1999 = Induction was performed with amniotomy plus oxytocin (including 9 women who received intravaginal prostaglandins prior to amniotomy); ^d Ravasia, 2000 = Induction without cervical ripening was performed with either oxytocin or amniotomy or a combination of both; ^e Locatelli, 2004 = A small part of those induced with oxytocin also received amniotomy; ^f Al-Zirqi, 2010 = Induction was performed by means oxytocin +/- amniotomy; ^g Ashwal, 2014 = Induction was performed by means of PGE2, extra-amniotic balloon or PGE2 followed by EAB; then, both in induction group and control group patients received oxytocin for augmentation; ^h Abraham, 2017 = The provider was allowed to place a cervical ripening balloon prior to starting oxytocin; ⁱ Fishel Bartal, 2019 = All included patients had premature rupture of membranes; ^j Dick, 2022 = All patients were induced with artificial rupture of membranes and awaited a spontaneous onset of labor; where it did not occur, oxytocin induction was performed; ^m Ji, 2022 = All patients were induced with CRB + oxytocin

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≥24 weeks in 4 articles,^{22,24,28,33} ≥28 in 1 study,²⁶ ≥34 in another one.³¹ In 2 studies it was generically stated that both term and preterm pregnancies were included.^{23,25} Finally, these data were not reported in 6 studies.^{16,18–21,27}

Enrolled patients had had previous vaginal deliveries (VDs) in 12 studies,^{16,20–23,25,27,28,31–34} with 2 of these studies only including large multiparas (≥6 deliveries).^{28,33} No previous VDs were planned in 3 articles,^{9,29,30} while 6 papers did not report this information.^{17–19,24,26,35} In 14 out of 21 studies, enrolled patients had only 1 prior low transverse CD,^{9,16–18,20,24,26–31,33,34} in 5 cases they had ≥1 CD,^{19,21,22,25,32} while in 2 studies these data were not reported.^{23,35} Most studies included only patients with prior low transverse CD,^{17,18,20,22,24,25,27,28,30–33,35} while 3 studies also included other types of uterine incisions.^{9,16,26} Finally, in 5 studies this information was not reported.^{19,21,23,29,34}

The definition of UR adopted within the original study was reported in 10 studies.^{9,19,21–23,25,27,28,32,33}

For each included study, the oxytocin protocol used, the UR cases and the incidences of VBAC/eCD in the intervention and control groups are shown in Tables 2, 3, and 4, for analysis related to any oxytocin use, use for induction only, and for augmentation only, respectively.

There was heterogeneity in the oxytocin protocols used across studies (Table 2). Most studies used low-dose protocols, with initial dose and amount of increase ≤2 mU/min, timing to next increase ≥30 min, and maximum dose ≤20 mU/min.^{9,19,21,23,24,28,30–33,35} Conversely, 2 studies used high-dose oxytocin protocol (>2 mU/min, <30 min and >20 mU/min, respectively),^{16,29} while 6 studies adopted mixed protocols.^{18,20,22,26,27,34} Finally, 2 studies did not report adequate information.^{17,25}

The quality assessment performed by m-NOS is summarized in Supplementary file 4. Overall, RoB was rated as “Low” in 9 cases,^{9,21,22,26–29,32,33} “Moderate” in 10 studies^{18–20,23–25,30,31,34,35} and “High” in 2 cases.^{16,17}

Synthesis of results

Primary outcome: UR

The results of all analyses performed for the primary outcome are summarized in Table 5.

Primary analyses: overall association. Overall, use of oxytocin during TOLAC, either for induction or augmentation, was associated with a significantly increased risk of UR compared with spontaneous TOLAC (Table 5). For any oxytocin use, the pooled OR was 1.94 (95% CI 1.36–2.77; $I^2=0\%$; $P=.0003$; $N=35,711$) (Figure 2A). Among patients receiving oxytocin for induction only, the OR was 2.07 (95% CI 1.28–3.36; $I^2=0\%$; $P=.003$; $N=28,737$) (Figure 2B), and for those receiving it solely for augmentation, the OR was 2.03 (95% CI 1.22–3.38; $I^2=0\%$; $P=.007$; $N=17,694$) (Figure 2C). Sensitivity analyses restricted to studies enrolling ≥1000 patients confirmed the robustness of these findings across all three analyses (Table 5).

No evidence of publication bias was detected, as the funnel plots for overall analyses in all 3 comparisons were symmetrical (Supplemental Figure 1).

Subgroup analyses: association based on oxytocin protocol parameters. Initial dose. No significant differences in UR risk were observed according to the initial oxytocin dose (≤2 vs >2 mU/min) in any of the three analyses (all $P>.10$) (Table 5). These results were consistent in sensitivity analyses (studies with ≥1000 patients).

Amount of increase. In the “any use” meta-analysis, dose increments ≤2 mU/min were associated with higher UR risk (OR 1.80; 95% CI 1.12–2.91; $I^2=0\%$; $P=.02$; $N=18,926$), whereas increments >2 mU/min showed no significant association ($I^2=46\%$; $P=.12$; $N=12,886$). A similar pattern was seen for the “induction only” analysis (≤2 mU/min: OR 2.34; 95% CI 1.26–4.33; $I^2=0\%$; $P=.007$; $N=15,203$), while results for “augmentation only” did not reach statistical significance ($P=.06$) (Table 5). Sensitivity

analyses (studies with ≥1000 patients) confirmed these findings.

Timing to next increase. Shorter intervals between dose increases (<30 minutes) were significantly associated with higher odds of UR across all analyses (Table 5): “any use” (OR 1.99; 95% CI 1.22–3.24; $I^2=0\%$; $P=.006$; $N=16,584$) (Figure 3), “induction only” (OR 2.36; 95% CI 1.23–4.54; $I^2=0\%$; $P=.01$; $N=12,219$), and “augmentation only” (OR 1.86; 95% CI 1.07–3.22; $I^2=0\%$; $P=.03$; $N=14,423$). No significant associations were found for intervals ≥30 minutes (all $P>.06$). Sensitivity analyses (studies with ≥1000 patients) confirmed results.

Maximum dose. Both moderate (≤20 mU/min) and high (>20 mU/min) maximum oxytocin doses were associated with increased UR risk compared with spontaneous TOLAC (Table 5). In the “any use” meta-analysis, the ORs were 1.82 (95% CI 1.06–3.16; $I^2=0\%$; $P=.03$; $N=15,870$) and 2.22 (95% CI 1.21–4.05; $I^2=5\%$; $P=.010$; $N=15,818$), respectively (Figure 4). In the “induction only” group, only ≤20 mU/min was significantly associated with risk (OR 2.69; 95% CI 1.23–5.91; $I^2=0\%$; $P=.01$; $N=12,079$), whereas in “augmentation only,” only >20 mU/min had increased odds (OR 3.24; 95% CI 1.15–9.16; $I^2=0\%$; $P=.03$; $N=3256$). Sensitivity analyses (studies with ≥1000 patients) showed only slight differences (Table 5).

Sensitivity analyses including studies in which the number of events was derived by conversion from reported UR incidence rates, did not modify the findings of the primary analyses (Supplementary File 5).

Secondary outcome: eCD

The results of all analyses performed for the secondary outcome are summarized in Table 6.

Overall, oxytocin use was not significantly associated with the risk of eCD in any of the three primary meta-analyses (Table 6).

Conversely, significant differences were noted when considering

TABLE 2
Results for primary and secondary outcomes—any oxytocin use (induction and/or augmentation)

Study (first author, year)	Oxytocin used for	Oxytocin protocol parameters					UR		Incidence of VBAC in oxytocin group vs control group	Incidence of eCD in oxytocin group vs control group
		Solution	Initial dose (mU/min)	Amount of increase (mU/min)	Timing to next increase (min)	Maximum dose (mU/min)	Oxytocin group	Control group		
Horestein, 1985	I or A	NR	NR	NR	NR	22	9/289	6/443	200/289 (69%) vs 395/443 (89%)	89/289 (31%) vs 48/443 (11%)
Lao, 1987	I	NR	4 mU/mL	NR	NR	64 mU/mL	0/102	1/529	86/102 (84.3%) vs 461/529 (87.1%)	16/102 (15.7%) vs 68/529 (12.9%)
Chua, 1989	I or A	NR	2.5	2.5	30	12.5	0/97	0/110	68/97 (70.5%) vs 74/110 (67.3 %)	29/97 (29.5%) vs 36/110 (32.7%)
Meehan, 1989	I or A	15 U in 1L 5% dextrose	NR	NR	NR	12	0/47	0/162	NR	NR
McNally, 1999	I	10 U in 1L saline	5	5	30	30	2/103	0/560	82/103 (79.6%) vs 487/560 (87%)	21/103 (20.4%) vs 73/560 (13%)
Zelop, 1999	I or A	NR	NR	1–2	15–20	20	20/1530	5/1142	NR	NR
Ravasia, 2000	I	NR	1–2	1–2	30	NR	2/274	7/1544	203/274 (74.1%) vs 1205/1544 (78%)	71/274 (25.9%) vs 339/1544 (22%)
Locatelli, 2004	I or A	5 UI in 500 mL saline	1.3–2.6	Doubled	40	42	2/263	1/842	NR	NR
Hoffman, 2004	I	NR	1	1–2	15	NR	2*/68	10*/536	45/68 (66.2%) vs 424/536 (78.9%)	23/68 (33.8%) vs 113/536 (21.1%)
Grossetti, 2007	I	NR	15 mL/h	NR	30	NR	2/148	11/1074	NR	NR
Cahill, 2007	I or A	NR	NR	NR	NR	1-5	15*/1323	49*/8205	NR	NR
						6-10	22*/1681	49*/8205	NR	NR
						11-20	30*/1689	49*/8205	NR	NR
						21-30	11*/532	49*/8205	NR	NR
Al-Zirqi, 2010	I	10 U in 100mL NaCl 9 mg/ml	5	5	30	30	4/555	51/9239	NR	NR

(continued)

TABLE 2
Results for primary and secondary outcomes—any oxytocin use (induction and/or augmentation) (continued)

Study (first author, year)	Oxytocin used for	Oxytocin protocol parameters					UR		Incidence of VBAC in oxytocin group vs control group	Incidence of eCD in oxytocin group vs control group
		Solution	Initial dose (mU/min)	Amount of increase (mU/min)	Timing to next increase (min)	Maximum dose (mU/min)	Oxytocin group	Control group		
Ashwal, 2014	A	10 U in 1L saline	2.5	2.5	20	NR	NR/1418	NR/348	NR	NR
Hochler, 2014	I or A	10 U in 1L saline or ringer lactate	1	1	30	20	2/498	4/1424	443/498 (89%) vs 1353/1424 (95%)	55/498 (11%) vs 71/1424 (5%)
Hehir, 2016	A	NR	5	5	15	30	5/485	7/1737	234/485 (48.2%) vs 1377/1737 (79.3%)	251/485 (51.8%) vs 360/1737 (20.7%)
Abraham, 2017	I or A	NR	1	1	30	NR	2/81	0/78	54/81 (66.7%) vs 62/78 (79%)	27/81 (33.3%) vs 16/78 (21%)
Fishel Bartal, 2019	I	2IU in 1L saline	2	2	20	NR	2/107	7/723	81/107 (75.7%) vs 590/723 (81.6%)	26/107 (24.3%) vs 133/723 (18.4%)
Familiari, 2020	A	5IU in 500mL saline	1	1	20–30	5	1/123	3/177	104/123 (84.6%) vs 120/177 (67.8%)	19/123 (15.4%) vs 57/177 (32.2%)
Hochler, 2020	I or A	10 U in 1L saline or ringer lactate	1	1	20–30	20	11/2706	19/7694	2076/2706 (76.7%) vs 5808/7694 (75.5%)	630/2706 (23.3%) vs 1886/7694 (24.5%)
Dick, 2022	I	NR	1	1	30	30	0/173	2/492	128/173 (73.9%) vs 400/492 (81.3%)	45/173 (26.1%) vs 92/492 (18.7%)
Ji, 2022	I	2.5 IU in 500mL saline	2	1–2	15–20	20	0/80	0/80	75/80 (93.8%) vs 62/80 (77.5%)	5/80 (6.2%) vs 18/80 (22.5%)
Total	-	-	-	-	-	-	144/12954	183/36791	-	-

A = augmentation; eCD = emergency cesarean delivery; I = induction; NR = not reported; OR = odds ratio; UR = uterine rupture; VBAC = vaginal birth after cesarean.

* Number of events derived by converting reported UR incidence rates; these studies are included in the [supplementary material](#)

Nicoli et al. Oxytocin dosing during trial of labor after cesarean to minimize the risk of uterine rupture. *Am J Obstet Gynecol* 2025.

TABLE 3

Results for primary and secondary outcomes—oxytocin used for induction only

Study (first author, year)	Oxytocin protocol parameters					UR		Incidence of VBAC in induction group vs control group	Incidence of eCD in induction group vs control group
	Solution	Initial dose (mU/min)	Amount of increase (mU/min)	Timing to next increase (min)	Maximum dose (mU/min)	Induction group	Control group		
Horestein, 1985	NR	NR	NR	NR	22	NR/32	6/443	23/32 (72%) vs 395/443 (89%)	9/32 (28%) vs 48/443 (11%)
Lao, 1987	NR	4 mU/mL	NR	NR	64 mU/mL	0/102	1/529	86/102 (84.3%) vs 461/529 (87.1%)	16/102 (15.7%) vs 68/529 (12.9%)
Chua, 1989	NR	2.5	2.5	30	12.5	0/22	0/110	NR/22 vs 74/110 (67.3 70.5%)	NR/22 vs 36/110 (32.7%)
Meehan, 1989	15IU in 1L 5% dextrose	NR	NR	NR	12	0/17	0/162	NR	NR
McNally, 1999	10 U in 1L saline	5	5	30	30	2/103	0/560	82/103 (79.6%) vs 487/560 (87%)	21/103 (20.4%) vs 73/560 (13%)
Zelop, 1999	NR	NR	1–2	15–20	20	9/458	5/1142	NR	NR
Ravasia, 2000	NR	1–2	1–2	30	NR	2/274	7/1544	203/274 (74.1%) vs 1205/1544 (78%)	71/274 (25.9%) vs 339/1544 (22%)
Locatelli, 2004	5 UI in 500 mL saline	1.3–2.6	Doubled	40	42	0/71	1/842	NR	NR
Hoffman, 2004	NR	1	1–2	15	NR	2*/68	10*/536	45/68 (66.2%) vs 424/536 (78.9%)	23/68 (33.8%) vs 113/536 (21.1%)
Grossetti, 2007	NR	15 mL/h	NR	30	NR	2/148	11/1074	NR	NR
Al-Zirqi, 2010	10 U in 100mL NaCl 9 mg/ml	5	5	30	30	4/555	51/9239	NR	NR
Hochler, 2014	10 U in 1L saline or ringer lactate	1	1	30	20	0/177	4/1424	153/177 (86%) vs 1353/1424 (95%)	24/177 (13.6%) Vs 71/1424 (5%)
Abraham, 2017	NR	1	1	30	NR	2/44	0/78	30/44 (68.2%) vs 62/78 (79%)	14/44 (31.8%) vs 16/78 (21%)

(continued)

TABLE 3
Results for primary and secondary outcomes—oxytocin used for induction only (continued)

Study (first author, year)	Oxytocin protocol parameters					UR		Incidence of VBAC in induction group vs control group	Incidence of eCD in induction group vs control group
	Solution	Initial dose (mU/min)	Amount of increase (mU/min)	Timing to next increase (min)	Maximum dose (mU/min)	Induction group	Control group		
Fishel Bartal, 2019	2IU in 1L saline	2	2	20	NR	2/107	7/723	81/107 (75.7%) vs 590/723 (81.6%)	26/197 (24.3%) vs 133/723 (18.4%)
Hochler, 2020	10 U in 1L saline or ringer lactate	1	1	20–30	20	3/713	19/7694	596/713 (83.6%) vs 5808/7694 (75.5%)	117/713 (16.4%) vs 1886/7694 (24.5%)
Dick, 2022	NR	1	1	30	30	0/173	2/492	128/173 (73.9%) vs 400/492 (81.3%)	45/173 (26.1%) vs 92/492 (18.7%)
Ji, 2022	2.5 IU in 500mL saline	2	1–2	15–20	20	0/80	0/80	75/80 (93.8%) vs 62/80 (77.5%)	5/80 (6.2%) vs 18/80 (22.5%)
Total	-	-	-	-	-	28/3112	118/26229	-	-

eCD = emergency cesarean delivery; NR = not reported; OR = odds ratio; UR = uterine rupture; VBAC = vaginal birth after cesarean.

* Number of events derived by converting reported UR incidence rates; these studies are included in the sensitivity analyses reported in the [supplementary material](#)

Nicoli et al. Oxytocin dosing during trial of labor after cesarean to minimize the risk of uterine rupture. *Am J Obstet Gynecol* 2025.

TABLE 4
Results for primary and secondary outcomes—oxytocin used for augmentation only

Study (first author, year)	Oxytocin protocol parameters					UR		Incidence of VBAC in augmentation group vs control group	Incidence of eCD in augmentation group vs control group
	Solution	Initial dose (mU/min)	Amount of increase (mU/min)	Timing to next increase (min)	Maximum dose (mU/min)	Augmentation group	Control group		
Horestein, 1985	NR	NR	NR	NR	22	NR/257	6/443	177/257 (69%) vs 395/443 (89%)	80/257 (31%) vs 48/443 (11%)
Chua, 1989	NR	2.5	2.5	30	12.5	0/75	0/110	52/75 (69.3%) vs 74/110 (67.3%)	23/75 (30.7%) vs 36/110 (32.7%)
Meehan, 1989	15IU in 1L 5% dextrose	NR	NR	NR	12	0/30	0/162	NR	NR
Zelop, 1999	NR	ND	1–2	15–20	20	11/1072	5/1142	NR	NR
Locatelli, 2004	5 UI in 500 mL saline	1.3–2.6	Doubled	40	42	2/192	1/842	NR	NR
Ashwal, 2014	10IU in 1L saline	2.5	2.5	20	NR	NR/1418	NR/348	NR	NR
Hochler, 2014	10 U in 1L saline or ringer lactate	1	1	30	20	2/321	4/1424	290/321 (90.3%) vs 1353/1424 (95%)	31/321 (9.7%) vs 71/1353 (5%)
Hehir, 2016	NR	5	5	15	30	5/485	7/1737	234/485 (48.2%) vs 1377/1737 (79.3%)	251/485 (51.8%) vs 360/1737 (20.7%)
Abraham, 2017	NR	1	1	30	NR	0/37	0/78	24/37 (64.9%) vs 62/78 (79%)	13/37 (35.1%) vs 16/78 (21%)
Familiari, 2020	5IU in 500mL saline	1	1	20–30	5	1/123	3/177	104/123 (84.6%) vs 120/177 (67.8%)	19/123 (15.4%) vs 57/177 (32.2%)
Hochler, 2020	10 U in 1L saline or ringer lactate	1	1	20–30	20	8/1993	19/7694	1480/1993 (74.3%) vs 5808/7694 (75.5%)	513/1993 (25/7%) vs 1886/7694 (24/5%)
Total	-	-	-	-	-	30/4328	39/13366	-	-

eCD = emergency cesarean delivery; NR = not reported; OR = odds ratio; UR = uterine rupture; VBAC = vaginal birth after cesarean.

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TABLE 5
Results of meta-analyses performed for the primary outcome

Primary outcome: UR	Any oxytocin use		Oxytocin for induction only		Oxytocin for augmentation only	
	OR (95% CI), N	P-value	OR (95% CI), N	P-value	OR (95% CI), N	P-value
Overall	1.94 (1.36-2.77), N=35,711	0.0003	2.07 (1.28-3.36), N=28,737	0.003	2.03 (1.22-3.38), N=17,694	0.007
Sensitivity analysis	1.89 (1.26-2.86), N=31,155	0.002	1.89 (1.10-3.25), N=24,442	0.02	2.19 (1.30-3.71), N=16,902	0.003
Subgroup analysis: initial dose						
≤ 2 IU/min	1.54 (0.89-2.66), N=16,254	0.12	1.72 (0.82-3.62), N=13,603	0.15	1.53 (0.75-3.09), N=11,847	0.24
> 2 IU/min	2.48 (0.80-7.69), N=12,886	0.12	4.25 (0.23-79.79), N=10,589	0.33	2.57 (0.81-8.15), N=2407	0.11
Sensitivity analysis						
≤ 2 IU/min	1.61 (0.86-3.01), N=14,140	0.13	1.57 (0.63-3.93), N=11,826	0.33	1.73 (0.82-3.64), N=11,432	0.15
> 2 IU/min	1.76 (0.82-3.78), N=12,016	0.15	1.31 (0.47-3.63), N=9794	0.61	2.57 (0.81-8.15), N=2222	0.11
Subgroup analysis: amount of increase						
≤ 2 IU/min	1.80 (1.12-2.91), N=18,926	0.02	2.34 (1.26-4.33), N=15,203	0.007	1.74 (0.97-3.14), N=14,061	0.06
> 2 IU/min	2.48 (0.80-7.69), N=12,886	0.12	4.25 (0.23-79.79), N=10,589	0.33	2.57 (0.81-8.15), N=2407	0.11
Sensitivity analysis						
≤ 2 IU/min	1.93 (1.14-3.27), N=16,812	0.01	2.43 (1.20-4.92), N=13,426	0.01	1.91 (1.04-3.52), N=13,646	0.04
> 2 IU/min	1.76 (0.82-3.78), N=12,016	0.15	1.31 (0.47-3.63), N=9794	0.61	2.57 (0.81-8.15), N=2222	0.11
Subgroup analysis: timing to next increase						
< 30 min	1.99 (1.22-3.24), N=16,584	0.006	2.36 (1.23-4.54), N=12,219	0.01	1.86 (1.07-3.22), N=14,423	0.03
≥ 30 min	1.76 (0.95-3.25), N=17,555	0.07	1.79 (0.87-3.70), N=15,708	0.12	3.53 (0.88-14.15), P=3.079	0.08
Sensitivity analysis						
< 30 min	2.15 (1.27-3.65), N=15,294	0.004	2.43 (1.14-5.18), N=11,229	0.02	2.02 (1.15-3.57), N=14,123	0.01
≥ 30 min	1.55 (0.80-3.00), N=15,861	0.19	1.34 (0.59-3.06), N=13,213	0.48	3.53 (0.88-14.15), P=2.779	0.08
Subgroup analysis: maximum dose						
≤ 20 IU/min	1.82 (1.06-3.14), N=15,870	0.03	2.69 (1.23-5.91), N=12,079	0.01	1.74 (0.97-3.14), N=14,131	0.06
> 20 IU/min	2.22 (1.21-4.05), N=15,818	0.010	2.18 (0.56-8.47), N=12,035	0.26	3.24 (1.15-9.16), N=3256	0.03
Sensitivity analysis						
≤ 20 IU/min	1.97 (1.13-3.46), N=14,994	0.02	2.69 (1.23-5.91), N=11,608	0.01	1.91 (1.04-3.52), N=13,646	0.04
> 20 IU/min	1.98 (0.96-4.11), N=13,121	0.07	1.31 (0.47-3.63), N=9794	0.61	3.24 (1.15-9.16), N=3256	0.03

UR = uterine rupture; N = number of patients included in the analysis.

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subgroups based on the oxytocin protocol parameters. As for initial dose and amount of increase, no significant association was found for doses ≤2 mU/min, whereas higher initial and incremental doses (>2 mU/min) were associated with increased eCD risk in sensitivity analyses (studies with ≥1000 patients) for any use and augmentation only (Table 6). Regarding timing to next increase, dose escalations performed at intervals ≥ 30

minutes were associated with higher risk of eCD in both the “any use” and “induction only” analyses, as well as in sensitivity analysis regarding use for augmentation only; in contrast, shorter intervals (<30 minutes) resulted associated with a higher risk of eCD just in sensitivity analysis for “induction only” use (Table 6). Finally, a maximum oxytocin dose >20 mU/min was consistently associated with increased odds of eCD across all analyses and

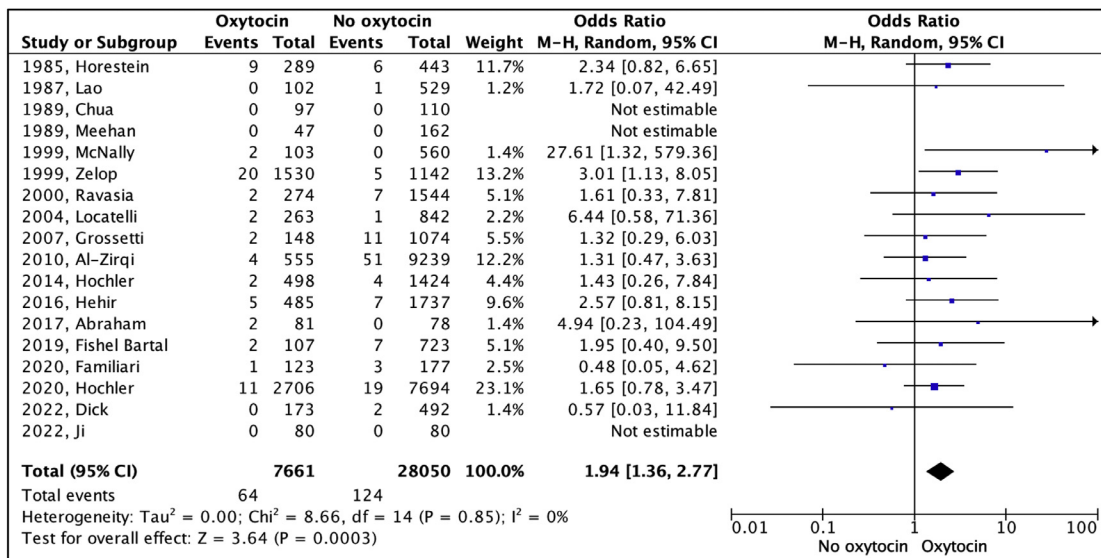
sensitivity analyses (Table 6). I² was consistently >50%.

Comment

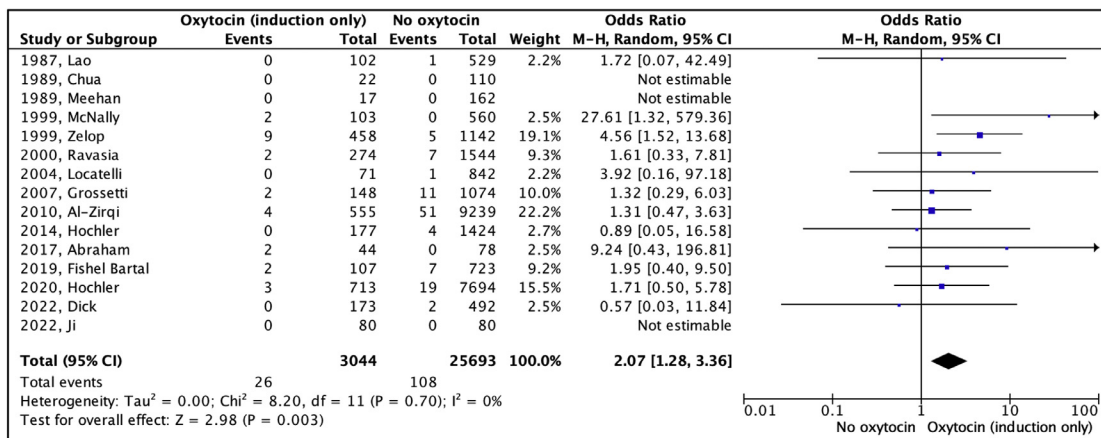
Principal findings

The results of this meta-analysis showed that oxytocin use during TOLAC, whether for any use, induction only, or augmentation only, was consistently associated with an approximately two-fold increase in the odds of UR compared to spontaneous TOLAC.

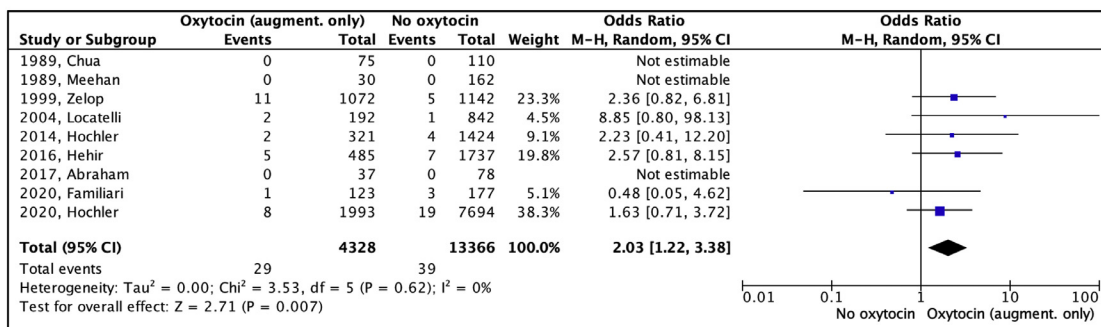
FIGURE 2
Forrest plots - Primary analyses: overall association



A



B



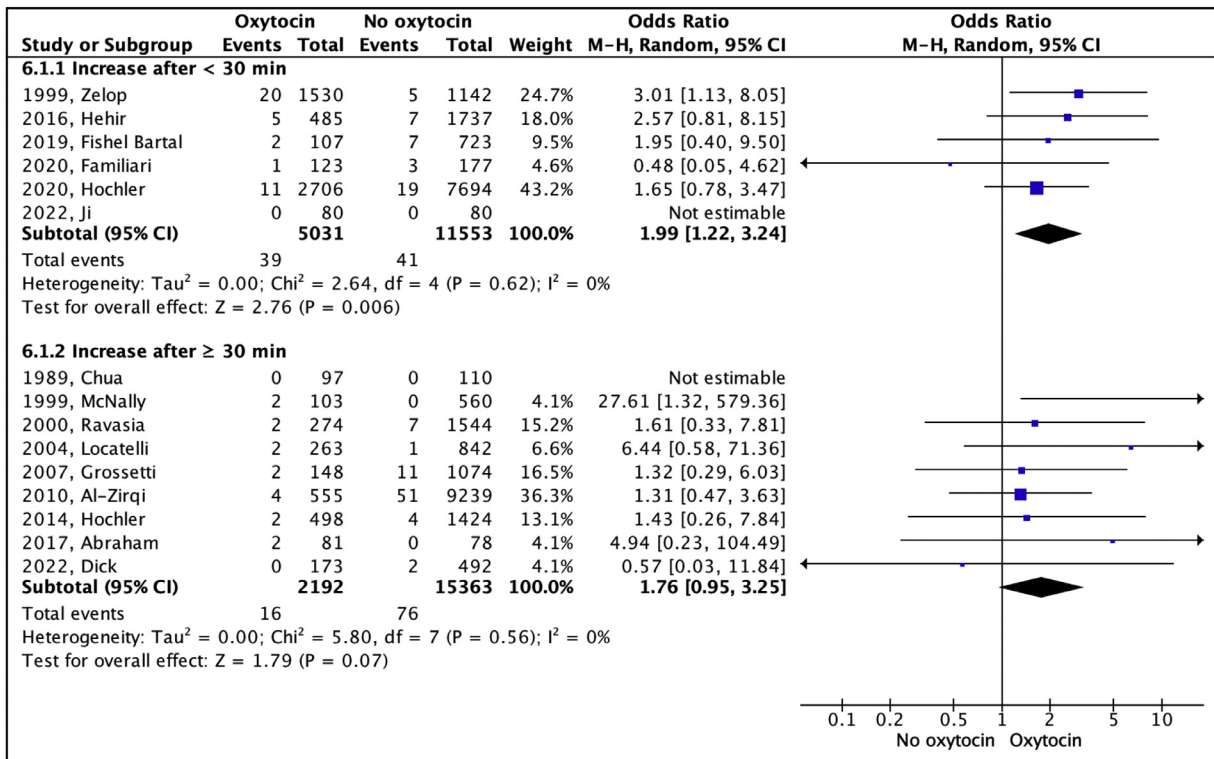
C

A) "Any oxytocin use" analysis; B) "Induction only" analysis; C) "Augmentation only" analysis.

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FIGURE 3

Forrest plot. Subgroup analyses: association based on timing to next increase (“any oxytocin use” analysis)



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Regarding the oxytocin protocol parameters, the initial dose showed no association with UR risk. A significant association was observed for smaller dose increments (≤ 2 mU/min) in some analyses, while larger increments (> 2 mU/min) were not associated with rupture. Dose escalations performed at intervals < 30 minutes were consistently associated with higher risk, whereas longer intervals (≥ 30 minutes) were not. Both moderate (≤ 20 mU/min) and high (> 20 mU/min) maximum oxytocin doses were significantly associated with increased odds of rupture, with a greater risk at higher doses.

As for the secondary outcomes, overall, oxytocin use was not significantly associated with the risk of eCD in any of the three analyses. However, among oxytocin protocol parameters, OR for eCD during TOLAC was significantly higher when the incremental doses were given at intervals ≥ 30 minutes, and in the case of a maximum dose > 20 mU/min.

Comparison with existing literature and interpretation

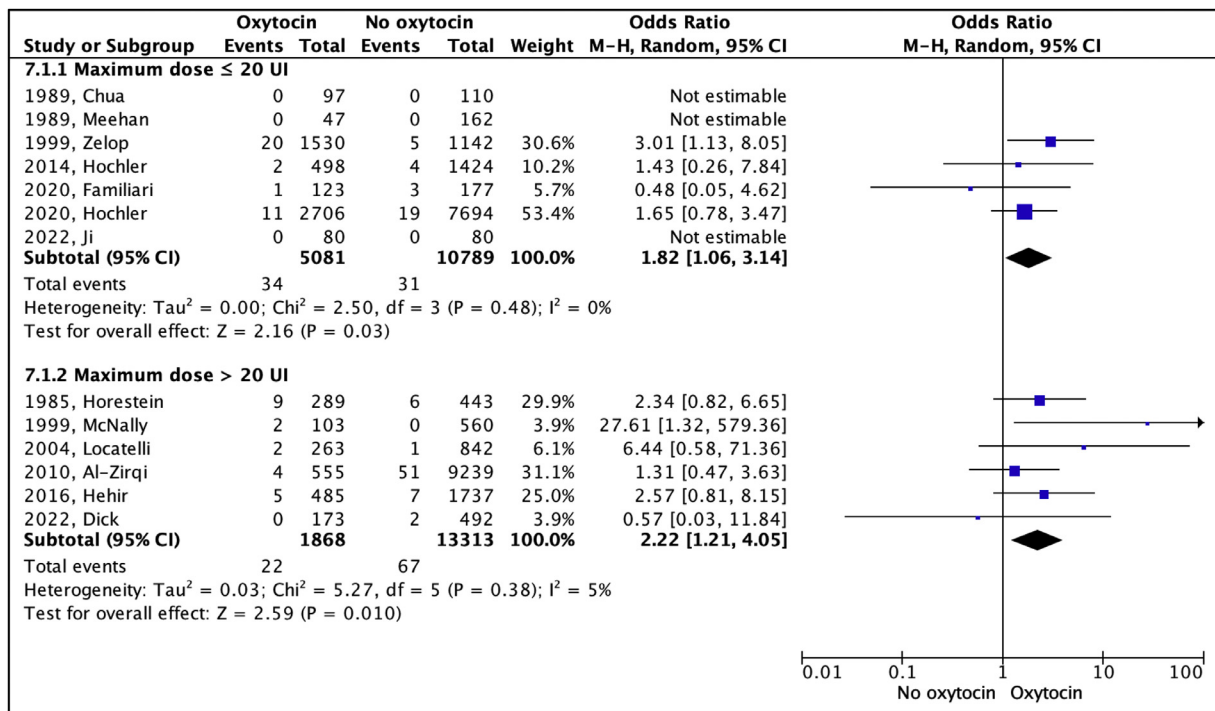
Our findings align with prior studies associating oxytocin use during TOLAC to an increased UR risk. Landon et al,⁵ in a large prospective study involving 17,898 patients undergoing TOLAC, reported significantly higher UR odds when oxytocin was used for either induction (AOR 3.01 (95% CI 1.66–5.46), $P < .001$) or augmentation (AOR 2.42 (95% CI, 1.49–3.93), $P < .001$), compared to spontaneous TOLAC. Although other studies did not find such an association,^{6,10} the overall trend points to a heightened UR risk with oxytocin use during TOLAC, likely compounded by inconsistent oxytocin protocols used across studies and the rarity of UR events, which hinders the production of high-quality evidence such as that from RCTs. Worth noting, while it cannot be excluded that this association reflects a direct effect of the oxytocin molecule *per se*, it is more likely attributable to the

broader induction or augmentation process occurring by means of oxytocin, which also encompasses other factors, such as an unfavorable cervix.

Anyway, when TOLAC does not occur spontaneously, oxytocin remains the primary option for induction, beyond the rupture of membranes.¹¹ Therefore, the focus of clinical debate should shift from *whether* to use it to *how* to tailor its administration to ensure safety and minimize the risk of rupture. In general, oxytocin can be infused by low-dose regimens, involving a starting dose of 0.5–2 mU/min and incremental increases of 1 to 2 mU/min every 15–40 minutes, or by high-dose regimens, where high doses, such as 4–6 mU/min or higher, are given from the beginning and increased rapidly.¹¹ In the context of TOLAC, low-dose regimens are generally preferred^{19,19,21,23,24,28,30–33,35} mainly due to concerns about UR, despite critically limited supporting data.

FIGURE 4

Forrest plot. Subgroup analyses: association based on maximum dose (“any oxytocin use” analysis).



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This meta-analysis suggested no significant association between initial oxytocin dose and UR. Consistently, Goetzl et al³⁶ found no significant difference in initial doses between UR cases and controls, although all patients received ≤ 2 mU/min. This finding is biologically plausible, as the initial dose represents only the onset of uterine stimulation, at which point the total amount of oxytocin is still too low to elicit excessive contractions or impose significant mechanical stress on the uterine scar.

As for the amount of increase, smaller escalation doses (≤ 2 mU/min) were associated with higher UR risk, while greater doses (> 2 mU/min) were not. This apparently paradoxical association likely reflects limited statistical power for the higher increment subgroup (considerably lower number of studies and patients, with wider CI; Table 5), as well as potential confounding by indication, since oxytocin protocols with smaller increments are often used in higher-risk patients. On the

other hand, this result may also indicate a hidden interplay among oxytocin protocol parameters: increment size *per se* may be less important than how frequently it is applied, as small but frequent increases can yield similar or greater cumulative uterotonic exposure.

Consistent with this, among the four key protocol parameters, the timing of dose escalation emerged as the most consistent predictor of risk. Intervals < 30 minutes between oxytocin increases were significantly associated with higher rupture odds in all analyses performed, while intervals ≥ 30 minutes were not. This finding supports a physiological mechanism whereby rapid stimulation may not allow adequate uterine adaptation, resulting in excessive contractility and scar stress. Notably, our results also indicated that slower oxytocin escalation is associated with a higher risk of eCD. This apparent paradox likely reflects the broader trade-off inherent in more conservative oxytocin

protocols, where slower stimulation reduces stress on the uterine wall, lowering rupture risk, but may slow labor progress, leading to increased rates of eCD. However, while reasonable and intuitive, longer delays between doses might not be universally beneficial, as some studies have shown that prolonged labor could, in turn, heighten the UR risk.³⁷

Finally, both moderate (≤ 20 mU/min) and high (> 20 mU/min) maximum doses were associated with significantly increased risk of UR, with higher odds at higher doses, consistent with a cumulative dose-response effect. Some studies in the literature^{10,36} did not find such an association, though small event numbers may have limited power. Conversely, our findings align with those from the large retrospective cohort by Cahill et al,²⁵ who demonstrated a dose-response relationship between maximum dose of oxytocin and UR during TOLAC. A subsequent nested case-control study by the same

TABLE 6
Results of meta-analyses performed for the secondary outcome

Secondary outcome: eCD	Any oxytocin use		Oxytocin for induction only		Oxytocin for augmentation only	
	OR (95% CI), N	P-value	OR (95% CI), N	P-value	OR (95% CI), N	P-value
Overall	1.40 (0.95-2.06), N=21,313	.09	1.28 (0.87-1.90), N=16,066	.21	1.59 (0.84-3.00), N=14,883	.15
Sensitivity analysis	1.83 (0.82-4.05), N=16,362	.14	1.28 (0.56-2.90), N=11,826	.56	2.03 (0.76-5.43), N=13,585	.16
Subgroup analysis: initial dose						
≤ 2 IU/min	1.17 (0.84-1.64), N=16,858	.35	1.13 (0.71-1.79), N=14,297	.86	1.11 (0.63-1.97), N=11,776	.72
> 2 IU/min	1.89 (0.72-4.95), N=3092	.20	1.71 (1.00-2.93), N=663	.05 (.0511)*	1.99 (0.45-8.73), N=2407	.36
Sensitivity analysis						
≤ 2 IU/min	1.37 (0.83-2.26), N=14,140	.22	1.28 (0.56-2.90), N=11,826	.56	1.38 (0.78-2.45), N=11,361	.27
> 2 IU/min	4.10 (3.32-5.07), N=2222	<.00001	NA		4.10 (3.32-5.07), N=611	<.00001
Subgroup analysis: amount of increase						
≤ 2 IU/min	1.17 (0.84-1.64), N=16,858	.58	1.13 (0.71-1.79), N=14,297	.61	1.11 (0.63-1.97), N=11,776	.72
> 2 IU/min	1.89 (0.72-4.95), N=3065	.20	1.71 (1.00-2.93), N=663	.05 (.0511)*	1.99 (0.45-8.73), N=2407	.36
Sensitivity analysis						
≤ 2 IU/min	1.37 (0.83-2.26), N=14,140	.22	1.28 (0.56-2.90), N=11,826	.56	1.38 (0.78-2.45), N=11,361	.27
> 2 IU/min	4.10 (3.32-5.07), N=2222	<.00001	NA		4.10 (3.32-5.07), N=2222	<.00001
Subgroup analysis: timing to next increase						
< 30 min	1.05 (0.49-2.26), N=14,516	.89	0.71 (0.39-1.30), N=10,091	.27	1.22 (0.41-3.68), N=12,209	.72
≥ 30 min	1.54 (1.17-2.04), N=5434	.002	1.71 (1.24-2.36), N=4868	.001	1.53 (0.91-2.58), N=1974	.11
Sensitivity analysis						
< 30 min	1.95 (0.46-8.32), N=12,622	.37	0.60 (0.49-0.74), N=8407	<.00001	2.09 (0.56-7.81), N=11,909	.27
≥ 30 min	1.70 (0.90-3.19), N=3740	.10	1.88 (0.80-4.47), N=3419	.15	1.93 (1.24-3.00), N=1674	.003
Subgroup analysis: maximum dose						
≤ 20 IU/min	0.79 (0.44-1.41), N=12,989	.42	0.79 (0.22-2.82), N=10,168	.72	0.96 (0.57-1.59), N=11,846	.86
> 20 IU/min	2.57 (1.54-4.29), N=4282	.0003	1.79 (1.26-2.55), N=1803	.001	4.10 (3.32-5.07), N=2922	<.00001
Sensitivity analysis						
≤ 20 IU/min	1.46 (0.59-3.63), N=12,322	.41	1.32 (0.27-6.39), N=10,008	.73	1.38 (0.78-2.45), N=11,361	.27
> 20 IU/min	4.10 (3.32-5.07), N=2222	<.00001	NA		4.10 (3.32-5.07), N=2222	<.00001

eCD = emergency cesarean delivery; N=number of patients included in the analysis.

* P-value derived from the CI reported by RevMan, using the log-transformed OR and its standard error

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group³⁸ suggested keeping oxytocin below 20 mU/min during TOLAC, as hazard ratios (HR) for UR rose sharply above this level.

Strengths and limitations

The first strength is the originality of the study design, as, to our best knowledge, no prior systematic reviews of the literature have investigated the effect of oxytocin on the UR risk during TOLAC while taking into account the different

oxytocin protocols used. Other key strengths include the extensive literature search, allowing for the inclusion of a considerable number of studies, and the rigorous methodology of the statistical analysis, including sensitivity analyses to test the robustness of the main results obtained.

Nevertheless, there are a number of limitations affecting our results. First, the control group included only spontaneous TOLACs, not alternative

methods of induction and/or augmentation. Second, most included studies had a retrospective design, lacking a priori sample size calculation and often resulting in limited statistical power. Combined with unbalanced intervention-to-control group ratios across such studies, this may have reduced comparability. Other concerns include heterogeneity in inclusion criteria and the moderate-to-high RoB in more than half of the included studies. Furthermore, only

English-language publications were included, which may have introduced language bias, as non-English studies might differ in design, reporting, or effect estimates. The main weakness of our study is that the oxytocin protocols used in the original studies were fixed, so data we have extracted for primary and secondary outcomes were the result of the entire protocol used. As a consequence, the results of our subanalyses for initial dose, amount of increase, timing to next increase, and maximum dose should be taken with caution, as the effect on one component of the protocol (ie, initial dose) may have been affected by one or more of the other parameters (ie, amount of increase, timing to next increase, maximum dose) in each analysis. Finally, the considerable variation in size of the included studies may have contributed to the heterogeneity observed in the meta-analysis. Smaller studies often reported no UR events or inconsistent findings, raising concerns about insufficient statistical power and the potential for spurious results. Therefore, when it comes to UR in the context of TOLAC, conclusions should primarily rely on data from larger, better-powered studies.

Conclusions and implications

Induction and/or augmentation with oxytocin during TOLAC was associated with a significantly increased risk of UR as compared to spontaneous TOLAC.

Collectively, our findings suggest that the temporal dynamics and cumulative exposure of oxytocin administration, rather than the initial or stepwise doses alone, likely represent the critical modifiable determinants of UR risk during TOLAC. Therefore, protocols emphasizing longer intervals between doses (≥ 30 minutes), limited maximum doses (≤ 20 mU/min), and avoidance of high cumulative doses may optimize safety during TOLAC. In addition, low-dose oxytocin protocols might avoid increasing the risk of eCD during TOLAC.

Despite limitations, our results are plausible and consistent with most of the existing literature, so they may serve a dual purpose, specifically to guide

clinicians to safely manage oxytocin during TOLAC, and to encourage further research seeking to confirm their reliability. In particular, answering with scientific certainty the question of which is the safest oxytocin protocol to adopt during TOLAC to minimize the risk of UR requires future studies, primarily RCTs, comparing two diverse oxytocin dosages for each oxytocin protocol element (eg, an oxytocin initial dose of ≤ 2 vs > 2 mU/min), while maintaining the other parameters (eg, amount of increase, timing to next increase and maximum dose) fixed.

Prospero registration

CRD42024556695. ■

CRedit authorship contribution statement

Pierpaolo Nicoli: Software, Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Moti Gulersen:** Writing – review & editing. **Jordan Beacham:** Data curation. **Hila Hochler:** Visualization, Data curation. **Alessandra Familiari:** Visualization, Data curation. **Anna Locatelli:** Visualization, Data curation. **Cynthia Abraham:** Visualization, Data curation. **Ettore Cicinelli:** Validation. **Amerigo Vitagliano:** Data curation, Software, Formal analysis. **Vincenzo Berghella:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.ajogmf.2025.101846](https://doi.org/10.1016/j.ajogmf.2025.101846).

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OBJETIVO

La oxitocina continúa siendo el pilar para la inducción del trabajo de parto y para el manejo del arresto del trabajo de parto durante la prueba de trabajo de parto después de cesárea (TOLAC, por sus siglas en inglés). Por lo tanto, la pregunta clínica no debería ser si usar oxitocina, sino cómo optimizar su administración. Este metaanálisis tuvo como objetivo evaluar qué protocolo de oxitocina, en términos de dosis inicial, incremento de la dosis, intervalo entre incrementos y dosis máxima, podría minimizar el riesgo de ruptura uterina (RU) durante el TOLAC.

FUENTES DE DATOS

Se realizaron búsquedas en PubMed, Embase y ClinicalTrials.gov hasta el 21 de septiembre de 2024.

CRITERIOS DE ELEGIBILIDAD DEL ESTUDIO

Se incluyeron estudios aleatorizados y no aleatorizados que evaluaran la asociación entre la inducción y/o la augmentación con oxitocina y la ruptura uterina durante el TOLAC en comparación con TOLAC espontáneo. Para ser incluidos, los estudios debían reportar al menos un parámetro del protocolo de oxitocina utilizado (es decir, dosis inicial, incremento de dosis, intervalo hasta el siguiente incremento o dosis máxima). El desenlace primario fue la ruptura uterina.

MÉTODOS

Las medidas de efecto se expresaron como razones de momios (OR) con intervalos de confianza (IC) del 95% y se agruparon utilizando el método de Mantel-Haenszel bajo un modelo de efectos aleatorios. La exposición a oxitocina se categorizó para realizar tres metaanálisis separados: cualquier uso (para inducción y/o augmentación), uso solo para inducción y uso solo para augmentación. En las tres comparaciones se realizaron análisis por subgrupos para evaluar diferencias según la dosis inicial de oxitocina (≤ 2 vs > 2 mU/min), el incremento de dosis (≤ 2 vs > 2 mU/min), el intervalo hasta el siguiente incremento (< 30 vs ≥ 30 minutos) y la dosis máxima (≤ 20 vs > 20 mU/min).

RESULTADOS

Se incluyeron 21 estudios observacionales con un total de 51,511 pacientes sometidas a TOLAC. El uso de oxitocina durante el TOLAC se asoció de manera consistente con un mayor riesgo significativo de ruptura uterina en todos los análisis (cualquier uso: OR 1.94, IC 95% 1.36–2.77, $P=.0003$; solo inducción: OR 2.07, IC 95% 1.28–3.36, $P=.003$; solo augmentación: OR 2.03, IC 95% 1.22–3.38, $P=.007$). Entre los parámetros del protocolo de oxitocina, la dosis inicial no mostró relación con el riesgo de ruptura uterina. Se encontró una asociación significativa en algunos análisis únicamente para incrementos ≤ 2 mU/min, aunque el subgrupo > 2 mU/min estuvo consistentemente subpotenciado. Se observó de manera uniforme un mayor riesgo de ruptura uterina cuando los incrementos de dosis se realizaban en intervalos < 30 minutos. Tanto las dosis máximas moderadas (≤ 20 mU/min) como las altas (> 20 mU/min) se asociaron significativamente con mayores probabilidades de ruptura uterina, con un mayor riesgo a dosis más altas.

CONCLUSIONES

Estos hallazgos muestran una asociación entre la dosificación de oxitocina durante el TOLAC y un mayor riesgo de ruptura uterina. En particular, sugieren que tanto el intervalo entre los incrementos como la exposición acumulativa a la oxitocina, más que la dosis inicial o el tamaño del incremento por sí solos, pueden influir de manera crítica en el riesgo de ruptura uterina durante el TOLAC. Los protocolos que adoptan intervalos de escalamiento más prolongados (≥ 30 minutos) y que limitan la dosis máxima (≤ 20 mU/min) podrían mejorar la seguridad durante el TOLAC. Se requiere evidencia confiable, como la proveniente de ensayos clínicos aleatorizados, para confirmar estos resultados y definir el régimen óptimo de oxitocina en el manejo del TOLAC.

Palabras clave

dosificación de oxitocina, ruptura uterina, prueba de trabajo de parto después de cesárea, inducción en TOLAC, inducción del trabajo de parto, parto por cesárea