OBSTETRICS High-dose vs low-dose oxytocin for labor augmentation: a systematic review

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The objective of this systematic review was to estimate the efficacy and safety of high-dose vs low-dose oxytocin for labor augmentation on the risk of cesarean section and on indicators of maternal and neonatal morbidity. We searched PubMed, MEDLINE, EMBASE, and the Cochrane Library for randomized clinical trials published until January 2010. Ten randomized clinical trials, including 5423 women, met the inclusion criteria. High-dose oxytocin was associated with a moderate decrease in the risk of cesarean section (relative risk [RR], 0.85; 95% confidence interval [CI], 0.75–0.97), a small increase in spontaneous vaginal delivery (RR, 1.07; 95% CI, 1.02-1.12), and a decrease in labor duration (mean difference: -1.54 hours, 95% CI, -2.44 to -0.64). While hyperstimulation was increased with high-dose oxytocin (RR, 1.91; 95% CI, 1.49-2.45), there was no evidence of an increase in maternal or neonatal morbidity. We conclude that high-dose oxytocin for labor augmentation is associated with a decrease in cesarean section and shortened labor.

Key words: active management, augmentation, oxytocin dose

Theⁱ rise in cesarean section continues to be a matter of obstetric concern.¹ Recent reports suggest that high cesarean rates may have an adverse impact on maternal and neonatal morbidity and mortality.² Dystocia is the leading indication for

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© 2010 Mosby, Inc. All rights reserved. doi: 10.1016/j.ajog.2010.03.007 primary cesarean section.^{3,4} Inadequate uterine activity has been described as the most frequent cause of dystocia.

Augmentation of labor with oxytocin is a frequent intervention in modern obstetric practice.⁵ When labor fails to progress, oxytocin is administered to augment contractile effort and to correct dystocia with the objective on achieving a normal vaginal delivery.⁶ Oxytocin has been demonstrated to increase the frequency and intensity of uterine contractions when spontaneous uterine contraction is inadequate and the progress of labor is slow. Oxytocin protocols can be categorized as high-dose or low-dose protocols depending on the initial dose and the amount and rate of sequential increases in dose. Despite the frequency with which oxytocin is used in clinical practice, there is little consensus regarding the optimal dose of oxytocin for labor augmentation.⁷

Over the last 2 decades, a number of randomized clinical trials have assessed the relative effectiveness of different oxy-tocin protocols for the treatment of dystocia,⁸⁻³⁴ including varying dose regimens. This systematic review was designed to estimate the efficacy and safety of high-dose vs low-dose oxytocin in the augmentation of labor on method of delivery and on indicators of maternal and neonatal morbidity.

MATERIALS AND METHODS Data sources

A comprehensive literature search was performed using several search strategies. Published studies were identified through manual searches and through a computerized search of the Cochrane Collaboration Pregnancy and Childbirth Group Trial Register, PubMed, MEDLINE, and EM-BASE in any language until January 2010. The key words were: oxytocin, dose, active management of labor (AML), randomized clinical trials, augmentation, and labor. References cited in these articles were manually searched to obtain additional articles.

Study selection

Two investigators (S-Q.W. and H-P.Q.) independently scrutinized the electronic searches and obtained full manuscripts of all citations that were potentially eligible studies for inclusion.

Included studies had to meet the following criteria. (1) Study design was a randomized controlled trial. (2) Population consisted of pregnant women in spontaneous labor and without prior use of oxytocin. (3) The study contrasted 2 interventions for labor augmentation: high-dose vs low-dose oxytocin. "High dose" was defined as an initial dose of ≥ 4 mU/min and dose increments of at least 4 mU/min; "low-dose" protocols were defined as those with an initial dose ranging between 1-4 mU/min with increments of 1-2 mU/min. (4) Outcomes measured at least 1 of the following: cesarean section, spontaneous vaginal delivery, operative vaginal delivery, duration of labor, hyperstimulation, postpartum hemorrhage, use of epidural analgesia, maternal blood transfusion, Apgar score, and neonatal complications.



FIGURE 1 Flow diagram for systematic review

Wei. High-vs low-dose oxytocin for labor augmentation. Am J Obstet Gynecol 2010.

TABLE 1 Summary of excluded and included randomized controlled trials									
Randomized controlled trials	Reasons for exclusion or inclusion								
Blanch et al ⁸ ; Hemminki et al ⁹ ; Hinshaw et al ¹⁰ ; Hunter ¹¹ ; Pattinson et al ¹² ; Read et al ¹³ ; Shennan et al ¹⁴	Excluded as compared early oxytocin for labor augmentation to routine care								
Bréart et al ¹⁵ ; Cammu and Van Eeckhout ¹⁶ ; Cluett et al ¹⁷ ; Cohen et al ¹⁸ ; Hogston and Noble ¹⁹ ; Serman et al ²⁰ ; Somprasit et al ²¹	Excluded as compared early oxytocin and early amniotomy to routine care								
Cummiskey et al ²²	Excluded as compared pulsatile-infusion oxytocin to continuous-infusion oxytocin								
Lazor et al ²³	Excluded as compared 2 low-dose oxytocin protocols								
Satin et al ²⁴	Excluded as compared 2 high-dose oxytocin protocols								
Bidgood and Steer ²⁵ ; Frigoletto et al ²⁶ ; Jamal and Kalantari ²⁷ ; Lopez-Zeno et al ²⁸ ; Majoko ²⁹ ; Merrill and Zlatnik ³⁰ ; Rogers et al ³¹ ; Sadler et al ³² ; Tabowei and Oboro ³³ ; Xenakis et al ³⁴	Included as met inclusion criteria: compared policy of high- dose to low-dose oxytocin for augmentation of labor								
Wei. High- vs low-dose oxytocin for labor augmentation. Am J Obstet Gynecol 2010.									

TABLE 2 Characteristic	TABLE 2 Characteristics of included studies											
Study	Country	Study design	Total sample size, n	Participants	Mean CD at randomization, cm	Labor progress at randomization	Interventions (detailed drug regimens)					
Bidgood and Steer ²⁵	United Kingdom	RCT	40	Nulliparae in spontaneous labor at term, vertex presentation	-	Dystocia: progression of CD <0.5 cm/h	High dose: oxytocin infusion started at 7 mU/min increased by 7 mU/min every 15 min, limited by frequency of 7 contractions in 15 min or by abnormality in FHR trace; Low dose: oxytocin infusion started at initial rate of 2 mU/min and increased by 2 mU/min every 15 min until stable phase of uterine activity detected					
Frigoletto et al ²⁶	USA	RCT	1915	Nulliparae in spontaneous labor, single term fetus, vertex presentation, without medical or obstetric complication	-	Normal	High dose: oxytocin initiated at 4 mU/min and increased by 4 mU/min every 15 min up to maximum 40 mU/min; Low dose: oxytocin initiated at 1-2 mU/min and increased periodically by 1-2 mU/min					
Jamal and Kalantari ²⁷	Iran	RCT	200	Women with CD \ge 3 cm and gestational age \ge 37 wk	3.6	Ineffective uterine contractions in beginning of active labor	High dose: oxytocin initiated at 4.5 mU/min and increased by 4.5 mU/min every 30 min; Low dose: oxytocin initiated at 1.5 mU/min and increased by 1.5 mU/min every 30 min					
Lopez-Zeno et al ²⁸	USA	RCT	705	Nulliparae in spontaneous labor at term, cephalic presentation, without previous uterine surgery	3.2	Normal	High dose: oxytocin initiated at 6 mU/min and increased by 6 mU/min every 15 min; Low dose: oxytocin initiated at 1 mU/min and increased by 1-2 mU/min every 15 min					
Majoko ²⁹	Zimbabwe	RCT	258	Nulliparae in spontaneous labor, singleton fetus, cephalic presentation, with normal fetal heart pattern	6.2	Normal	High dose: oxytocin initiated at 10 mlU/min and infusion rate doubled every 60 min; Low dose: oxytocin initiated at 4 mlU/min and infusion rate doubled every 30 min					
Merrill and Zlatnik ³⁰	USA	RCT	491	$CD \ge 3$ cm, at least 10 uterine contractions/h, >24 wk gestation with living fetus	4.8	Normal	High dose: oxytocin initiated at 4.5 mU/min and increased by 4.5 mU/min every 30 min; Low dose: oxytocin initiated at 1.5 mU/min and increased by 1.5 mU/min every 30 min					
Wei. High- vs low-dos	e oxytocin for lab	oor augmenta	tion. Am J O	bstet Gynecol 2010.			(continued)					

Studies were excluded if the dose of oxytocin in 1 or both groups was not specified. Reporting of time intervals in labor varied across studies. Some reported the total duration of labor by study group,^{31,33} others reported the interval from admission to delivery,^{25,28} and 1 study reported the interval from the study intervention to delivery.³⁰ Prolonged labor was defined as total labor duration of >12 hours. Postpartum hemorrhage was defined as blood loss >500 mL.

			Total		Mean CD at		
Study	Country	Study design	sample size, n	Participants	randomization, cm	Labor progress at randomization	Interventions (detailed drug regimens)
Rogers et al ³¹	USA	RCT	405	Nulliparous women at term who had attended for antenatal care, cephalic presentation, without medical or obstetric complication or fetal abnormities	2.9	Normal	High dose: oxytocin initiated at 6 mU/min and increased by 6 mU/min every 30 min; Low dose: oxytocin initiated at 1 mU/min and increased by 1 mU/min every 30-40 min
Sadler et al ³²	New Zealand	RCT	651	Nulliparous women in spontaneous labor, singleton pregnancy, no severe cardiac disease, no uterine scar, and no proven contracted pelvis	4.5	Normal	High dose: oxytocin initiated at 6 mU/min and increased by 6 mU/min every 20 min up to 42 mU/min; Low dose: oxytocin initiated at 1 mU/min and increased by 1 mU/min every 20 min up to 8 mU/min, then increased by 2 mU/min up to 20 mU/min
Tabowei and Oboro ³³	Nigeria	RCT	448	Nulliparae, singleton fetus, cephalic presentation	_	Normal	High dose: oxytocin initiated at 6 mU/min and increased by 6 mU/min every 15 min until either a frequency of 5 contractions/10 min, each lasting at least 40 seconds is achieved or a maximum of 36 mU/min oxytocin infusion rate is reached; Low dose: oxytocin initiated at 2 mU/min and increased by 2 mU/min every 30 min, until a frequency of at least 3 contractions/10 min, lasting at least 40 seconds each is achieved
Xenakis et al ³⁴	USA	RCT	310	Nulliparous and multiparous patients in term in active labor	5.8	Arrest of dilatation: no cervical change for 2 h after latent phase of labor completed and cervix dilated \geq 4 cm; or arrest of dilatation: no change in station of presenting part, at full dilatation, for >1 h	High dose: oxytocin initiated at 4 mU/min and increased by 4 mU/min every 15 min until adequate uterine contractility achieved; Low dose: oxytocin initiated at 1 mU/min increased by 1 mU/min every 30 min up to 4 mU/min, then increased by 1 mU/min

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Tabulation and integration

The quality of the controlled trials was assessed separately by 2 independent reviewers (S-Q.W. and W.D.F.) in duplicate for 4 types of potential bias: selection bias, performance bias, detection bias, and attrition bias–based on the criteria of the Cochrane Handbook for Systematic Reviews of Interventions.³⁵ Disagreements between evaluators were resolved by discussion with a third reviewer (Z-C.L.) to achieve consensus. In 1 trial,²⁶ randomization was performed <30 weeks' gestation and approximately one third of the women were excluded

I	IADLE 3
	Oxytocin dose administered for labor augmentation in included trials

	Oxytocin dos (mU/min)	e range	Maximum oxytocin dose (mU/min) (mean or median ^a)		
Study	High dose	Low dose	High dose	Low dose	
Bidgood and Steer ²⁵	7–	2–	_	-	
Frigoletto et al ²⁶	4–40	1,2–	_	-	
Jamal and Kalantari ²⁷	9–90	3–30	36 ^a	18 ^a	
Lopez-Zeno et al ²⁸	6–	1–	17.3 ± 9.4	10.8 ± 6.7	
Majoko ²⁹	10-40	4–16	_	-	
Merrill and Zlatnik ³⁰	4.5-80.0	1.5–31.7	15.6 ± 0.7	7.8 ± 0.3	
Rogers et al ³¹	6—	1–	13 ± 9	6 ± 5	
Sadler et al ³²	6–	1–	16.2 ± 8.9	12.0 ± 7.2	
Tabowei and Oboro ³³	6–	2–	_	_	
Xenakis et al ³⁴	4–40	1–18	9.3 ± 5.2	4.7 ± 2.9	

from the analysis after randomization as they became ineligible for the intervention. Only cesarean section was reported by intention to treat. This study was only included for the cesarean section outcome. Data were abstracted independently by the 2 reviewers and results compiled. Of the 10 trials included in the systematic review, 5 studies^{26,28,31-33} contrasted AML to a more conservative approach to care, ie, early administration of highdose oxytocin compared to a delayed low-dose oxytocin regimen. In the remaining 5 studies,^{25,27,29,30,34} the contrast consisted of a simple comparison of

	High-D	ose	Low-D	ose		Risk Ratio	Risk Ratio
Study or Subgroup					Weight		
3.1.1 High-dose oxyte	ocin (Activ	ve Man	agement	t proto	col) versu	s low-dose oxytocin	1
Frigoletto 1995	197	1009	176	906	45.0%	1.01 [0.84, 1.21]	
opez-Zeno 1992	37	351	50	354	12.1%	0.75 [0.50, 1.11]	
Rogers 1997	15	200	24	205	5.7%	0.64 [0.35, 1.18]	
Sadler 2000	30	320	32	331	7.6%	0.97 [0.60, 1.56]	
Fabowei 2003	20	221	36	227	8.6%	0.57 [0.34, 0.95]	
Subtotal (95% CI)		2101		2023	79.1%	0.89 [0.77, 1.03]	•
Fotal events	299		318				
Heterogeneity: Chi ² = 6	6.56, df = 4	4 (P = 0	.16); I ² =	39%			
Fest for overall effect:	Z = 1.60 (F	P = 0.11)				
3.1.2 High-dose versu							
Bidgood 1987	5	19	7	21	1.6%	0.79 [0.30, 2.07]	
Jamal 2004	5	100	9	100	2.2%	0.56 [0.19, 1.60]	
Vajoko 2001	10	125	11	133	2.6%	0.97 [0.43, 2.20]	
Verrill 1999	26	249	20	242	4.9%	1.26 [0.72, 2.20]	
Kenakis 1995	16	154 647	40	156 652	9.6% 20.9%	0.41 [0.24, 0.69]	
Subtotal (95% CI)		047	07	002	20.9%	0.72 [0.53, 0.98]	
Fotal events	62	(D - 0	87	500/			
Heterogeneity: Chi ² = 9				56%			
Foot for overall offects	2 – 2.10 (r	0.04	•)				
Fest for overall effect:							▲
Fest for overall effect∷ Fotal (95% CI)		2748		2675	100.0%	0.85 [0.75, 0.97]	\bullet
	361	2748	405	2675	100.0%	0.85 [0.75, 0.97]	•
Fotal (95% CI) Fotal events					100.0%	0.85 [0.75, 0.97]	◆
Fotal (95% CI)	17.09, df =	9 (P =	0.05); l ² :		100.0%	0.85 [0.75, 0.97]	0.2 0.5 1 2 Favours experimental Favours cont

high-dose to low-dose oxytocin for labor augmentation. For the analysis of our main outcome, cesarean section, studies were stratified according to these 2 types of comparison.

The data were extracted and statistical analysis carried out using Review Manager (RevMan) 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). Data on dichotomous outcomes were combined using the Mantel-Haenszel method, and measures of effect are presented as relative risk (RR) with 95% confidence interval (CI). For continuous data, we used the sample size weighted mean difference when outcomes were measured in the same way between trials. We used forest plots to shows the point estimate for each study (with 95% CIs), with a diamond at the bottom representing the pooled point estimate with 95% CIs for each outcome of interest. The presence of significant heterogeneity was explored by the interaction test (I²) statistic.³⁵ In cases where I^2 exceeded 50%, we pooled results using random effects models and explored the results for sources of variation.

RESULTS

The search strategy resulted in 426 potentially relevant citations. Preferred reporting items for systematic reviews and metaanalyses flow diagram³⁶ (Figure 1) shows an overview of the study selection process. Twenty-seven relevant randomized controlled trials were retrieved for more detailed assessments (Table 1). Seventeen trials were excluded for the following reasons: 14 trials¹⁰⁻²³ were excluded as early oxytocin administration and/or amniotomy was compared to routine care; a trial²² comparing pulsatile to continuous oxytocin infusion was excluded; and 2 trials^{23,24} comparing 2 high-dose or 2 low-dose oxytocin regimens were excluded. Ten trials,²⁵⁻³⁴ including 5423 women, were included in the final analysis. The included trials and characteristics of the women at the time of randomization are summarized in Table 2. All 10 trials that met the eligibility criteria were evaluated by 2 reviewers independently with respect to the 4 criteria

relating to potential bias. The oxytocin dosage was double-masked in only 1 trial³⁰–the bags containing high-dose or low-dose oxytocin solutions were prepared by the hospital pharmacy. Ran-domization blinding, when performed, was achieved by centralization of the process in the hospital pharmacy in 1 study³⁰ or by sealed envelopes in the remaining studies. Three trials^{25,27,34} enrolled women with established delays in labor progress. The remaining trials enrolled women who were in normal spontaneous labor at the time of randomization.

In all studies, the contrast consisted of high-dose oxytocin infusion compared to low-dose oxytocin, as shown in Tables 2 and 3. The high-dose regimens varied across the trials; starting doses ranged from 4–10 mU/min, with increases in dose ranging from 4–7 mU/min and maximum rates ranging from 4–90 mU/ min. Low-dose regimens commenced infusion at from 1-4 mU/min, with rate increases ranging from 1–2 mU/min and maximum rates ranging between 1–31.7 mU/min.

The effect of high-dose vs low-dose oxytocin augmentation on the cesarean section rate is presented in Figure 2. Highdose oxytocin augmentation was associated with a moderate reduction in the risk of cesarean section (RR, 0.85; 95% CI, 0.75-0.97). There was no evidence of heterogeneity across trials ($I^2 = 47\%$). In the stratified analysis, the effect of the intervention appeared to be more marked in the stratum of trials involving a simple comparison of high-dose to low-dose oxytocin (RR, 0.72; 95% CI, 0.53-0.98) than in those contrasting AML (including highdose oxytocin) with a more conservative approach to care (including low-dose oxytocin) (RR, 0.89; 95% CI, 0.77-1.03). Overall, the number needed to treat was 50: for every 50 patients treated by highdose oxytocin augmentation, 1 cesarean section is avoided.

The effect of high-dose oxytocin augmentation on the rate of spontaneous vaginal delivery is shown in Figure 3. High-dose oxytocin was associated with a small but statistically significant increase in spontaneous vaginal deliveries (RR, 1.07; 95% CI, 1.02–1.12). There was

FIGURE 3 Effect of oxytocin dos	e on spont	taneous vaginal delivery
High-Dose	Low-Dose	Risk Ratio

	High-D	ose	Low-De	ose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bidgood 1987	6	19	5	21	0.5%	1.33 [0.48, 3.65]	
Lopez-Zeno 1992	225	351	205	354	22.1%	1.11 [0.98, 1.25]	
Majoko 2001	112	125	116	133	12.2%	1.03 [0.94, 1.12]	+
Rogers 1997	150	200	148	205	15.8%	1.04 [0.92, 1.17]	
Sadler 2000	227	320	245	331	26.1%	0.96 [0.87, 1.05]	
Tabowei 2003	144	221	136	227	14.5%	1.09 [0.94, 1.26]	+
Xenakis 1995	110	154	81	156	8.7%	1.38 [1.15, 1.65]	
Total (95% CI)		1390		1427	100.0%	1.07 [1.02, 1.12]	◆
Total events	974		936				
Heterogeneity: Chi ² =	14.15, df =	6 (P =	0.03); l ² =	= 58%		-	
Test for overall effect:	Z = 2.63 (F	> = 0.00	08)			Favo	0.5 0.7 1 1.5 2 urs experimental Favours control

Cl, confidence interval; df, degrees of freedom; M-H, Mantel Haenszel.

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heterogeneity across trials ($I^2 = 58\%$; P < .01), but the directions of the association consistently favored the high-dose intervention, with the exception of 1 trial.³²

Five trials^{25,28,30,31,33} reported on the effect of the intervention on mean labor intervals (labor duration,^{31,33} time from admission,^{25,28} or initiation of oxytocin³⁰ to delivery). High-dose vs low-dose oxytocin augmentation was associated with a significant shortening of these intervals (weighted mean difference: -1.54 hours; 95% CI, -2.44 to -0.64). However, there was significant heterogeneity across the trials ($I^2 = 96\%$; P < .01). Three trials³¹⁻³³ reported the proportion with labor duration >12 hours (RR, 0.46; 95% CI, 0.30-0.70). There was significant heterogeneity across the trials for this measure of effect $(I^2 = 53\%; P = .12).$

High-dose oxytocin augmentation was associated with a substantially increased risk of hyperstimulation (RR, 1.91; 95% CI, 1.49–2.45). There was no heterogeneity across the trials ($I^2 = 35\%$; P = .19) (Figure 4). However, there were no statistically significant differences between high-dose and low-dose oxytocin augmentation groups with respect to the proportion with fetal heart rate abnormalities, fetal distress, or neonatal morbidity indicators (Table 4).

There was no evidence of an effect of high-dose oxytocin augmentation on a range of other adverse maternal process and outcome indicators including use of epidural analgesia, postpartum hemorrhage (>500 mL), maternal blood transfusion, uterine atony, uterine rupture, shoulder dystocia, and chorioamnionitis (Table 4).

COMMENT

In this systematic review, we found that high-dose oxytocin augmentation was associated with a statistically significant

FIGURE 4

Effect of oxytocin dose on hyperstimulation

	High-Do	se	Low-Do	ose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Bidgood 1987	7	19	0	21	0.6%	16.50 [1.01, 270.78]	
Jamal 2004	14	100	8	100	10.4%	1.75 [0.77, 3.99]	+
Merrill 1999	97	249	44	242	58.1%	2.14 [1.57, 2.92]	=
Rogers 1997	22	200	16	205	20.6%	1.41 [0.76, 2.60]	+
Xenakis 1995	7	154	8	156	10.3%	0.89 [0.33, 2.38]	
Total (95% CI)		722		724	100.0%	1.91 [1.49, 2.45]	◆
Total events	147		76				
Heterogeneity: Chi ² =	6.11, df = 4	(P = 0	.19); I ² =	35%			
Test for overall effect:	Z = 5.09 (P	< 0.00	0001)			F	avours experimental Favours control

Cl, confidence interval; df, degrees of freedom; M-H, Mantel Haenszel.

Wei. High-vs low-dose oxytocin for labor augmentation. Am J Obstet Gynecol 2010.

TABLE 4

Effect of high-dose vs low-dose oxytocin augmentation on obstetric and neonatal outcomes

•	-	•				
Outcome	Studies	High-dose oxytocin	Low-dose oxytocin	RR	95% CI	Heterogeneity, %ª
Perinatal mortality	3 ^{29,30,34}	8/535	7/532	1.17	0.44-3.11	66
Spontaneous vaginal delivery	7 ^{25,28,29,31-34}	974/1390	936/1427	1.07	1.02–1.12	58
Instrumental delivery	7 ^{25,28,29,31-34}	283/1390	291/1427	1.00	0.86–1.15	0
Cesarean delivery	10 ²⁵⁻³⁴	361/2748	405/2675	0.85	0.75–0.97	47
Labor duration >12 h	3 ³¹⁻³³	75/741	156/763	0.46	0.30–0.70	53
Hyperstimulation	5 ^{25,27,30,31,34}	147/722	76/724	1.91	1.49–2.45	35
Use of epidural analgesia	4 ^{28,31,32,34}	630/1025	617/1046	1.04	0.97–1.11	3
Postpartum hemorrhage ^b	4 ^{30-32,34}	67/923	69/934	1.00	0.73–1.37	0
Maternal blood transfusion	2 ^{28,34}	2/505	2/510	1.01	0.14–7.14	0
Uterine atony	1 ³⁴	2/154	2/156	1.01	0.14–7.10	-
Uterine rupture	1 ³⁰	0/249	1/242	0.32	0.01–7.91	-
Shoulder dystocia	2 ^{28,34}	8/505	5/510	1.62	0.53–4.90	0
Chorioamnionitis	2 ^{30,34}	33/403	44/398	0.75	0.50–1.14	0
Intrapartum meconium	3 ^{28,29,31}	73/676	92/692	0.82	0.62-1.09	23
FHR abnormality	3 ^{27,28,30}	108/700	111/696	0.96	0.76–1.20	24
Fetal distress	4 ^{29,30,32,33}	19/915	15/933	1.30	0.66–2.54	0
Meconium aspiration	1 ²⁹	2/125	1/133	2.13	0.20–23.18	-
Apgar score <7 at 5 min	6 ^{25,29-32,34}	18/1074	15/1089	1.18	0.61–2.28	0
Umbilical artery pH <7.10	2 ^{28,30}	20/607	14/597	1.42	0.72–2.78	0
Admission to NICU	5 ^{28,29,31,32,34}	65/1150	64/1179	1.05	0.76–1.46	0
Very satisfied with labor	1 ³²	190/243	169/225	1.04	0.94–1.15	_

Cl, confidence interval; FHR, fetal heart rate; NICU, neonatal intensive care unit; RR, relative risk.

^a Measured by interaction test (I²)-heterogeneity score of >50% suggests high variability between study outcomes, making metaanalysis result unreliable; ^b Postpartum hemorrhage refers to >500 mL.

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reduction in cesarean delivery. Based on the data from these trials, 1 cesarean is avoided for every 50 patients treated by high-dose oxytocin augmentation. High-dose oxytocin was also associated with an increase in spontaneous vaginal deliveries and a shortened labor. While the risk of hyperstimulation was increased with high-dose oxytocin, there was no evidence of an increase in adverse maternal or neonatal outcomes with this approach to care.

A frequent challenge for obstetricians is how to reduce maternal and neonatal morbidity when faced with arrested or protracted progress in labor. Although oxytocin is widely used in obstetric care, there is a lack of consensus with respect to the optimal oxytocin dosage, safety, and efficacy of this intervention. Relative to vaginal delivery, cesarean section has been shown to be associated with a range of serious maternal³⁷ and neonatal³⁸ morbidities. The rate of cesarean delivery has been shown to be associated with the need for postpartum antibiotic treatment² and an increased risk of disorders of placentation and unexplained stillbirths in subsequent pregnancies.³⁹ We were unable to demonstrate a reduction in maternal or neonatal morbidity associated with this reduction in cesarean section.

Our results indicate that high-dose oxytocin augmentation is associated with an increased risk of uterine hyperstimulation. Hyperstimulation can be associated with negative effects on fetal oxygen status and fetal heart rate patterns.⁴⁰ We have no information on the

specific frequency or severity of fetal heart rate tracing abnormalities associated with the hyperstimulation observed in included trials. The results from our study provide no evidence of an increase in adverse maternal or neonatal outcomes associated with high-dose oxytocin use.

Variations of AML are widely used in managing slow progress in labor in the belief that oxytocin augmentation reduces the need for cesarean section.⁴¹ The full package of active management has been recently reported to be associated with a modest, but nonstatistically significant reduction in cesarean deliveries (RR, 0.88; 95% CI, 0.77–1.01).⁴² AML includes early administration of high-dose oxytocin augmentation for prolonged labor. In a previous systematic re-

view focusing on the timing for the oxytocin administration (early vs delayed), we failed to demonstrate an effect of early intervention on the rate of cesarean section (RR, 0.87; 95% CI, 0.71–1.06).⁴³ The results of the current review, including our stratified analysis, suggest that the high-dose oxytocin may be more important in preventing cesarean section than the actual timing of the oxytocin intervention.

A cost-analysis comparing high-dose vs low-dose oxytocin protocols was documented in only 1 trial.³⁰ The authors estimated an hourly cost for intravenous oxytocin administration with standard maternal and fetal monitoring. For example, if one assumes a cost of \$140/h,³⁰ and assuming that labor was shortened by approximately 1.5 hours with highdose oxytocin augmentation, the average reduction in the labor and delivery cost for the high-dose group thus would approximate \$210/patient. These savings would have occurred secondary to shortening of labor and do not include any estimates of cost reduction secondary to decreased cesarean delivery rates.

Our review has some limitations. First, the decision criteria for cesarean section were not standardized in most studies and could have been applied in an imbalanced fashion across study groups. Second, most of the trials were conducted without blinding, which may have resulted in procedure bias, with the decision to proceed to cesarean section influenced by the provider's knowledge of the oxytocin dose. Third, we have limited data on compliance to the respective protocols in most trials. In addition, most of the trials have no documentation of women's views concerning the treatment administered. It is possible that high-dose oxytocin could be associated with an increase in labor pain; however none of the trials documented this outcome.

In summary, high-dose oxytocin augmentation of labor was found to be associated with a moderate reduction in the rate of cesarean section, a small increase in the rate of spontaneous vaginal deliveries and shortened labor, with potential significant cost savings in clinical care. Further large, simple double-masked trials are needed to determine the safety, effectiveness, acceptability, and cost implications of this approach in obstetric care. In planning oxytocin augmentation for labor management, the maternal and fetal characteristics including medical history, parity, and indicators of maternal and fetal well-being should be considered. Women should be informed of both the potential beneficial effects of high-dose oxytocin augmentation on mode of delivery as well as its possible effects on comfort.

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