The Effect of Early Oxytocin Augmentation in Labor

A Meta-Analysis

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OBJECTIVE: To estimate the effects of early augmentation with oxytocin for slow progress of labor on the delivery method and on indicators of maternal and neonatal morbidity.

DATA SOURCES: We conducted electronic database searches of PubMed, MEDLINE, EMBASE, and the Cochrane Library for articles published through February 2009 using the keywords "oxytocin," "augmentation," "active management of labor," "cesarean section," and "labor." Primary authors were contacted directly if the data sought were unavailable.

METHODS OF STUDY SELECTION: We included randomized controlled trials comparing early oxytocin augmentation with a more conservative approach to care in labor. We included only those studies in which membrane management was similar in the two groups. Early oxytocin augmentation was defined as immediate oxytocin administration when dystocia was identified. Data were extracted by two authors independently and evaluated for potential sources of bias. Relative risk (RR) and 95% confidence interval (CI) were calculated using fixed and random effects models.

TABULATION, INTEGRATION, AND RESULTS: Nine trials with 1,983 women met the inclusion criteria. Early oxytocin was associated with an increase in the probability of spontaneous vaginal delivery (RR 1.09, 95% CI 1.03–1.17). For every 20 patients treated with early oxytocin augmentation, one additional spontaneous vaginal delivery is expected. Although the point estimate for the effect on cesarean delivery (RR 0.87, 95% CI 0.71–1.06) and on operative vaginal delivery (RR 0.84, 95% CI 0.70–1.00) showed modest protective effects, the CIs for both estimates included the null effect. A decrease in antibiotic use (RR 0.45, 95% CI 0.21–0.99) was observed with early intervention. Early oxytocin was associated with an increased risk of hyperstimulation (RR 2.90, 95% CI 1.21–6.94) without evidence of adverse neonatal effects. Women in the early oxytocin group reported higher levels of pain and discomfort in labor.

CONCLUSION: Early oxytocin for augmentation in labor is associated with an increase in spontaneous vaginal delivery.

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The rise in the operative delivery rate, particularly cesarean delivery, continues to be a matter of obstetric concern.[1] Continued increase in cesarean deliveries may influence maternal and fetal mortality and morbidity.[2] Prolonged labor or dystocia has been described as one of the leading indications for cesarean delivery in situations where labor ceases to progress to spontaneous vaginal delivery.[3,4] Efforts to improve the medical management of dystocia have the potential to decrease the risk of cesarean delivery and to decrease both maternal and infant morbidity.

Dystocia is a term used for abnormalities of labor progress and usually refers to abnormally slow cervical dilatation.[4] O'Driscoll proposed a partogram that includes as a diagnostic criterion for dystocia a 1 cm/h line originating at admission.[5] Philpott proposed an alternative partogram in which the intervention

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Table 1. Characteristics of the Included Studies

Study	Country	Study Design	Total Sample Size (n)	Participants
Blanch et al 1998[31]	United Kingdom	RCT	41	Women in active phase of spontaneous labor with intact membranes, cephalic presentation in term
Bidgood and Steer 1987[34]	United Kingdom	RCT	60	Nulliparae in spontaneous labor at term, vertex presentation
Hemminki et al 1985[35]	Finland	RCT	57	Women in spontaneous labor in active phase, single fetus with cephalic presentation
Hinshaw et al 2008[36]	United States	RCT	412	Nulliparae in spontaneous labor at term, singleton fetus with vertex presentation
Hunter 1993[37]	Canada	RCT	532	Nulliparae in spontaneous labor, single term fetus, vertex presentation
Labrecque et al 1994‡	Canada	RCT	80	Nulliparae in spontaneous labor, single term fetus, cephalic presentation
Pattinson et al 2003[38]	South Africa	RCT	694	Nulliparae in term in the active phase without maternal and fetal complications
Read et al 1981[39]	United States	RCT	14	Women in active labor with failure to progress over 1 h
Shennan et al 1995[40]	United Kingdom	RCT	93	Nulliparae in labor, singleton and vertex presentation, no oxytocin use before entry to the study

RCT, randomized controlled trial.
* Cervical dilatation at randomization, values are given as mean or ‡ median.
† Group 1, early oxytocin augmentation group; group 2, control group.
‡ Unpublished trial.

threshold for dystocia is based on an action line that is parallel to that proposed by O'Driscoll but four hours to the right.[6] Peisner et al found that more than 50% of patients in spontaneous labor had not entered the active phase by 4 cm of cervix dilatation and suggests that dystocia should be diagnosed only in cases of delay after cervical dilatation has reached 5 cm.[7]

Active management of labor has been proposed as an alternative approach to the problem of dystocia, as well as a strategy to reduce the rate of cesarean delivery.[5] Active management is based on the hypothesis that the most frequent cause of dystocia is inadequate uterine action. Oxytocin administration, a key component of the active management of labor, has been demonstrated to increase the frequency and intensity of uterine contractions. Augmentation of labor with oxytocin is a frequent intervention in modern obstetric practice.[8] When labor fails to progress, oxytocin is administered to augment contractile effort in the belief that this will enable labor to progress to a normal vaginal delivery. Early intervention with oxytocin is not without its risks. Uterine hyperstimulation and fetal heart rate abnormalities may result from oxytocin administration.[9] The frequency of such complications needs to be better quantified.

Over the past two decades, a number of randomized clinical trials have assessed the effectiveness of early oxytocin administration, either alone or in combination with other interventions.[10–30] To date, there is a lack of consensus with respect to optimal timing for oxytocin augmentation in the presence of a labor delay. This systematic review was designed to estimate the effects of early oxytocin augmentation for delay in labor on method of delivery and on indicators of maternal and neonatal morbidity. Given recent calls for a more rational approach to the use of oxytocin,[8] the present review is particularly relevant.

SOURCES

A comprehensive literature search was performed using several search strategies. Published studies were identified through manual searches and through a computerized search of PubMed, MEDLINE, and EMBASE in any language through February 2009. The keywords were "oxytocin," "augmentation," "active management of labor," "cesarean section," and

Cervical Dilatation* (cm)	Labor Progress at Randomization	Intervention†
4.9	Dystocia: the rate of progress crossed the action line on the partogram, or no progress over 2 h	Group 1: immediate amniotomy and oxytocin Group 2: amniotomy followed by 4 h of expectant management
–	Dystocia: progression of cervical dilatation less than 0.5 cm/h	Group 1: immediate oxytocin infusion Group 2: expectant management for 8-h period
3.7	Dystocia: no progress more than 2 h	Group 1: immediate oxytocin infusion Group 2: ambulation without oxytocin for 4-h period
3.7	Dystocia: no progress more than 2 h	Group 1: immediate oxytocin infusion Group 2: ambulation without oxytocin for 4-h period
3.5	Normal	Group 1: oxytocin use if cervical dilatation less than 1 cm/h for 2 h Group 2: oxytocin use if cervical dilatation less than 0.5 cm/h for 4 h
2.7	Normal	Group 1: oxytocin use if cervical dilatation less than 1 cm/h for 2 h Group 2: expectant management for 8-h period
4.6	Normal	Group 1: oxytocin use if the line crossed by a single-line partogram Group 2: oxytocin use if the action line reached by a two-line partogram
4.4	Failure to progress over 1 h	Group 1: oxytocin infusion Group 2: ambulation
3.7	Normal	Group 1: oxytocin infusion Group 2: expectant management unless labor progress considered unacceptably slow

"labor." We attempted to identify unpublished reports through the Trial Registry of the Cochrane Collaboration Pregnancy and Child birth Review Group. Data from an unpublished trial was obtained through direct communication with the investigators.

STUDY SELECTION

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

Included studies had to meet the following criteria: 1) study design–a randomized controlled trial, 2) population–pregnant women in labor and without prior use of oxytocin, 3) interventions–compared a policy of early augmentation of labor with oxytocin with a more conservative form of management, and 4) outcomes–measured at least one of the following: cesarean delivery, spontaneous vaginal delivery, operative vaginal delivery, duration of labor, analgesia, hyperstimulation of labor, postpartum hemorrhage, maternal blood transfusion, antibiotic use, vaginal tears, and neonatal complications. Early oxytocin augmentation refers to the study intervention in which women in the experimental group were administered oxytocin immediately on the diagnosis of dystocia based on the predefined criteria (Table 1). The timing of oxytocin augmentation in the early-augmentation group varied across the studies, with a mean (or median) cervical dilatation at the time of oxytocin commencement of 5 cm or less. For patients allocated to conservative management, oxytocin administration was deferred for a further period, usually from 4 to 8 hours (Table 1). To isolate the effects of oxytocin, we selected only those trials in which membrane management was similar and standardized in the two comparison groups. Studies comparing oxytocin combined with amniotomy with management in which the membranes were left intact or with routine care were excluded from this review.[10–21]

The quality of the controlled trials was assessed separately by two independent reviewers (S.Q.W. and W.D.F.) in duplicate for four 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. Disagreements between evaluators were resolved by discussion with a third reviewer (Z.C.L.) to achieve

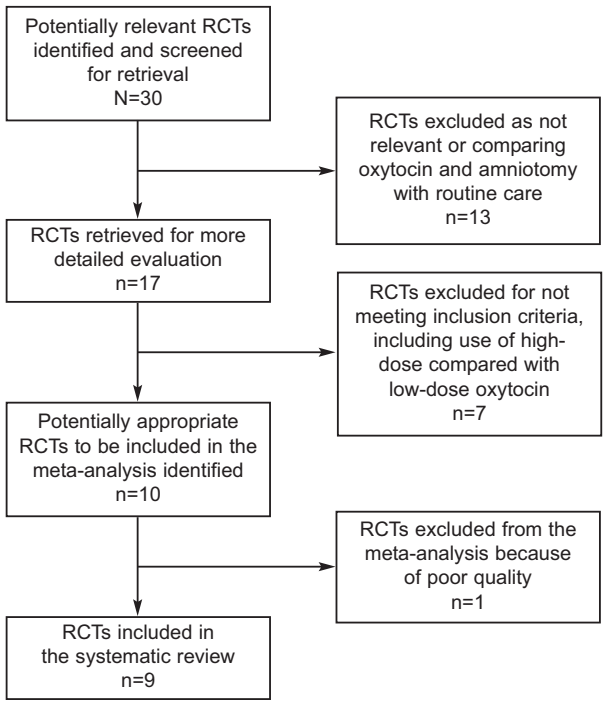

Fig. 1. Quality of Reporting of Meta-analyses flowchart. RCT, randomized controlled trial. *Wei. Early Oxytocin for Augmentation of Labor. Obstet Gynecol 2009.*

consensus. In one trial,[31] patients were randomly allocated to one of three management protocols: control (group 1), oxytocin in automatic infusion system (group 2), or high-dose oxytocin (group 3). After discussion, we included the trial, combining the results from the two intervention groups in the meta-analysis. Data were abstracted independently by the two reviewers and results compiled.

The data were extracted and statistical analysis carried out using Review Manager (RevMan) 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). 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 and event rate–weighted mean difference when outcomes were measured in the same way between trials. Each forest plot shows a point estimate for each study (with 95% CIs), with a diamond at the bottom representing the pooled point estimate with 95% CI for each outcome of interest. The presence of significant heterogeneity was explored by I^2 statistics.[32] In cases in which I^2 exceeded 50%, we pooled results using random effects models and explored the results for sources of variation.

RESULTS

A total of 30 randomized clinical trials were identified. A Quality of Reporting of Meta-analyses flow chart[33] (Fig. 1) shows an overview of the study-selection process. Of the 30 studies, 21 were excluded for the following reasons (Table 2): 14[10–23] because the comparisons did not meet our eligibility criteria, six because they studied only high-dose compared with low-dose oxytocin,[24–29] and one[30] because it had a large number of postrandomization exclusions (attrition rate 18%). Nine trials comprising 1,983 women were included in the analysis. The included trials and characteristics of the women at the time of randomization to the studies are summarized in Table 1. Of the nine trials that were identified, one was unpublished (Labrecque M, Brisson-Carroll G, Fraser W, Plourde D. Evaluation of obstetrical labor augmenta-

Table 2. Summary of Excluded and Included Randomized Controlled Trials

Randomized Controlled Trials	Reasons for Exclusion or Inclusion
Bréart 1992[10],Cammu 1996[11], Cluett 2004[12], Cohen1987[13], Frigoletto 1995[14], Hogston 1993[15], Lopez-Zeno 1992[16], Rogers 1997[17], Sadler 2000[18], Serman 1995[19], Somprasit 2005[20], Tabowei 2003[21]	Excluded because oxytocin+amniotomy compared with routine care
Rouse 1994[22]	Excluded because compared oxytocin+amniotomy with oxytocin
Cummiskey 1989[23]	Excluded because compared pulsatile-infusion oxytocin with continuous-infusion oxytocin
Satin 1992[24], Lazor 1993[25], Xenakis 1995[26], Merrill 1999[27], Majoko 2002[28], Jamal 2004[29]	Excluded because compared high-dose with low-dose oxytocin
Cardozo 1990[30]	Excluded because of a large number of postrandomization exclusions
Blanch 1998[31], Bidgood 1987[34], Hemminki 1985[35], Hinshaw 2008[36], Hunter 1993[37], Labrecque 1994*, Pattinson 2003[39], Read 1981[39], Shennan 1995[40]	Included because study met the inclusion criteria and compared a policy of early augmentation of labor with oxytocin with a more conservative form of management

* Unpublished trial.

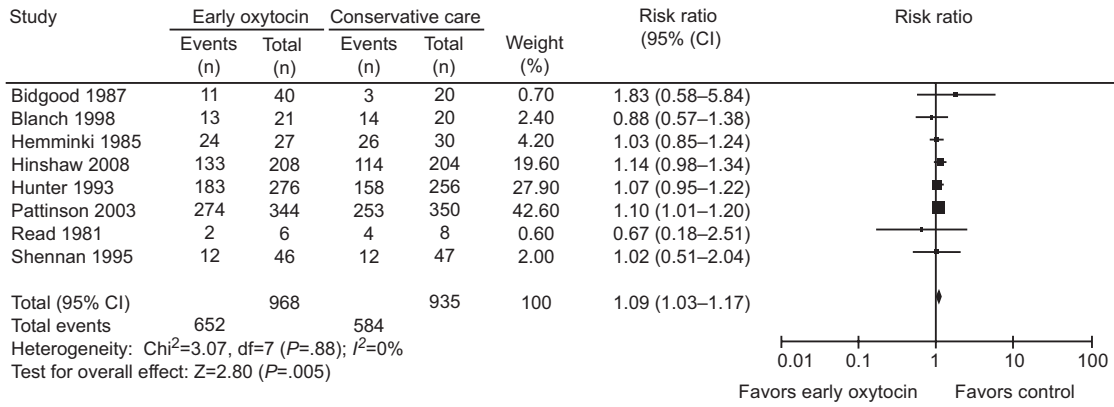

Fig. 2. Forest plot of studies comparing early oxytocin augmentation and conservative care, examining the effect on spontaneous vaginal delivery. CI, confidence interval.

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tion with oxytocin during the latent phase: a pilot study. 1994). Eight were published in peer-reviewed journals.[31,34–40] All nine trials that met the eligibility criteria were evaluated by two reviewers independently with respect to the four criteria relating to potential bias. Oxytocin use was blinded in only one trial.[40] Randomization blinding, when performed, was by coded ampoules of either oxytocin or placebo in one study[40] and by sealed envelopes in the remaining studies (Labrecque et al, unpublished trial).[33–39]

Five trials enrolled women with established slow progress in labor.[33–36,39] The remaining trials enrolled women who were in normal spontaneous labor, allocating them either to an intention to implement early oxytocin if abnormal progress ensued or to more conservative management. The characteristics of the included trials are presented in Table 1. In all studies, the more interventionist policy consisted of early oxytocin infusion for slow progress in labor; oxytocin was used in women in the control group only if a more marked delay in labor progress ensued. The severity of delay that justified oxytocin use in the control group varied from routine care to an 8-hour period of expectant management after randomization. In seven of the nine trials, participating women underwent amniotomy if the membranes were intact before randomization. In one trial,[31] amniotomy was performed in both groups at the time of randomization. In another trial,[38] shortly after recruitment commenced, concerns were raised about the possible association between membrane rupture and vertical transmission of human immunodeficiency virus. An amendment to the protocol was introduced whereby artificial rupture of membranes was to be avoided in both groups. We performed a sensitivity analysis excluding these two trials,[31,38] and there was no significant effect of their exclusion on outcomes ($P>.05$).

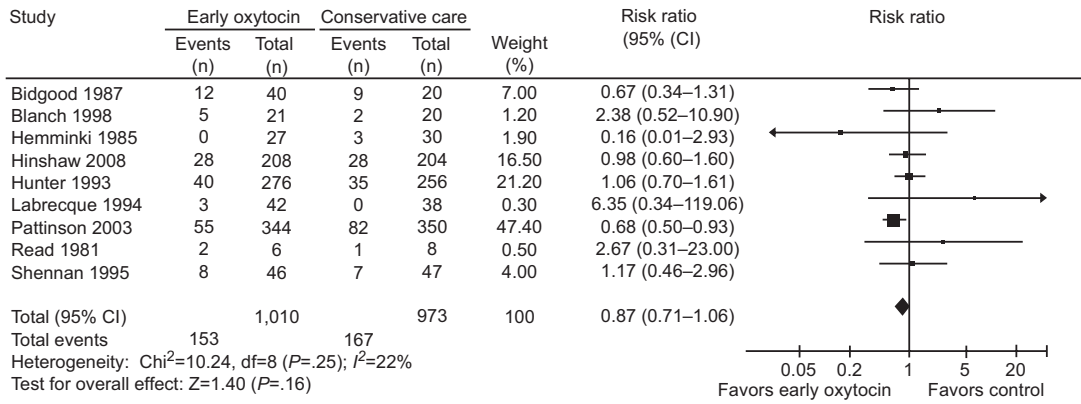

Fig. 3. Forest plot of studies comparing early oxytocin augmentation and conservative care, examining the effect on cesarean delivery. CI, confidence interval.

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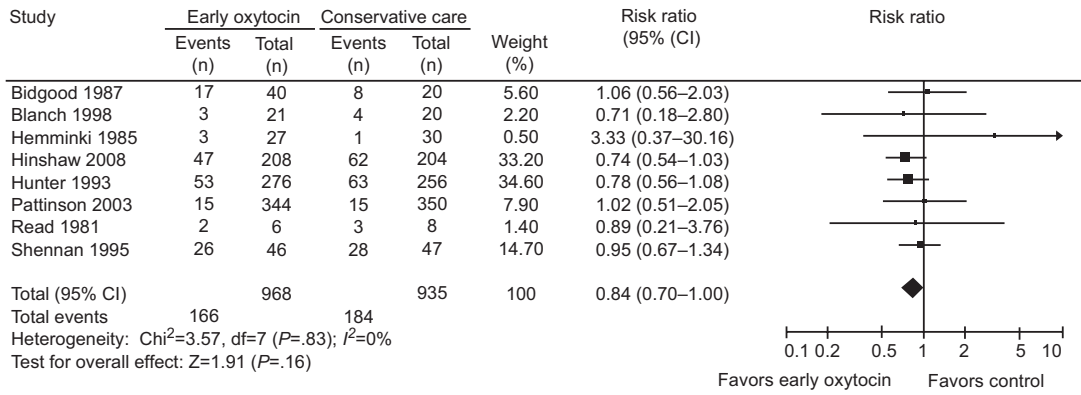

Fig. 4. Forest plot of studies comparing early oxytocin augmentation and conservative management, examining the effect on operative vaginal delivery. CI, confidence interval.

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The effect of oxytocin augmentation on the rate of spontaneous vaginal delivery is presented in Figure 2. Early oxytocin was associated with an increase in spontaneous vaginal deliveries (RR 1.09, 95% CI 1.03–1.17). There was no evidence of heterogeneity across trials. The number needed to treat was 20. For every 20 patients treated with early oxytocin augmentation, one additional spontaneous vaginal delivery was expected. Figure 3 shows the effect of oxytocin augmentation on the cesarean delivery rate. The point estimate suggested a modest reduction in the cesarean delivery rate but included the null effect (RR 0.87, 95% CI 0.71–1.06). Similarly, there was a modest reduction in operative vaginal deliveries with early oxytocin augmentation; however, the null effect could not be excluded (RR 0.84, 95% CI 0.70–1.00) (Fig. 4).

Four trials (Labrecque et al, unpublished trials),[33–35] reported on the mean interval from admission (or randomization [Labrecque et al, unpublished trial][33]) to delivery. There was no statistical evidence of a reduction in the duration of this interval associated with early oxytocin augmentation (weighted mean difference −1.36 hours, 95% CI −2.82 to 0.09). There was a protective effect of early intervention on the use of antibiotics in labor or postpartum (RR 0.45, 95% CI 0.21–0.99) (Table 3). Only one trial reported on intrapartum fever.[36] In this study, although the point estimate suggested a protective effect of early oxytocin on fever (RR 0.48), the null effect could not be excluded (95% CI 0.14–1.60). There was no evidence of an effect of early oxytocin augmentation on a range of other adverse maternal outcome indicators, including postpartum

Table 3. Effect of Early Oxytocin Augmentation of Slow Labor on Maternal and Neonatal Outcomes

Outcome	Studies	Early Oxytocin	Control	RR	95% CI	Heterogeneity* (%)
Use of epidural analgesia	5[31,35–37, Labrecque†]	376/574	372/548	0.97	0.85–1.12	47
Hyperstimulation	2[34,36]	23/248	6/224	2.90	1.21–6.94	0
Postpartum hemorrhage‡	3[35,36,40]	50/281	52/281	0.95	0.67–1.35	19
Maternal blood transfusion	2[36,37]	16/484	15/460	1.03	0.51–2.05	0
Vaginal tears	1[35]	6/27	9/30	0.74	0.30–1.81	–
Pyrexia	1[36]	4/208	8/204	0.49	0.15–1.60	–
Antibiotic use§	2[36,37]	9/484	19/460	0.45	0.21–0.99	0
Fetal or neonatal death	3[36–38]	3/828	1/810	2.33	0.35–15.64	0
Fetal distress	4[31,35–37]	16/532	15/510	1.06	0.53–2.12	15
Apgar score less than 7 at 5 min	6[31,34–37,40]	11/618	10/577	0.99	0.44–2.26	0
Jaundice or hyperbilirubinemia	4[35–37,40]	16/557	25/537	0.66	0.38–1.16	0
Admission to SCBU	5[31,35–37,40]	36/578	35/557	0.97	0.63–1.50	0

RR, relative risk; CI, confidence interval; SCBU, special care baby unit.

* Measured by the interaction test (I^2). A heterogeneity score of more than 50% suggests a high variability between study outcomes, making the meta-analysis result unreliable.

† Unpublished trial.

‡ Postpartum hemorrhage refers to greater than 500 mL.

§ Antibiotic use refers to maternal antibiotic use in labor or postpartum.

hemorrhage (greater than 500 mL), maternal blood transfusion, and use of epidural analgesia or narcotics.

Oxytocin augmentation was associated with a substantially increased risk of hyperstimulation (RR 2.90, 95% CI 1.21–6.94). However, there were no statistically significant differences between the early-oxytocin and conservative-management groups with respect to fetal or neonatal outcome indicators (Table 3).

Five studies assessed the effects of the policy of labor management on subjective outcomes. Blanch[34] used the Labor Agentry Scale to assess maternal satisfaction and found no difference between study groups. Labrecque et al (unpublished trial) reported that women in the early augmentation group were less satisfied with pain relief than were women in the control group (P=.003). Hemminki[35] reports that a larger percentage of women in the oxytocin-augmentation group than in the control group viewed the treatment they received as unpleasant (52% compared with 10%, P<.01). Hinshaw[36] studied postnatal depression and attitudes toward pregnancy and showed no differences between the two groups. Read[39] reports that women in the early-oxytocin group were more likely to have increased pain compared with women in the control group (100% compared with 12.5%, P<.01).

CONCLUSION

The main finding of our review was the increase in spontaneous vaginal deliveries associated with a policy of early oxytocin use. For every 20 patients treated by early oxytocin augmentation, one additional spontaneous vaginal delivery is expected. Although we were unable to confirm statistically an effect on the competing outcomes of cesarean delivery and operative vaginal delivery, the point estimates indicate that reductions in both of these procedures contributed to the increase in spontaneous vaginal deliveries. The results of the studies reporting on maternal views indicate that women in the early-oxytocin group were more likely to report an unpleasant experience or to be dissatisfied with pain in labor. The risk of hyperstimulation was increased substantially with early oxytocin. However, there were no significant associations between early oxytocin augmentation and adverse neonatal outcomes.

A frequent dilemma for obstetricians is how to minimize maternal and neonatal morbidity when faced with arrested progress in labor. Although oxytocin is used widely in obstetric care, there is a lack of consensus with respect to the optimal timing, risks, and benefits of the intervention. Both forms of operative delivery are associated with increased morbidity: operative vaginal delivery increases both maternal and neonatal trauma,[41] and cesarean delivery increases maternal febrile morbidity and postpartum complications.[1,2] Although we were unable to demonstrate a reduction in maternal or neonatal morbidity associated with this increase in spontaneous deliveries, most studies did not provide data on vaginal and perineal tears. The results of the studies reporting on maternal views indicate that women in the early-oxytocin group were more likely to report an unpleasant experience or to be dissatisfied with pain relief in labor. Oxytocin could increase the intensity of uterine contractions and thus increase pain; however, this effect might be counterbalanced by the higher likelihood of spontaneous delivery.

A decreased requirement for antibiotic use was noted in the intervention group. The potential mechanism of this effect is uncertain. Information on why the antibiotics were administered was not provided in the included trials. There were no data available on chorioamnionitis in the nine trials.

Our results indicate that early 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.[42] We have no information on the frequency or severity of fetal heart rate tracing abnormalities associated with this hyperstimulation in included trials. The results from our study provide no evidence of an increase in adverse maternal or neonatal outcomes associated with oxytocin use; the meta-analysis was relatively underpowered to detect rare serious maternal and neonatal adverse outcomes owing to the small sample sizes in most trials.

Variations of the active management of labor described by O'Driscoll et al are used widely in managing slow progress of labor in the belief that oxytocin augmentation minimizes the need for cesarean delivery for dystocia.[5] Oxytocin as a key component of active management of labor has been assessed for the effect on the cesarean delivery rate in a number of randomized clinical trials.[33–40] The full package of active management recently has been reported to be associated with a modest but not statistically significant reduction in the rate of cesarean deliveries (RR 0.88, 95% CI 0.77–1.01).[43] We previously reported that early oxytocin and early amniotomy were associated with a small, nonsignificant reduction in the rate of cesarean deliveries (OR 0.88, 95% CI 0.72–1.07) compared with a more conservative approach.[44] There is a need for better information concerning the effects of oxytocin, both in patients with conservatively managed membranes

and in those in whom amniotomy is performed. In a systematic review of amniotomy as an isolated intervention, the point estimate of the effect of amniotomy suggested an increased risk of cesarean delivery (RR 1.26, 95% CI 0.98–1.62), although the 95% CI included the null effect.[45] However, when combined with oxytocin, the direction of the effect appears to be reversed. [44] In this systematic review, amniotomy was performed in both groups for patients with intact membranes, either before or at the time of randomization. This balanced management of the membranes had the effect of isolating early oxytocin as the main contrast between groups. However, by subjecting patients in both groups to amniotomy, the actual number of cesarean deliveries may have been increased. The common practice of including amniotomy as a complement to oxytocin for labor augmentation may not be beneficial and indeed could mask the benefits of oxytocin. Our systematic review does not address the question of the effects of oxytocin use in the context of intact membranes. There is a need for studies of oxytocin alone as a strategy for labor augmentation in patients with intact membranes.

Our review has some limitations. First, in most trials, there is a lack of documentation of other aspects of care during childbirth such as continuous professional support, mobility, and positions during labor. Two included trials[35,39] compared early oxytocin with ambulation. We conducted a sensitivity analysis by excluding these two trials; the results were similar. It was difficult to determine how these cointerventions interacted with the medical components of active management and their effects on clinical outcomes. Second, we have limited data on compliance to the respective protocols in most trials. There were protocol deviations in one trial[38] whereby 27.0% of women in the early-intervention group did not receive oxytocin when indicated, and there was a delay in administration in a further 6.1%. Third, the degree of delay that justified the use of oxytocin augmentation varied across trials. It is possible that the criteria used for the diagnosis of dystocia could affect cesarean delivery rates. Finally, this meta-analysis focused on the timing of oxytocin augmentation and not on the dose used. The oxytocin regimens used in the included studies varied with respect to dose of oxytocin. A recent review that studied high-dose compared with low-dose oxytocin for labor augmentation found no evidence of an effect of dose on delivery method.[46]

In summary, early oxytocin augmentation of labor is associated with an increase in the rate of spontaneous vaginal delivery. The variability in the labor management protocol across trials calls for a larger trial to obtain more solid conclusions. Further research is needed to determine the safety, efficacy, acceptability, and cost implications of this approach in obstetric care. In planning labor management, women should be informed of both the potential beneficial effects of early oxytocin augmentation on delivery method as well as its possible effects on discomfort and pain. The approach to care should take into consideration the woman's views.

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