American Journal of Obstetrics and Gynecology (2006) **194**, 809–14

ELSEVIER

American Journal of Obstetrics & Gynecology

www.ajog.org

Epidural analgesia associated with low-dose oxytocin augmentation increases cesarean births: A critical look at the external validity of randomized trials

Andrew J. Kotaska, MD,[a] Michael C. Klein, MD,[b] Robert M. Liston, MD[a]

Department of Obstetrics and Gynaecology,[a] Department of Family Practice,[b] University of British Columbia, Vancouver, British Columbia, Canada

Received for publication June 9, 2005; revised August 5, 2005; accepted September 29, 2005

KEY WORDS
Epidural analgesia
External validity
Oxytocin
Cesarean section
Randomized trials

Objective: Randomized controlled trials suggest epidural analgesia (EA) does not increase the frequency of cesarean births compared with opioid analgesia. We analyzed trials comparing EA with opioid analgesia to determine their external validity in contemporary North American practice.

Study design: Randomized controlled trials comparing EA with opioid analgesia were identified from the Cochrane database and Medline and included if they reported labor outcomes and management protocols. Labor management was then compared with current obstetric practice determined from surveys of North American teaching maternity units and clinical practice guidelines.

Results: Of 19 trials identified, 8 were included. Seven trials used Active Management of Labor protocols that used high-dose oxytocin; each demonstrated no epidural-related increase in cesarean births. One trial that used low-dose oxytocin demonstrated a marked increase in cesarean births. Most large North American obstetric units use low-dose oxytocin.

Conclusion: Randomized trials showing no effect of EA on cesarean section (CS) rate lack external validity in much of North American practice. The limited data available suggest EA and low-dose oxytocin used together increase the CS rate. Early detection of dystocia and high-dose oxytocin augmentation should be considered for women receiving EA; those delivering in low-dose oxytocin settings should be advised of a probable increase in the likelihood of CS.

The strengths of randomized controlled trials (RCTs) have vaulted them to the status of gold standard among research methodologies. Nonetheless, generalizability of their results to individual patients and practice settings remains a concern.[1,2] RCTs and systematic reviews have evolved sophisticated methods of assessing and reporting the internal validity of trials, while largely neglecting issues of external validity.[1] A trial must be internally valid to be external valid, but internal validity alone does not ensure generalizability. Assessing external validity requires a comparison of trial conditions and subjects with real-world clinical settings and populations. Such assessments are rare in the literature, leaving

Reprints not available from the authors. Address correspondence to Andrew J. Kotaska, University of British Columbia, Department of Obstetrics & Gynaecology 2H30, B. C. Women's Hospital, 4490 Oak Street, Vancouver, B. C. V6H3V5, Canada

E-mail: Kotaska@bulkley.net

0002-9378/$ - see front matter © 2006 Mosby, Inc. All rights reserved.
doi:10.1016/j.ajog.2005.09.014

Table I Randomized trials comparing EA with opioid analgesia: Trial characteristics and analgesia regimens

Study	n			Cross-over		Bupivicaine	Fentanyl	Meperidine	
	O	E	% P_0	O→E	E→O	Conc.	Conc.	Dose (mg)	PRN Interval
Bofill et al[3]	51	49	100	24%	4%	0.125%	1.5 μg/mL	*	q1-2 h
Clark et al[4]	162	156	100	52%	3%	0.125%	1 μg/mL	50-75 IV	q90 min
Howell et al[9]	185	184	100	28%	N/A	0.25%	—	50-100 IM	N/A
Loughnan et al[5]	310	304	100	56%	14%	0.125%	—	100 IM	q2 h × 3
Ramin et al[6,†]	437	432	56	—	—	0.125%	2 μg/mL	50 IV	Max 200/4 h
Ramin (ITT)	666	664	52	15%	N/A	0.125%	2 μg/mL	50 IV	Max 200/4 h
Sharma et al[7]	357	358	54	2%	1%	0.125%	2 μg/mL	50 IV PCA	10-15 mg q10 min
Sharma et al[8]	233	226	100	6%	N/A	0.0625%	2 μg/mL	50 IV PCA	15 mg q10 min
Thorp et al[16]	45	48	100	2%	0	0.125%	—	75 IV	q90 min

O, Opioid; *E,* epidural; *P_0,* nulliparous; *IV,* intravenous; *IM,* intramuscular; *ITT,* intention to treat analysis; *PCA,* patient controlled analgesia.

* Butorphanol 1-2 mg IV q1-2 h.

† Protocol-compliant subjects only.

most decisions regarding the external validity of evidence up to individual practitioners.

The effect of epidural analgesia (EA) on labor progress and delivery outcome has been controversial for decades. Early retrospective reports showing increased cesarean section (CS) rates associated with EA have since been refuted by RCTs.[3-9] The current Cochrane meta-analysis comparing EA with opioid analgesia found no increase in CS rate and better analgesia with EA. However, EA prolonged labor, increased fetal malposition, oxytocin augmentation and instrumental delivery, and was associated with more maternal fever and hypotension, but no difference in neonatal outcome.[10]

Additional systematic reviews have reached similar conclusions, leading to consensus within obstetric and anesthesia circles that EA does not increase the risk of CS.[11,12] The American College of Obstetricians and Gynecologists (ACOG) committee opinion on pain relief during labor reflects this belief: EA provides the best pain relief during labor and a woman's request for one is indication enough to provide it.[13] Accordingly, from 1981 to 1997, epidural usage increased from 22% to 66% of all US births.[8] Paralleling the sharp rise in epidural usage has been a rise in CS rate. The discrepancy between high contemporary CS rates and the low CS rates reported in trials forming the Cochrane meta-analysis prompted us to examine the external validity of published RCTs in contemporary North American practice.

Material and methods

All RCTs comparing EA with parenteral opioid analgesia in labor were identified from the 2003 Cochrane meta-analysis and Medline (1966-2003). Trials involving low-risk singleton cephalic term pregnancies were included if they described labor management practices and reported labor outcomes, including the incidence of CS. Information on subject parity, labor management, oxytocin augmentation, and delivery method were summarized. Trial research methodology was reviewed, but our focus was on external rather than internal validity. The University of British Columbia's Research Ethics Board approved the study.

Questionnaires were sent to the Obstetrics and Gynecology department chairs of all 17 Canadian medical schools. Data on labor management practices, oxytocin protocols, EA availability, and CS rates were requested, and incomplete responses were followed up by telephone. A convenience sample of 10 large US maternity units was determined from a geographically broad but otherwise nondirected Internet search of academic department and hospital Web sites. Similar information was obtained by telephone or email from attending, resident, or nursing staff; however, information on CS rates and Active Management of Labor (AML) use were not reliably available. ACOG and Society of Obstetricians and Gynaecologists of Canada (SOGC) dystocia and labor management guidelines were reviewed.[14,15] Labor management practices in academic North American practice were then compared with those found within RCTs comparing epidural with opioid analgesia.

Results

Of 19 randomized trials identified, 8 were included: 5 from the 2003 Cochrane review[3,4,6,7,16] and 2 from Medline.[5,8,9] Eleven trials were excluded because labor management and/or outcome data were lacking (8), because they were subsets of other trials (1), or because they were in abstract form only (2). Included trials are summarized in Tables I and II. All 8 trials, except Ramin et al, reported an intention-to-treat analysis. Intention-to-treat data for Ramin has since been published and is included separately.[17] All trials required women to be in active labor before analgesia was administered and included only

Table II Randomized trials comparing EA with opioid analgesia: Labor protocols and CS rates

			Oxytocin augmentation		Oxytocin protocol			C/S rate		
Study	AML	IUPC Goal (MVU)	O (%)	E (%)	Start dose (mU/min)	Increase (mU/min)	Interval (min)	O (%)	E (%)	*P* =
Bofill et al[3]	Yes	200-250	82	69	6	6	q30	6	10	NS
Clark et al[4]	Yes	<240	72	75	6	6	q15	14	10	NS
Howell et al[9]*	Yes	N/A	55	62	2.5	2.5 then 5	q30	9	7	NS
Loughnan et al[5]	Yes	†	57	61	4	4	q15	13	12	NS
Ramin et al[6,‡]	Yes	200-250	23	32	6	6	q40	4	9	.002
Ramin (ITT)	Yes	200-250	N/A	N/A	6	6	q40	6	6	NS
Sharma et al[7]	Yes	200-250	15‡	33‡	6	6	q40	5	4	NS
Sharma et al[8]	Yes	200-250	45	34	6	6	q40	9	7	NS
Thorp et al[16]	No	N/A	27	58	1	1	q30-45	2	25	<.05

MVU, Montevideo units.

* Data from University Hospital of North Staffordshire.

† Clinical goal: 7 contractions in 15 min.

‡ Protocol compliant subjects only.

women in spontaneous labor, except Loughnan et al,[5] in which 30% of women were induced. All trials compared intravenous or intramuscular narcotic with 0.125% bupivicaine epidural infusions, with or without fentanyl, except Sharma et al[8] (0.0625% infusion) and Howell et al[9](0.25% boluses). Six trials included only nulliparous women and 2 included women of mixed parity.

Later trials are consistent in their approach to labor management but differ markedly from Thorp et al.[16] In contrast to Thorp et al, all used AML-style protocols involving artificial rupture of membranes on admission, vaginal examinations every 1 to 2 hours, oxytocin for cervical dilation less than 1 cm/h, and usually intrauterine pressure catheters (IUPC) to diagnose and manage dystocia. Their oxytocin augmentation protocols used 4 to 6 times the dose used by Thorp et al. Thorp et al noted a marked difference in CS rate associated with EA (25%) versus opioid analgesia (2%), whereas all later trials maintained very low CS rates in the range of 9% to 10% in both the EA and opioid arms.

Crossover hampered the interpretation of intention-to-treat analysis in many studies, particularly those studies involving only nulliparous women.[5,6,7,11] In Bofill et al[3] and Howell et al,[9] one quarter of women randomly assigned to opioid analgesia received EA, and in Clark et al[4] and Loughnan et al,[5] more than half received EA. Conventionally, crossover rates above 5% to 10% call the internal validity of a randomized trial into question.[11] Only Thorp et al[16] and Sharma had crossover rates under 10%. No trial reported assessment of possible reduction in CS rate in both arms of the trial compared with the baseline rate before institution of the trial or in nonparticipants (Hawthorne effect).

ACOG and SOGC dystocia guidelines support the use of low-dose oxytocin.[14,15] ACOG supports the use of either low or high-dose oxytocin regimens starting from 0.5 to 6 mU/min with increases from 1 to 6 mU/min at intervals of 15 to 40 minutes. No qualification is made for the presence of EA. SOGC guidelines recommend low-dose oxytocin starting at 1 to 2 mU/min with increases of 1 to 2 mU/min at intervals of 30 to 60 minutes. Fifteen responses were obtained from 17 Canadian academic maternity units (Table III); 10 responses were obtained from large geographically diverse US centers (Table IV). EA is universally available in all units 24 hours per day, 7 days per week. With few exceptions, the maternity units sampled used low-dose oxytocin and do not use AML-style protocols.

Comment

Despite the Cochrane reviewer's conclusion that "the results of the trials are consistent with each other," the Cochrane meta-analysis of RCTs comparing EA with opioid analgesia demonstrates great heterogeneity: Thorp's results differ markedly from those of the other trials in the meta-analysis.[10] Clark et al attributed this discrepancy to differences in oxytocin use and labor management, concluding that "Our more aggressive use of oxytocin than in the Thorp et al and Ramin et al trials may in part be responsible for our lower and equal cesarean delivery rate.…By adopting an aggressive attitude toward labor management… and adhering to strict criteria for the diagnosis of dystocia, clinicians may administer epidural analgesia without increasing the cesarean delivery rate."[4] In the Cochrane and other meta-analyses, the results of Thorp et al have been statistically overwhelmed by the larger sample sizes of the subsequent trials; yet despite the rigor of these analyses, the importance of labor management and oxytocin dosage to the external validity of the evidence remains underappreciated.[10-12,18]

Crossover hampers the internal validity of 4 studies and is examined in detail by Lieberman and

Table III Labor management in Canadian academic maternity units

Center	AML	Oxytocin augmentation			C/S rate (%)	Approx.EA rate (%)	Deliveries per y*
		Initial dose (mU/min)	Increment (mU/min)	Interval (min)			
1	No	1-2	1-2	q30-60	28	68	7000
2	No	2	2	q30	26	58	12000
3	No	1-2	1-2	q30-60	25	50	4500
4	Yes	2 (4)†	2 (4)†	q30	19	61	3000
5	No	1	3	q30	21	80	5000
6	No	1,2,4	4	q30	21	52	5000
7	No	1-2	1-2	q30	21	71	5500
8	Yes	1-2	1-2	q30	24	80	2500
9	No	2	2	q30	25	80	9000
10	No	2	2	q30	30	59	3000
11	No	2	1-2	q30	24	60	3000
12	No	2	2	q15	16	85	2500
13	No	1	1	q30	25	90	8500
14	No	1-2	2	q30	26	70	5500
15	No	1-2	1-2	q30	28	70	2300

* Approximate; some values represent more than 1 hospital.
† Higher dose for nulliparous women.

Table IV Labor management in US academic maternity units

US region	Oxytocin augmentation			Deliveries per y*
	Initial dose (mU/min)	Increment (mU/min)	Interval (min)	
Northwest	0.5	1-2	q30	2000
California	1	1-2(4†)	q20-30	3400
California	1-2	1-2	q30	9000
California	1	1	q20-30	3000
California	1	1-2	q30	2000
Central	1-2	1-2	q20-30	4500
New York	1-2	1-2	q20-30	5000
New England	1-2	1-2	q15-30	9400
Northwest	6 or 1‡	6 or 1-2‡	q40	2500
New England	2	2	q15	9000

* Approximate; some values represent more than 1 hospital.
† "Fast-track" for nulliparous parturients: increase by 4 mU/min.
‡ Optional low- or high-dose protocol.

O'Donoghue[11] in their meta-analysis. When significant numbers of subjects cross from one treatment group into another but remain in their original group for purposes of analysis, the statistical validity of any findings is seriously diluted. Crossover rates of 5% to 10% have been suggested as a threshold above which a study becomes suspect. Restricting crossover from opioid to EA presents an ethical dilemma as it would involve more pain for women randomly assigned to opioid analgesia. Nonetheless, although crossover rates of 25% to 50% may have been ethically unavoidable in certain trials, they provide much less information about the true effect of EA on labor and CS rate. Grouping them in meta-analysis with studies lacking crossover limits both internal and external validity. Combining studies of nulliparous women with trials involving women of mixed parity also limits the external validity of the analysis for either group alone.

In Dublin, birthplace of AML, CS rates are among the lowest in the industrialized world, particularly in spontaneously laboring nulliparous women, most of whom now receive EA.[19] For unclear reasons, efforts to reproduce AML outside of Ireland have met with varied success.[20-22] Nonetheless, evidence that epidurals do not increase cesarean births comes exclusively from settings in which dystocia is aggressively diagnosed and treated with oxytocin starting at 4 to 6 mU/min, reaching 12 mU/min within 1 hour if needed. Such data are not valid in settings in which dystocia is diagnosed less rigorously and oxytocin is started at 1 to 2 mU/min. Among RCTs comparing EA with opioid analgesia, Thorp alone has validity in practice settings using low-dose oxytocin.

A single RCT provides thin evidence; and Thorp et al involved only 93 women before the trial was stopped early because of the large difference in CS rate. Additional information on the combination of low-dose oxytocin and EA is provided by 2 RCTs that did not compare epidural versus opioid analgesia and were not included in our analysis. Instead, both Xenakis et al[23] and Merril and Zlatnik[24] randomly assigned laboring women with a 70% epidural rate to either low- or high-dose oxytocin. Xenakis et al randomly assigned 310 women of mixed parity to low-dose oxytocin starting at 1 mU/min increasing by 1 mU/min every 30 minutes or to high-dose oxytocin starting at 4 mU/min increasing by 4 mU/min every 15 minutes (an 8-fold

difference in dose-increase per unit time). The CS rate in the high-dose group was 10% versus 26% in the low-dose group ($P = .001$). Interestingly, the average maximum dose of oxytocin in the high-dose group was 9 mU/min, suggesting the rate of increase is more important than the maximum dose.

Merril and Zlatnik enrolled 1307 women and compared 1.5 mU/min with 4.5 mU/min increments every 30 minutes (a 3-fold difference in dose-increase per unit time) for both augmentation and induction. Length of labor, the primary outcome, was shortened with high-dose oxytocin in both groups. Although the study was not designed to look at effect on CS, a nonsignificant reduction in CS rate was noted with high-dose oxytocin for induction (11.3% vs15.0%), in nulliparous women (11.7% vs 17.3%) and for "cephalopelvic disproportion" (5.9% vs 11.9%). The greater difference in CS rates found in the trial of Xenakis et al may stem from a greater relative increase in oxytocin dose between arms than in the trial of Merril and Zlatnik, suggesting a dose-response curve with medium-dose oxytocin only partially correcting the dystocic effects of EA.

Collectively, the 7 studies showing no increase in CS rate with EA (predominantly in nulliparous women) achieved CS rates under 10% in both arms, far lower than the 20% to 25% reported for populations overall. This suggests the possibility of a Hawthorne effect: an improvement in labor management and a reduction in CS rate conferred to all trial subjects. Early detection and treatment of dystocia, enforced by protocol in these seven studies, has been shown to lower CS rate. Unfortunately, baseline oxytocin augmentation information and CS rates were not reported, precluding detection of a Hawthorne effect. An alternative explanation is that these centers had particularly low CS rates to begin with, which would further limit the trials' external validity. This was certainly true for the Sharma and Ramin studies, in which baseline institutional CS rates were consistently under 10%. Conversely, the 25% CS rate in Thorp's EA group was more typical of contemporary population CS rates, as was the 26% CS rate in low-dose oxytocin arm of the trial of Xenakis et al, highlighting the importance of dystocia management and high-dose oxytocin in the presence of EA.

Our analysis has limitations. Although it is comprehensive for Canadian teaching maternity units, it may not be representative of nonacademic community practice. However, teaching hospitals using SOGC guidelines set practice standards in most Canadian provinces and we are aware of only 1 community hospital currently using high-dose oxytocin. Our examination of US practice is less comprehensive. Certain US centers, particularly those associated with the included US trials, use high-dose oxytocin. Although geographically diverse, our convenience sample of just 10 large US maternity units provides only a brief sketch of oxytocin use across the nation. A more comprehensive analysis of US practice would better clarify the magnitude of the current gap in external validity; however, clinicians, aware of their own labor management policies, can judge for themselves the external validity of the evidence in their individual setting.

EA provides superior pain relief to opioid analgesia in labor, but there are important consequences to its use. Even with AML and the diluting effect of crossover, RCTs demonstrate longer labors and a doubling of malposition and operative vaginal delivery rates (with associated perineal trauma) with EA.[10] These effects are likely more pronounced in low-dose oxytocin settings. By compensating for the slowing effect of EA on labor, however, high-dose oxytocin can prevent an increase in CS rate. The drawback of high-dose oxytocin is an increased incidence of hyperstimulation, not associated with adverse neonatal outcome.[15,19-25]

RCTs showing no effect of EA on CS rate lack external validity in practice settings using low-dose oxytocin for labor augmentation, including most Canadian teaching and many large US maternity units. The sole RCT comparing EA and non-EA in a low-dose oxytocin setting and 2 RCTs comparing oxytocin dosage in high EA rate settings suggest EA increases the risk of CS. A trial comparing oxytocin doses in parturients with EA is urgently needed; however, until further evidence is available, women choosing EA should have dystocia assiduously diagnosed and management with high-dose oxytocin should be considered. Women requesting EA in low-dose oxytocin settings should be advised of a probable increased likelihood of CS. Future RCTs evaluating the effect of oxytocin dosage on CS rate in women with EA should include baseline pretrial data as well as data on nonparticipants to detect any Hawthorne effect.

RCTs and systematic reviews preferentially report parameters of internal validity. Structured assessments of external validity are uncommon in the current literature. Consequently, gaps exist between the conditions found in RCTs and those in real-world practice. Our analysis of labor management protocols reveals a gap between RCTs examining the effect of EA on CS rate and contemporary North American obstetric practice. As suggested by Rothwell, increased systematic assessment and reporting of the external validity of RCTs may assist clinicians to avoid such gaps and more effectively translate evidence into practice.[1]

References

1. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" Lancet 2005;365: 82-93.
2. Tonelli MR. The philosophical limits of evidence-based medicine. Acad Med 1998;73:1234-40.

3. Bofill JA, Vincent RD, Martin RW, Norman PF, Werhan CF, Morrison JC. Nulliparous active labor, epidural analgesia, and cesarean delivery for dystocia. Am J Obstet Gynecol 1997; 177:1465-70.
4. Clark A, Carr D, Loyd G, Cook V, Spinnato J. The influence of epidural analgesia on cesarean delivery rates: a randomized, prospective clinical trial. Am J Obstet Gynecol 1998;179: 1527-33.
5. Loughnan BA, Carli F, Romney M, Dore CJ, Gordon H. Randomized controlled comparison of epidural bupivicaine versus pethidine for analgesia in labour. Br J Anaesth 2000;84:715-9.
6. Ramin SM, Gambling DR, Lucas MJ, Sharma SK, Sidawi JE, Leveno KJ. Randomized trial of epidural versus intravenous analgesia during labour. Obstet Gynecol 1995;86:783-9.
7. Sharma SK, Sidawi JE, Ramin SM, Lucas MJ, Leveno KJ, Cunningham G. A randomized trial of epidural versus patient-controlled meperidine analgesia during labor. Anesthesiology 1997;87:487-94.
8. Sharma SK, Alexander JM, Messick G, Bloom SL, McIntire DD, Wiley J, Leveno KJ. A randomized trial of epidural analgesia versus intravenous meperidine analgesia during labor in nulliparous women. Anesthesiology 2002;96:546-51.
9. Howell CJ, Kidd C, Roberts W, Upton P, Lucking L, Jones PW, et al. A randomised controlled trial of epidural compared with non-epidural analgesia in labour. BJOG 2001;108:27-33.
10. Howell CJ. Epidural versus non-epidural analgesia for pain relief in labour. Cochrane Database Syst Rev 2003;2:CD000331.
11. Lieberman E, O'Donoghue C. Unintended effects of epidural analgesia during labor: a systematic review. Am J Obstet Gynecol 2002; 186(Suppl Nature):S31-68.
12. Leighton BL, Halparin SH. The effects of epidural analgesia on labor, maternal, and neonatal outcomes: a systematic review. Am J Obstet Gynecol 2002;186(Suppl Nature):S69-77.
13. American College of Obstetricians and Gynecologists Committee on Obstetric Practice. Pain relief during labor. Washington (DC): The College; 2000. ACOG committee opinion no. 231.
14. Society of Obstetricians and Gynaecologists of Canada. Dystocia. Ottawa, Canada: SOGC; 1995. SOGC Policy statement no. 40.
15. American College of Obstetricians and Gynecologists. Dystocia and augmentation of labor. Washington (DC): The College; 2003. ACOG practice bulletin no. 49.
16. Thorp JA, Hu DH, Albin RM, Mcnitt J, Meyer BA, Cohen GR, et al. The effect of intrapartum analgesia on nulliparous labor: a randomized, controlled, prospective trial. Am J Obstet Gynecol 1993;169:851-8.
17. Sharma SK, Leveno KJ. Update: epidural analgesia during labor does not increase cesarean births. Curr Anesthesiol Reports 2000; 2:18-24.
18. Thacker SB, Stroup DF. Methods and interpretation in systematic reviews: commentary on two parallel reviews of epidural analgesia during labor. Am J Obstet Gynecol 2002;186(Suppl Nature):S78-80.
19. Bohra U, Donnelly J, O'Connell MP, Geary MP, MacQuillan K, Keane DP. Active management of labour revisited: the first 1000 primiparous labours in 2000. J Obstet Gynaecol 2003;23:118-20.
20. Frigolletti F, Lieberman E, Lang J, Cohen A, Barss V, Ringer S, et al. A clinical trial of active management of labor. N Eng J Med 1995;333:745-50.
21. Lopez-Zeno J, Peaceman A, Adashek J, Socol M. A controlled trial of a program for the active management of labor. N Engl J Med 1992;326:450-4.
22. Akoury H, Brodie G, Caddick R, McLaughin V, Pugh P. Active management of labor and operative delivery in nulliparous women. Am J Obstet Gynecol 1988;158:255-8.
23. Xenakis EMJ, Langer O, Piper JM, Conway D, Berkus MD. Low-dose versus high-dose oxytocin augmentation of labor: a randomized trial. Am J Obstet Gynecol 1995;173:1874-8.
24. Merril D, Zlatnik F. Randomized, double-masked comparison of oxytocin dosage in induction and augmentation of labor. Obstet Gynecol 1999;94:455-63.
25. Satin A, Leveno K, Sherman M, Brewster D, Cunningham F. High- versus low-dose oxytocin for labor stimulation. Obstet Gynecol 1992;80:111-6.