American Journal of Obstetrics and Gynecology (2005) **192**, 747–52

ELSEVIER

American Journal of OBSTETRICS and GYNECOLOGY

www.ajog.org

Prospective randomized clinical trial of inpatient cervical ripening with stepwise oral misoprostol vs vaginal misoprostol

Iris Colón, MD, Kaytha Clawson, MD, Kennith Hunter, DPA, Maurice L. Druzin, MD, M. Mark Taslimi, MD*

Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, Calif, and Department of Political Science and Public Administration, Jacksonville State University, Jacksonville, Ala

Received for publication November 19, 2004; revised December 20, 2004; accepted December 21, 2004

KEY WORDS
Misoprostol
Cervical ripening
Labor induction
Hyperstimulation

Objective: The purpose of this study was to compare the efficacy and safety of stepwise oral misoprostol vs vaginal misoprostol for cervical ripening before induction of labor.
Study design: Two hundred and four women between 32 to 42 weeks of gestation with an unfavorable cervix (Bishop score ≤ 6) and an indication for labor induction were randomized to receive oral or vaginal misoprostol every 4 hours up to 4 doses. The oral misoprostol group received 50 μg initially followed by 100 μg in each subsequent dose. The vaginal group received 25 μg in each dose. The primary outcome was the interval from first misoprostol dose to delivery. Patient satisfaction and side effects were assessed by surveys completed after delivery.
Results: Ninety-three (45.6%) women received oral misoprostol; 111 (54.4%) received vaginal misoprostol. There was no difference in the average interval from the first dose of misoprostol to delivery in the oral (21.1 + 7.9 hrs) and vaginal (21.5 + 11.0 hrs, P = NS) misoprostol groups. The incidence of hyperstimulation in the oral group was 2.2% vs 5.4% in the vaginal group, P = NS. Eighteen patients in the oral group (19.4%) and 36 (32.4%) in the vaginal group underwent cesarean section ($P < .05$). This difference was attributed to better tolerance of more doses of misoprostol by the women in the oral group. There was no difference in side effects (nausea, vomiting, diarrhea, shivering) between groups. Fourteen percent of women in the vaginal group versus 7.5% in the oral group were dissatisfied with the use of misoprostol (P = NS).
Conclusion: Stepwise oral misoprostol (50 μg followed by 100 μg) appears to be as effective as vaginal misoprostol (25 μg) for cervical ripening with a low incidence of hyperstimulation, no increase in side effects, a high rate of patient satisfaction, and is associated with a lower cesarean section rate.

Oral presentation at the 25th Annual Meeting of the Society for Maternal-Fetal Medicine, February 7-12, 2005, Reno, Nev.
* Reprint requests: M. Mark Taslimi, MD, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Stanford University, 300 Pasteur Drive, Room HH333, Stanford, CA 94305-5317.
E-mail: mtaslimi@stanford.edu

0002-9378/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.ajog.2004.12.051

Induction of labor has merit as a therapeutic option when the benefits of delivery outweigh the risks of continuing the pregnancy. Lack of adequate cervical ripening is a known obstacle to successful labor induction and expeditious delivery.[1] Obstetricians use a variety of agents and methods to ripen the uterine cervix, achieve a shorter induction to delivery interval, and potentially lower the cesarean section rate. Acceptable methods for cervical ripening include synthetic prostaglandin E1 (PGE1) and prostaglandin E2 (PGE2) analogs, continuous oxytocin infusion, and mechanical cervical dilators.

One of the most widely used agents for cervical ripening is misoprostol, a synthetic methyl ester of prostaglandin E1, approved for the prevention of peptic ulcer disease by the FDA, but not approved for obstetric indications.[2] Nevertheless, its use for cervical ripening and labor induction has been extensively studied, and has been accepted as an effective and safe method for these purposes.[3,4]

Vaginal, as well as oral, misoprostol administration has been used, but the optimal dose of oral misoprostol has not been established.[5-15] In general, higher doses of oral misoprostol are associated with improved efficacy but higher rates of hyperstimulation and maternal side effects than vaginal misoprostol.[16-18] Oral misoprostol at 100 μg or 200 μg every 3 to 6 hours has been shown to have the same or improved efficacy as vaginal misoprostol but higher rates of uterine contractile abnormalities.[7,9,19] In contrast, titrated low-dose oral misoprostol (20 μg every 2 hours increased to 40 μg) has been demonstrated to be as efficacious as dinoprostone (PGE2 analog) with no difference in hyperstimulation or other side effects.[10]

Oral misoprostol is an attractive option, as it is inexpensive and stable at room temperature, and has the potential for providing increased patient satisfaction because of its noninvasive route of administration. Moreover, the possibility of misplacement is eliminated.

Previous studies have shown rapid absorption of oral misoprostol with peak plasma concentration at 34 ± 17 minutes and a nadir at 120 minutes. In contrast, vaginal misoprostol peaks at 80 ± 27 minutes, and declines slowly.[20]

Based on pharmacokinetics, previously published regimens, and incidence of side effects, we chose a novel dosing regimen of oral misoprostol. We hypothesized that stepwise dosing of oral misoprostol (50 μg followed by 100 μg) would be as effective for cervical ripening as vaginal misoprostol in the ACOG approved dose of 25 μg every 4 hours, without increasing the rates of hyperstimulation, and with the potential for greater patient satisfaction.

Material and methods

We conducted this prospective randomized clinical trial in the Department of Obstetrics and Gynecology at the Labor and Delivery Unit in Lucile Packard Children's Hospital, Stanford University. This hospital serves as a Northern California tertiary referral center for high-risk pregnancies. Patients were recruited from March 3, 2003 through July 25, 2004. This study was approved by the Institutional Review Board, and written informed consent was obtained from each participant.

Inclusion criteria included pregnancy between 32 and 42 weeks of gestation admitted for induction of labor because of either obstetric or medical complications, Bishop score ≤ 6, intact or ruptured membranes, cephalic presentation, and a reassuring fetal heart rate (FHR) pattern. Exclusion criteria included nonreassuring fetal heart rate pattern, any contraindication to labor and/or vaginal delivery (placenta previa, vasa previa, active genital herpes), uterine scar, suspected placental abruption with abnormal FHR pattern, vaginal bleeding other than "bloody show," cervical dilation of ≥ 4 cm, uterine contractions ≥ 3 in 10 minutes, significant maternal cardiac, renal or hepatic disease, maternal glaucoma, or hypersensitivity to misoprostol or prostaglandin analogs.

Treatment arm allocation was determined by the use of a computer-generated table of random numbers. The randomization assignments were placed into opaque, sealed envelopes. All eligible women were invited to participate and, after obtaining informed written consent, the next envelope in sequence was opened by the patient's obstetrician to determine the treatment allocation.

Women assigned to the stepwise oral misoprostol arm received 50 μg initially, followed by 100 μg every 4 hours up to 4 doses; those assigned to the vaginal misoprostol arm received 25 μg every 4 hours up to 4 doses. All women had continuous electronic FHR and uterine contraction monitoring. Subsequent doses of misoprostol were withheld if adequate uterine activity (≥ 3 contractions in 10 minutes) or a Bishop score ≥ 8 had been achieved, or active labor had begun. If needed, oxytocin was initiated 4 hours after the last misoprostol dose. Amniotomy was used liberally at the discretion of the managing obstetricians.

Uterine contractility patterns and FHR monitoring tracings were evaluated after delivery by the first author, who was blinded to study group assignment. Tachysystole was defined as >5 contractions in 10 minutes for 2 consecutive 10-minute periods. Hypertonus was defined as a single contraction lasting more than 2 minutes. Hyperstimulation syndrome was defined as tachysystole or hypertonus with nonreassuring FHR changes. FHR changes considered to be nonreassuring were late decelerations, severe variable decelerations, prolonged decelerations, tachycardia, or reduced FHR variability as defined by the National Institute of Child Health and Human Development Research Planning Workshop.[21,22]

Table I Baseline demographics

Characteristic	Oral misoprostol (n = 93)	Vaginal misoprostol (n = 111)	*P* value
Maternal age (y)	28.1 ± 6.7	27.2 ± 6.4	NS
Gestational age (wk)	38.8 ± 1.9	39.1 ± 1.8	NS
Parity (no.)			
Nulliparous	56 (60.2%)	85 (76.6%)	< .01
Multiparous ≥1	37 (39.8%)	26 (23.4%)	
Ethnicity			NS
White	23 (24.7%)	25 (22.5%)	
African American	1 (1.1%)	6 (5.4%)	
Hispanic	52 (55.9%)	59 (53.2%)	
Asian	5 (5.4%)	6 (5.4%)	
Indian	4 (4.3%)	5 (4.5%)	
Other	8 (8.6%)	10 (9.0%)	
Bishop score ≤2	48 (51.6%)	70 (63.1%)	NS
Intact membranes	89 (95.7%)	104 (93.7%)	NS

Data presented as mean ± SD or number (%).

Table II Indications for induction

Induction	Oral misoprostol (n = 93)	Vaginal misoprostol (n = 111)	*P* value
Postdates	30 (32.3%)	46 (37.3%)	NS
Hypertension	26 (28.0%)	29 (26.1%)	NS
Diabetes	10 (10.8%)	7 (6.3%)	NS
Oligohydramnios	7 (7.5%)	8 (7.2%)	NS
Others	20 (21.5%)	21 (18.9%)	NS

Data presented as number (%).

The primary outcome was the interval from first misoprostol dose to delivery. The sample size calculation (n = 194) was based on an alpha of .05 and a beta of .20 to detect a 4-hour difference. Secondary outcomes were incidence of tachysystole, hypertonus, and hyperstimulation syndrome, vaginal delivery achieved within 24 hours, the rate of cesarean section, patient satisfaction, and neonatal outcomes. Treatment side effects and patient satisfaction were assessed by surveys completed in the postpartum ward.

Statistical analyses were performed using χ^2 test, Fisher exact test, linear regression, Student *t* test, and analysis of variance (ANOVA) where appropriate. SPSS for Windows, version 12.0 (SPSS Corporation, Chicago, Ill) statistical software was used for all computations.

Results

A total of 212 women were enrolled in the study: 8 were excluded because they did not meet inclusion criteria. Of the 204 women included, 93 (45.6%) received oral misoprostol, and 111 (54.4%) received vaginal misoprostol.

Table III Time intervals to delivery

Characteristic	Oral misoprostol (n = 93)	Vaginal Misoprostol (n = 111)	*P* value
First dose to delivery (h)	21.1 ± 7.9	21.5 ± 11.0	NS
First dose to vaginal delivery (h)	19.3 ± 6.7	18.0 ± 8.3	NS
Vaginal delivery in 12 h	12 (16.0%)	18 (24.0%)	NS
Vaginal delivery in 24 h	56 (74.7%)	63 (84.0%)	NS

Data presented as mean ± SD or number (%).

Table IV Mode of delivery

Characteristic	Oral misoprostol (n = 93)	Vaginal misoprostol (n = 111)	*P* value
All vaginal deliveries	75 (80.6%)	75 (67.6%)	< .05
Spontaneous	71 (94.7%)	68 (90.6%)	NS
Assisted	4 (5.3%)	7 (9.3%)	NS
Cesarean sections	18 (19.4%)	36 (32.4%)	< .05

Data presented as number (%).

Demographic characteristics are shown in Table I. The groups were similar with respect to age, gestational age, ethnicity, and Bishop score ≤2 at entry. There were more nulliparous women in the vaginal group (76.6% vs 60.2%, $P < .01$). The indications for induction are shown in Table II, and were similar between both groups. The most common indications were postdates and hypertension.

There was no difference in the average interval from the first dose of misoprostol to delivery in the oral (21.1 ± 7.9 hrs) and vaginal (21.5 ± 11.0 hrs, P = NS) misoprostol groups. When looking only at the women who delivered vaginally, there was no difference in the average interval from first dose to vaginal delivery between the oral (19.3 ± 6.7 hrs) and vaginal (18.0 ± 8.3 hrs, P = NS) groups. This finding held true after controlling for parity. Among the women who delivered vaginally, there was no difference in the number that delivered within 12 hours and within 24 hours between the 2 groups (Table III).

The mean number of misoprostol doses given was 1.84 ± 0.8 in the oral group, and 1.55 ± 0.7 in the vaginal group ($P < .01$). The mean interval between the first and second doses of misoprostol was 4.8 ± 1.8 hours in the oral group versus 4.5 ± 0.8 hours in the vaginal group (P = NS). The mean interval between subsequent doses ranged between 4.3 ± 0.5 hours to 5.7 ± 4.9 hours (P = NS). Twenty (9.8%) women made it to a Bishop score of ≥8. The most common indications for withholding a subsequent dose were adequate contractions (55.9%) or active labor (31.4%). Oxytocin augmentation was started in 91 (97.8%) women in the oral

Table V Characteristics of cesarean deliveries

Characteristic	Oral misoprostol (n = 18)	Vaginal misoprostol (n = 36)	*P* value
Indication			
Failure to progress	13 (72.2%)	21 (58.3%)	NS
NRFHT	4 (22.2%)	13 (36.1%)	NS
Others	1 (5.6%)	2 (5.6%)	NS
Parity			
Nulliparous	15 (83.3%)	35 (97.2%)	NS
Multiparous ≥1	3 (16.7%)	1 (2.8%)	NS
Doses of misoprostol			
1	2 (11.1%)	23 (63.9%)	< .01
≥2	16 (88.9%)	13 (36.1%)	

Data presented as number (%).

group, and in 108 (97.3%) women in the vaginal group (P = NS).

The mode of delivery differed significantly between groups (Table IV). Eighteen patients in the oral group (19.4%), and 36 (32.4%) in the vaginal group underwent cesarean section ($P < .05$). In a regression model, 21% and 30% of mode of delivery was explained by birth weight quartile and by primiparity, respectively.

The indications for cesarean deliveries are shown in Table V. There were no significant differences in the indications for cesarean delivery between groups. Among cesarean sections that were performed for failure to progress, there were no differences between study groups in the rates of arrest of dilation, arrest of descent, or active labor not achieved.

Other characteristics of the cesarean deliveries are shown in Table V. Fifty of the 54 cesarean sections were in nulliparas. There was no significant difference in the number of nulliparous women per group. The number of women in each study arm that received only 1 dose of misoprostol before cesarean section differed significantly; 11.1% in the oral vs 63.9% in the vaginal arm ($P < .01$). The majority (69.6%) of the women in the vaginal arm did not receive the second dose because they had achieved adequate uterine activity (≥3 contractions in 10 minutes). Of the 23 patients in the vaginal arm that received only 1 dose of misoprostol, 60.9% underwent cesarean section for failure to progress.

There were no significant differences in the occurrence of tachysystole, hypertonus, or hyperstimulation between groups (Table VI). Two of the women (both in the vaginal group) who experienced hyperstimulation syndrome received tocolysis (terbutaline or nitroglycerin). Of the 8 cases of hyperstimulation syndrome, only 1 woman (vaginal group) needed urgent delivery by cesarean section.

Nonreassuring FHR patterns that needed urgent delivery were noted in 8 (8.6%) of the women in the oral group, and in 18 (16.2%) of the women in the vaginal group. Of these, 5/8 and 12/18 underwent cesarean delivery.

Table VI Characteristics of labor, maternal outcomes, and side effects

	Oral misoprostol (n = 93)	Vaginal misoprostol (n = 111)	*P* value
Labor			
Oxytocin augmentation	91 (97.8%)	108 (97.3%)	NS
Epidural analgesia	79 (84.9%)	95 (85.6%)	NS
Tachysystole	26 (28.0%)	28 (25.2%)	NS
Hypertonus	4 (4.3%)	5 (4.5%)	NS
Hyperstimulation	2 (2.2%)	6 (5.4%)	NS
Use of tocolysis for hyperstimulation	0	2 (1.8%)	NS
Maternal outcomes			
Excessive blood loss	11 (11.8%)	18 (16.2%)	NS
Fever	5 (5.4%)	13 (11.7%)	NS
Retained placenta	1 (1.1%)	0	NS
Maternal side effects	(n = 67)	(n = 86)	
Nausea	9 (13.4%)	13 (15.1%)	NS
Vomiting	9 (13.4%)	11 (12.8%)	NS
Diarrhea	1 (1.5%)	1 (1.2%)	NS
Shivering	9 (13.4%)	11 (12.8%)	NS

Data presented as number (%).

Table VII Neonatal outcomes

	Oral misoprostol (n = 93)	Vaginal misoprostol (n = 111)	*P* value
Birth weight (g)	3283 ± 610	3352 ± 547	NS
Birth weight >4000 g	9 (9.7%)	14 (12.6%)	NS
Apgar score <7			
1 min	4 (4.3%)	16 (14.4%)	< .05
5 min	0	0	
Meconium passage	9 (9.7%)	11 (9.9%)	NS
Admission to neonatal intensive care unit	11 (11.8%)	11 (9.9%)	NS

Data presented as mean ± SD or number (%).

Treatment side effects and delivery complications were similar between the 2 groups (Table VI).

A total of 153 postdelivery surveys were completed. Patient satisfaction scores revealed that 98.5% of the women in the oral group and 98.8% in the vaginal group were satisfied with their total experience at the hospital during their induction of labor. Fourteen percent of women in the vaginal group vs 7.5% in the oral group were dissatisfied with the use of misoprostol (P = NS).

There were no differences in neonatal outcomes (Table VII) except in Apgar scores <7 at 1 minute, which were more frequent in the vaginal group (14.4% vs 4.3%, $P < .05$). Cord gases were obtained in 59

women (28.9%). Only 4 (2 in each group) had arterial pH <7.10.

Comment

Multiple trials have shown that misoprostol is an effective agent for cervical ripening and labor induction. Vaginal, as well as oral, misoprostol administration has been used, with 25 μg every 4 hours of vaginal misoprostol widely accepted as the most effective regimen with the least number of complications. The optimal dose of oral misoprostol has not been established.

Our purpose was to study the effectiveness of a novel dosing regimen of oral misoprostol (50 μg followed by 100 μg) compared with the standard regimen of vaginal (25 μg) misoprostol every 4 hours. Our rationale stems from the proven efficacy of oral misoprostol, and the hypothesis that our stepwise regimen would be as effective as vaginal misoprostol without increasing rates of complications.

Our study has demonstrated that stepwise oral misoprostol appears to be as effective as vaginal misoprostol for cervical ripening before labor induction. The average interval from first dose to vaginal delivery was similar between groups, and the same number of women in each study arm achieved vaginal delivery in 24 hours.

There was a low incidence of hyperstimulation in both groups (oral group 2.2% vs vaginal group 5.4%, P = NS). This compares favorably to a generally accepted incidence of hyperstimulation of 7% with vaginal administration.[4]

Our study found stepwise oral misoprostol to be well tolerated, with no increase in maternal side effects compared with vaginal misoprostol. Furthermore, the majority of the patients were satisfied with their hospital experience, and few women reported dissatisfaction with the route of administration (vaginal group 14% vs oral group 7.5%, P = NS).

Perhaps the most significant finding of our study is the lower cesarean section rate in the women who received the oral regimen. Detailed analysis was performed on the subgroup of women who underwent cesarean delivery. The only characteristic that was found to explain the difference in cesarean section rates was the number of misoprostol doses administered before delivery. The majority of patients in the vaginal arm received only 1 dose of misoprostol for ripening because they were found to be contracting ≥3 times in 10 minutes when the next dose was due.

Our interpretation is that patients tolerated the initial 50 μg oral misoprostol dose better than the 25 μg vaginal dose. Although the initial vaginal dose provided adequate uterine activity, it may paradoxically have been less effective in its primary goal of cervical ripening, as excess uterine contractions prevented further dosing. It is probable that the initial 50 μg oral dose prepared the cervix and the uterus to tolerate further doses of misoprostol, and this resulted in a higher rate of vaginal delivery. Other hypotheses to explain the lower cesarean section rate in the oral group include a dose-related or bioavailability effect, more effective priming of the myometrium to respond to endogenous/exogenous oxytocin, or simply a random effect of small numbers.

Our protocol might be considered conservative in that it called for discontinuation of misoprostol after ≥3 uterine contractions in 10 minutes were achieved, regardless of the strength of the contractions. While some patients with very mild contractions might safely benefit from additional misoprostol doses, this is a well-described protocol used in numerous peer-reviewed studies of cervical ripening with misoprostol. Moreover, the cesarean rates observed in both arms of this study compare favorably with those described in previous studies where misoprostol was also used for ripening of an unfavorable cervix. Our study has the limitation of lack of blinding, which may introduce a potential for bias.

In conclusion, we have shown that stepwise oral misoprostol appears to be as effective as vaginal misoprostol for cervical ripening with a low incidence of hyperstimulation, no increase in side effects, high rate of patient satisfaction, and is associated with a lower cesarean section rate.

References

1. Bishop E. Pelvic scoring for elective induction. Obstet Gynecol 1964;24:266-9.
2. Goldberg AB, Greenberg MB, Darney PD. Drug therapy: misoprostol and pregnancy. N Engl J Med 2001;344:38-47.
3. Committee on Obstetrics. Induction of labor. Washington: American College of Obstetricians and Gynecologists; 1999. ACOG Practice Bulletin No. 10.
4. Wing D. Labor induction with misoprostol. Am J Obstet Gynecol 1999;181:339-45.
5. Fisher SA, Mackenzie VP, Davies GAL. Oral versus vaginal misoprostol for induction of labor: a double-blind randomized controlled trial. Am J Obstet Gynecol 2001;185:906-10.
6. Wing DA, Ham D, Paul RH. A comparison of orally administered misoprostol with vaginally administered misoprostol for cervical ripening and labor induction. Am J Obstet Gynecol 1999;180:1155-60.
7. Wing DA, Park MR, Paul RH. A randomized comparison of oral and intravaginal misoprostol for labor induction. Obstet Gynecol 2000;95:905-8.
8. How HY, Leaseburge L, Khoury JC, Siddiqi TA, Spinnato JA, Sibai BM. A comparison of various routes and dosages of misoprostol for cervical ripening and induction of labor. Am J Obstet Gynecol 2001;185:911-5.

9. Toppozada MK, Anwar MYM, Hassan HA, El-Gazaerly WS. Oral or vaginal misoprostol for induction of labor. Int J Gynecol Obstet 1997;56:135-9.
10. Dallenbach P, Boulvain M, Viardot C, Irion O. Oral misoprostol or vaginal dinoprostone for labor induction: a randomized controlled trial. Am J Obstet Gynecol 2003;188:162-7.
11. Hofmeyr GJ, Alfirevic Z, Matonhodze B, Brocklehurst P, Campbell E, Nikodem VC. Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial. BJOG 2001;108:952-9.
12. Windrim R, Bennett K, Mundle W, Young DC. Oral administration of misoprostol for labor induction: a randomized controlled trial. Obstet Gynecol 1997;89:392-7.
13. Ngai SW, To WK, Lao T, Ho PC. Cervical priming with oral misoprostol in pre-labor rupture of membranes at term. Obstet Gynecol 1996;87:923-6.
14. Wing DA, Fassett MJ, Guberman C, Tran S, Parrish A, Guinn D. A comparison of orally administered misoprostol to intravenous oxytocin for labor induction in women with favorable cervical examinations. Am J Obstet Gynecol 2004;190:1689-96.
15. Le Roux PA, Olarogun JO, Penny J, Anthony J. Oral and vaginal misoprostol compared with dinoprostone for induction of labor: a randomized controlled trial. Obstet Gynecol 2002; 99:201-5.
16. Adair CD, Weeks JW, Barrilleaux S, Edwards M, Burlison K, Lewis DF. Oral or vaginal misoprostol administration for induction of labor: a randomized, double-blind trial. Obstet Gynecol 1998;92:810-3.
17. Carlan SJ, Bouldin S, Blust D, O'Brien WF. Safety and efficacy of misoprostol orally and vaginally: a randomized trial. Obstet Gynecol 2001;98:107-12.
18. Bartha JL, Comino-Delgado R, Garcia-Benasach F, Martinez-Del-Fresno P, Moreno-Corral LJ. Oral misoprostol and intracervical dinoprostone for cervical ripening and labor induction: a randomized comparison. Obstet Gynecol 2000;96:465-9.
19. Carlan SJ, Blust D, O'Brien WF. Buccal versus intravaginal misoprostol administration for cervical ripening. Am J Obstet Gynecol 2002;186:229-33.
20. Zieman M, Fong S, Benowitz N, Banskter D, Darney P. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997;90:88-92.
21. National Institute of Child Health and Human Development Research Planning Workshop. Electronic fetal heart rate monitoring: research guidelines for interpretation. Am J Obstet Gynecol 1997;177:1385-90.
22. Freeman RK. Problems with intrapartum fetal heart rate monitoring interpretation and patient management. Obstet Gynecol 2002;100:813-26.