OBSTETRICS

Induction of labor using one dose vs multiple doses of misoprostol: a randomized controlled trial

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BACKGROUND: Misoprostol is a common agent that is used to ripen the cervix and induce labor, yet there is no clear evidence of the optimal number of doses needed to achieve a higher rate of vaginal delivery.

OBJECTIVE: Our primary objective was to compare the rate of vaginal delivery within 24 hours between a 1-dose and a multiple-dose regimen of misoprostol for the induction of labor.

STUDY DESIGN: A randomized controlled trial was conducted from March 2016 to March 2017 that compared a single dose to up to 4 doses of misoprostol. Randomization was stratified by parity. Women with a singleton pregnancy ≥37 weeks gestation with intact membranes who had been admitted for labor induction with a Bishop score ≤6 were included. Our primary outcome was the rate of vaginal delivery within 24 hours. Secondary outcomes included time to vaginal delivery, cesarean delivery rate, and maternal and neonatal morbidity. Based on a power of 80%, an alpha of .05, and the assumption that 50% of women in the multiple-misoprostol group would deliver vaginally in 24 hours, a sample size of 220 patients was needed to detect a 20% increase in vaginal delivery rate within 24 hours in the 1-misoprostol group. Continuous variables were compared with the use of the Mann-Whitney test. Categoric variables were compared with the use of the Fisher's exact test. Probability values <.05 were considered statistically significant.

RESULTS: Two hundred fifty women were assigned randomly. Demographics and clinical characteristics were similar between groups. In the univariate analysis, there was no difference in the rate of vaginal delivery within 24 hours between the 1-misoprostol group and the multiple-dose group (41.7% vs 44.7%, respectively; *P*=.698) or time to vaginal delivery (1187 min vs 1321 min, respectively; *P*=.202). The 1-misoprostol group had a greater cesarean delivery rate (35.8% vs 22.8%; *P*=.034). In a Poisson regression that controlled for Bishop score before the initiation of oxytocin, parity, gestational age, body mass index, estimated fetal weight, artificial rupture of membrane at <6 cm, and Foley balloon placement, the treatment group was no longer associated with cesarean delivery rate. Instead, a Bishop score of <4 before the initiation of oxytocin and nulliparity were associated significantly with cesarean delivery rate.

CONCLUSION: In this first randomized controlled trial in the literature to compare a single with a multiple dosing of misoprostol, we found that the 1-dose regimen is an acceptable alternative for the induction for labor, especially for multiparous women and for patients with a Bishop score >4 after the first dose.

Key words: cesarean delivery, induction of labor, misoprostol, oxytocin, vaginal delivery rate

Rates of induction of labor have increased dramatically in the United Sates to nearly 40% of pregnancies, according to some studies.[1-3] Induction of labor increases the risk of cesarean delivery.[3] Nulliparity, patient's race, having an "unripe" cervix at the time of the induction, greater maternal age, body mass index, fetal weight, and length of induction are all associated with "failed inductions" that lead to a cesarean birth.[3-6] Nearly 50% of inductions occur in women with an unfavorable cervix.[2,7] An "unripe" cervix, typically characterized by a Bishop score of ≤6, has been associated with an increase in the cesarean delivery rate by 2- to 3-fold.[3,8]

Several cervical ripening techniques are thought to decrease the risk of a cesarean delivery. The most commonly used drugs for this purpose are prostaglandins.[9] Misoprostol is a synthetic analogue of prostaglandin E1 with a plasma half-life of <1 hour when given vaginally.[10] There are multiple studies that have evaluated different doses and different routes of delivery.[11-13] The dose most commonly recommended is 25 or 50 μg of misoprostol vaginally. However, there are few studies that address the repeat dosing and frequency of dosing of misoprostol. Although 3 hours might be the most appropriate interval based on the half-life, it is not known how well serum level correlates with clinical effect. Also, it is unknown whether repeat doses result in a cumulative effect or whether there is a latency period between the application of the drug and biochemical changes in the cervix. One study suggested a single dose is most effective if it is given 12 hours before oxytocin is initiated.[14] Repeat dosing may extend the latent phase of labor. A longer latent phase of labor is associated with an increased rate of cesarean delivery, chorioamnionitis, endometritis, and uterine atony.[15] The early addition of oxytocin may potentiate the action of prostaglandin and decrease the latency period. Prostaglandins have a close functional interaction with oxytocin. Oxytocin leads to the release of arachidonic acid and myometrial transcription of the cyclooxygenase-2 gene, which insures continuous prostaglandin production.[16] In addition, pretreatment with prostaglandins has been shown to increase the myometrial response to oxytocin significantly.[17]

We hypothesized that repeating the dose of misoprostol extends the cervical

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AJOG at a Glance

Why was this study conducted?

This study evaluated whether multiple doses of misoprostol are needed to expedite vaginal delivery in a patient with an unripe cervix.

Key Findings

Compared with women who received multiple dose of misoprostol, women who received 1 dose of misoprostol had a similar rate of vaginal delivery within 24 hours.

What does this add to what is known?

One dose of misoprostol is an acceptable regimen for the induction of labor.

ripening time and thus decreases the proportion of women who deliver vaginally within 24 hours after the administration of the first dose of misoprostol. Therefore, the objective of our study was to compare the rate of vaginal delivery within 24 hours among patients who undergo induction of labor between those who receive a single dose of misoprostol with those receive up to 4 doses of this medication.

Materials and Methods

We conducted a randomized-controlled study at the 2 labor units of the Montefiore Medical Center to compare the vaginal delivery rate within 24 hours between women assigned to 1 dose of misoprostol vs those assigned to a multiple-dose regimen for cervical ripening before induction of labor. Before study initiation, approval was obtained from the institutional review board of the Albert Einstein College of Medicine and registered with ClinicalTrials.gov (NCT02680314).

Participants were nulliparous and multiparous English-speaking women, ages 18−50 years, with singleton term pregnancies (≥37 weeks gestation), and with a Bishop score of ≤6 who were admitted for either elective or indicated induction of labor. Women were excluded if there was a contraindication to misoprostol or vaginal delivery, a fetal death, major fetal anomaly, fetal growth restriction, nonreassuring antepartum fetal testing, or premature rupture of membranes.

Patients were approached in the labor unit by an obstetric physician before the start of their induction. Eligibility criteria were confirmed before obtaining written consent. The participants were assigned randomly to 1 of the 2 treatment groups. Allocation concealment procedures occurred with the use of sequentially numbered, opaque sealed envelopes. A block randomization sequence of 4 was used, as determined by Randomization.com. Patients were stratified based on whether they were nulliparous or multiparous. Because of the nature of the study, neither the patients nor the labor providers were blinded to the assigned treatment group.

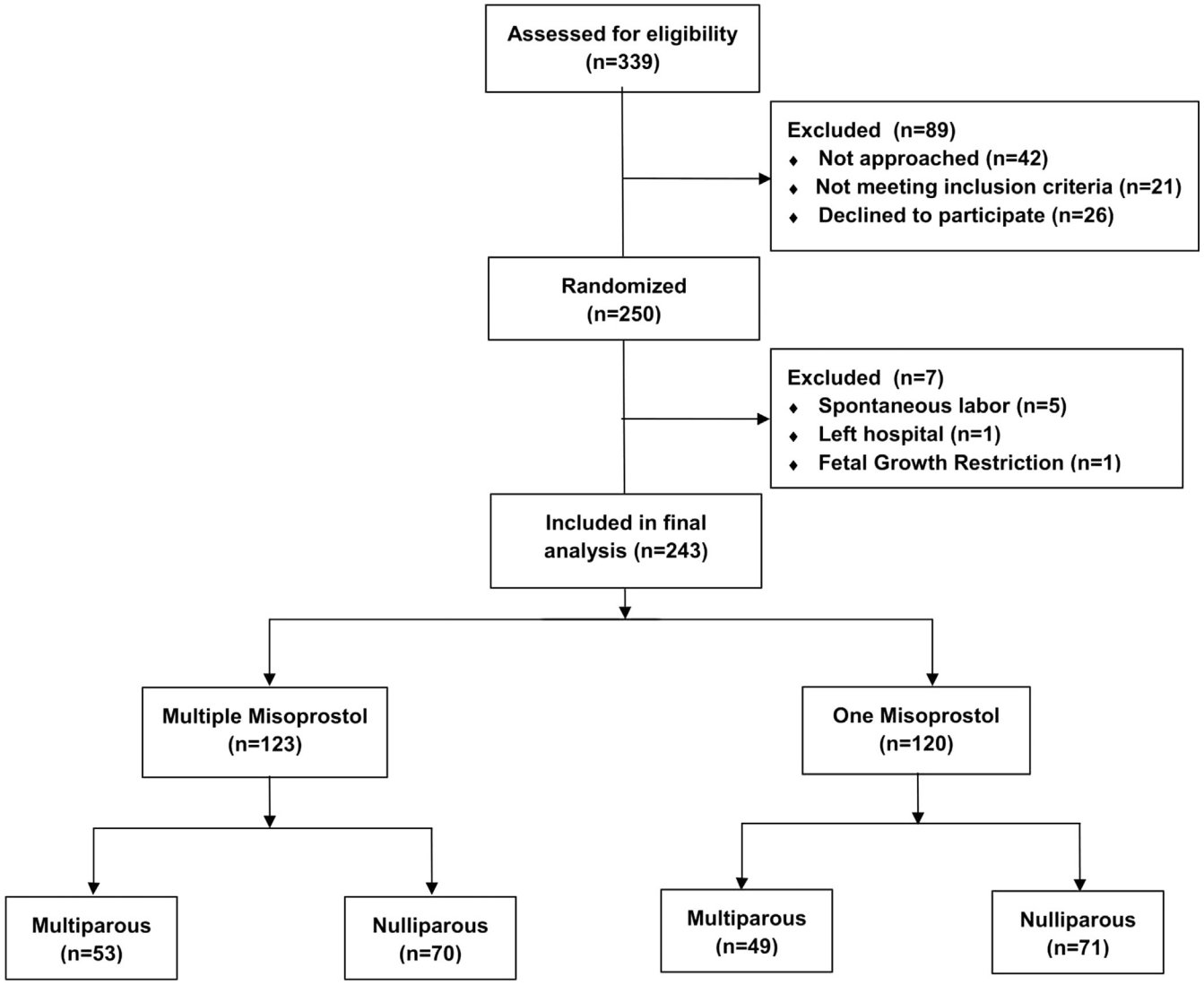
For all patients who were enrolled, misoprostol 25 μg was to be administered vaginally. For the group who received only 1 dose, oxytocin was started 4−6 hours after the patient received misoprostol to initiate labor if clinically indicated. In the multiple-dose misoprostol group, misoprostol 25 μg was administered vaginally every 4−6 hours for a maximum of 4 doses. Before insertion of each repeat dose, the patient's condition was evaluated. If the Bishop score was >6, the patient was contracting regularly, or fetal monitoring was not category I, no further misoprostol was given. Instead, oxytocin could be initiated if the patient was not in labor and as per our labor and delivery protocol. Our oxytocin protocol begins with 2 milliunits per minute (mU/min) of oxytocin, which is increased by 2 mU/min every 30 minutes until uterine contraction frequency becomes every 2−3 minutes and contractions last 40−60 seconds, up to a maximum dose of oxytocin of 30 mU/min. Labor providers could perform an amniotomy at any point during the labor course but were encouraged to wait until the patient was at least 4 cm dilated. The use of cervical Foley balloons was at the discretion of the labor providers if the patient did not appear to be a good candidate for oxytocin (for example, because of a category II fetal heart trace or too frequent contractions) or if the Bishop score did not improve after 18 hours of induction.

The primary outcome measure was vaginal delivery within 24 hours that was defined as time from the first dose of misoprostol to vaginal delivery time. Secondary outcome measures were vaginal delivery within 12 hours, delivery within 24 hours regardless of mode, time to vaginal delivery, time to delivery regardless of mode, total vaginal and cesarean delivery rates, indications for and factors associated with cesarean delivery, cervical dilation before cesarean delivery, Bishop score before the start of oxytocin, and rate of oxytocin use. Other maternal secondary outcomes were rates of maternal chorioamnionitis, endometritis, postpartum hemorrhage, need for blood transfusion, third- and fourth-degree lacerations, maternal intensive care unit admission, and death. Neonatal outcomes analyzed were Apgar scores, cord blood pH, serious neonatal complications (defined as hypoxic-ischemic encephalopathy, intraventricular hemorrhage grade 3 and 4, severe respiratory distress syndrome, necrotizing enterocolitis, culture-proven presumed neonatal sepsis), and neonatal intensive care admissions >48 hours.

Trained research staff reviewed the electronic medical record and collected all maternal demographics; induction, labor, and delivery information; and maternal and neonatal outcomes. After 61.6% patients were enrolled, an independent data safety monitoring board evaluated the study's safety using predefined adverse outcomes and recommended the study continue without changes.

A data safety monitoring board was established to evaluate the safety of the study independently. The Board performed an interim safety analysis for predefined adverse outcomes and recommended to continue the study without changes.

FIGURE
Flowchart of patients enrolled in the study



This flowchart shows that 276 women were approached for enrollment, 26 declined enrollment and 7 were excluded post-randomization leading to a final sample size was 243 participants.

EFW, estimated fetal weight.

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The sample size was calculated with the assumption that 50% of women would deliver vaginally within 24 hours in the multiple misoprostol group[18] and that the use of a single dose of misoprostol would increase the vaginal delivery rate within 24 hours by 20%, given that there would be no delay in the start of oxytocin when clinically indicated. Assuming a 10% crossover-exclusion rate and a 6% withdrawal rate, we determined that a sample size of 220 patients (110 patients per group) would be necessary to achieve a power of 80% and an alpha of .05.

Intention-to-treat and as-treated analyses were performed. Continuous variables were compared with the use of the Mann-Whitney test. Categoric variables were compared with the use of the Fisher's exact test. Poisson regression was used to determine factors that predicted an increased risk of cesarean delivery. Relative risk and 95% confidence interval are reported. Probability values $<.05$ were considered statistically significant.

TABLE 1
Maternal characteristics by randomized treatment group

Characteristic	Misoprostol		*P* value
	One dose (n=120)	Multiple doses (n=123)	
Age, y[a]	27 (23–32)	27 (24–32.5)	.524
Body mass index, kg/m^2[a]	33 (28.9–38.3)	33.3 (28.9–38)	.390
Race/ethnicity, n (%)			.470
Black/African	38 (33)	44 (39.6)	
Hispanic	57 (49.6)	53 (47.7)	
Nulliparous, n (%)	71 (59.2)	70 (56.9)	.795
Gestational age at induction, wk[a]	40.2 (38.6–40.6)	40.1 (39–40.6)	.739
Bishop score at induction[a]	2 (1–3)	2 (1–3)	.114
Artificial rupture of membrane	65 (55.1%)	71 (60.2%)	.510
Artificial rupture of membrane <6 cm dilation, n (%)	50 (41.7%)	61 (49.6%)	.500
Dilation at amniotomy[a]	4 (3–5)	5 (4–6)	.079
Cervical Foley use, n (%)	27 (22.5)	35 (28.5)	.306
Pregestational diabetes mellitus, n (%)	5 (4.2)	6 (4.9)	1.000
Gestational diabetes mellitus, n (%)	15 (12.5)	19 (15.4)	.581
Chronic hypertension, n (%)	12 (10)	9 (7.3)	.500
Gestational hypertension, n (%)	32 (26.7)	35 (28.5)	.776
Preeclampsia without severe features, n (%)	11 (9.2)	11 (8.9)	1.000
Preeclampsia with severe features, n (%)	13 (10.8)	15 (12.3)	.841
Other medical morbidity, n (%)	41 (34.2)	55 (44.7)	.115
Indication for induction, n (%)			.694
Late term or postterm[b]	46 (38.3)	41 (33.3)	
Maternal[c]	44 (36.7)	54 (43.9)	
Fetal[d]	27 (22.5)	25 (20.3)	
Elective[e]	3 (2.5)	3 (2.4)	

[a] Data are given as median (interquartile range); [b] Defined as ≥41 weeks of gestation; [c] Examples include diabetes mellitus, chronic hypertension, gestational hypertension, preeclampsia, cardiac disease, or other chronic medical condition in which induction was recommended; [d] Examples include oligohydramnios, polyhydramnios, and abnormality on fetal testing; [e] Examples of "other" include maternal cardiac disease and lupus.

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Results

Two hundred seventy-six women were approached for enrollment; 26 women (9.4%) declined enrollment, and 250 women were assigned randomly into 1 of the 2 treatment groups (Figure). Seven women were excluded after the randomization (5 women went into spontaneous labor and did not receive misoprostol; 1 woman left the hospital against medical advice, and 1 woman met sonographic criteria for intrauterine growth restriction). The final sample size was 243 participants. There was no difference in the demographic and clinical characteristics of both treatment groups including body mass index, race/ethnicity, parity, Bishop score at induction, indication for induction, and rate of cervical Foley use (Table 1).

The main results of the study are presented in Table 2. There was no statistically significant difference in the vaginal delivery rate within 24 hours between the 1-misoprostol group and multiple-dose regimen group (41.7% vs 44.7%; *P*=.698, respectively). When the data were stratified by parity, there was also no statistical significant difference in the vaginal delivery rate within 24 hours (nulliparous: *P*=.703; multiparous: *P*=1.000). The vaginal delivery rate within 12 hours and the total delivery rate within 24 hours were not significantly different between the 2 groups, both overall and when stratified by parity. The time to vaginal delivery was 1187 minutes for the 1-misoprostol group and 1321 minutes for the multiple misoprostol growth (*P*=.202). When the data were stratified by parity, the time to vaginal delivery was also not significantly

TABLE 2
Vaginal delivery rates and timing between treatment groups

Outcome	Misoprostol		*P* value
	One dose (n=120)	Multiple doses (n=123)	
Vaginal delivery within 12 hr, n (%)	20 (16.7)	18 (14.6)	.725
Nulliparous	2 (2.8)	2 (2.9)	1.000
Multiparous	18 (36.7)	16 (30.2)	.533
Vaginal delivery within 24 hr, n (%)	50 (41.7)	55 (44.7)	.698
Nulliparous	17 (23.9)	19 (27.1)	.703
Multiparous	33 (67.3)	36 (67.9)	1.000
Delivery within 24 hr, n (%)	61 (50.8)	64 (52.0)	.898
Nulliparous	25 (35.2)	23 (32.9)	.859
Multiparous	36 (73.3)	41 (77.4)	.818
Time to vaginal delivery, min[a]	1187 (695–1628)	1321 (900.5–1735)	.202
Nulliparous	1505 (1084–1915)	1630 (1214–2045)	.511
Multiparous	912 (659–1328)	933 (617–1353)	.525
Time to delivery, min[a]	1410 (909.2–2070)	1407 (927–1958)	.775
Nulliparous	1776 (1306–2282)	1652 (1286–2155)	.576
Multiparous	986 (662–1444)	1100 (619–1407)	.791

[a] Data are given as median (interquartile range).

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different (nulliparous: *P*=.511; multiparous: *P*=.525).

The cesarean delivery rate was greater in the 1-misoprostol group compared with the multiple-misoprostol group (*P*=.034; 35.8% vs 22.8%). When the data were stratified by parity, this difference was noted only for nulliparous women (nulliparous: *P*=.016; multiparous: *P*=1.000; Table 3). However, misoprostol group assignment was no longer associated with cesarean delivery rate in a regression analysis that controlled for parity, body mass index, gestational age, estimated fetal weight, Bishop score before starting oxytocin, early artificial rupture of membrane (ie, at <6 cm of dilation), and Foley balloon placement. Bishop score before starting oxytocin was inversely proportional to the risk of cesarean delivery (relative risk, 0.47; 95% confidence interval, 0.29–0.75). C-statistic evaluations revealed that a Bishop score <4 before starting oxytocin was the most predictive cutoff for cesarean delivery, after adjustment for the variables listed in Table 4. A Poisson regression showed that, in addition to a Bishop score < 4, parity was a statistically significant predictor of risk of cesarean delivery (Table 4).

There were no significant differences in the indication for cesarean delivery between groups (Table 3). For women who had a cesarean delivery, the mean maximum cervical dilation achieved was 5 cm for both groups. The proportion of women who achieved ≥6 cm in cervical dilation before undergoing a cesarean delivery was also similar for the 1-misoprostol group and the

TABLE 3
Cesarean delivery rate and indication between treatment groups

Maternal outcome	Misoprostol, n (%)		*P* value
	One dose (n=120)	Multiple doses (n=123)	
Cesarean delivery	43 (35.8)	28 (22.8)	.034
Nulliparous	35 (49.3)	20 (28.6)	.016
Multiparous	8 (16.3)	8 (15.1)	1.000
Indication for cesarean delivery			.822
Failed induction	9 (21.4)	4 (14.3)	
Arrest of dilation	19 (45.2)	14 (50)	
Arrest of descent	10 (23.8)	9 (32.1)	
Nonreassuring fetal heart rate tracing	3 (7.1)	1 (3.6)	
Elective	1 (2.4)	0	

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TABLE 4
Poisson regression analysis predicting risk of cesarean delivery

Variables	Odds ratio	95% Confidence interval	*P* value
Parity (multiparous vs nulliparous)	0.49	0.3–0.83	.008
Body mass index ≥30 kg/m^2	1.78	1–3.19	.052
Gestational age ≥41 wk	1.32	0.84–2.07	.235
Estimated fetal weight ≥4000 g	1.45	0.85–2.47	.171
Bishop Score ≥4 before oxytocin	0.47	0.3–0.74	.001
Treatment group (multiple vs 1)	0.81	0.51–1.27	.355
Artificial rupture of membrane <6 cm	1.01	0.65–1.57	.965
Foley balloon placed	1.1	0.68–1.78	.711

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multiple-misoprostol group (34.9% vs 46.4%; P=.600). Both groups had similar rates of use of oxytocin. However, the mean amount of oxytocin used was 2 mU/min more for the 1-misoprostol group. The Bishop score at the initiation of oxytocin and the time lapsed from the last dose of misoprostol to the initiation of oxytocin were similar for both groups (Table 5).

Table 6 shows that there were no statistically significant differences in the other secondary maternal and neonatal outcomes between the 2 groups. There was 1 case of intensive care unit admission (in the 1-misoprostol group) and 1 uterine rupture (in the multiple-misoprostol group). There were no cases of thromboembolism, hysterectomy, or death. There were no cases of hypoxic-ischemic encephalopathy, intraventricular hemorrhage grade 3 or 4, severe respiratory distress syndrome, necrotizing enterocolitis, or death.

Three patients (1.62%) received dinoprostone for cervical ripening because of a change in fetal heart rate and the development of a maternal contraction pattern that precluded the use of misoprostol. Fifteen participants (6.2%) crossed over to the other treatment group: 3 in the multiple-misoprostol group and 12 in the 1-misoprostol group. The median Bishop score of those who crossed from the 1-dose to the multiple-dose group was 3.5. These crossovers were typically due to provider preference. A 1-sided *t* test showed that the individuals who crossed from the 1-misoprostol group to the multiple-misoprostol group tended to have a Bishop score of less than 6 (*P*=.0006).

In a planned "as-treated" analysis, there was no difference in the vaginal delivery rate within 24 hours. However, the time to vaginal delivery was 1113 minutes for the 1-misoprostol group compared with 1328 minutes for the multiple-misoprostol growth (*P*=.05). Additionally, the difference in the overall and nulliparous cesarean delivery rates was not noted to be significantly different (overall: *P*=.152; nulliparous: *P*=.08, multiparous: *P*=1; data not shown).

TABLE 5
Oxytocin use between treatment groups

	Misoprostol		
Variables	One dose (n=120)	Multiple doses (n=123)	*P* value
Oxytocin used, n (%)	103 (85.8)	95 (77.2)	.099
Maximum dose of oxytocin used, mU/min[a]	10 (6–16)	8 (6–12)	.023
Bishop score at the start of oxytocin[a]	4 (2–5)	5 (3–6)	.124
Time from first dose misoprostol to start of oxytocin, min[a]	391 (302–596)	693 (541.5–879.5)	<.001
Time from last dose of misoprostol to start of oxytocin, min[a]	374 (280.5–588)	466 (305.5–630.5)	.139

mU/min, milliunits per minute.

[a] Mean (interquartile range).

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Comment

Our study demonstrated that there was no difference in the proportion of women who delivered vaginally within 24 hours with either a 1-misoprostol dose or multiple-misoprostol dose regimen. A Poisson regression analysis showed that treatment group assignment did not increase the cesarean delivery risk. Rather, the greatest risk factor for cesarean birth was a Bishop score <4 before the start of oxytocin. We found no difference between the 2 treatment groups in the Bishop score before the initiation of oxytocin. The use of a single dose of misoprostol for cervical ripening before the start of induction of labor with oxytocin, if clinically appropriate, is an acceptable alternative to the multiple-dose regimen. The ability to use a single dose of misoprostol for the induction of labor without compromising the vaginal delivery rate and time to vaginal delivery would likely be an attractive option for many patients and providers.

This is the first randomized controlled trial published that was designed to evaluate whether the traditional practice of using repeat doses of misoprostol for cervical ripening impacts rates of timely vaginal delivery. Girija and Manjunath[19] performed a randomized trial that compared up to 3 doses of 25 μg to a

TABLE 6
Secondary maternal and fetal outcomes between treatment groups

Variable	Misoprostol		*P* value
	One dose (n=120)	Multiple doses (n=123)	
Maternal outcome			
Epidural dilation <4, n (%)	65 (63.7)	63 (61.8)	.885
Terbutaline use, n (%)	8 (7.1)	8 (7)	1.000
Tachysystole, n (%)	7 (5.9)	8 (6.6)	1.000
Intrapartum fever, n (%)	22 (18.3)	14 (11.4)	.150
Postpartum fever, n (%)	11 (9.2)	10 (8.1)	.822
Chorioamnionitis, n (%)	20 (16.7)	15 (12.2)	.364
Endometritis, n (%)	6 (5)	4 (3.3)	.536
Change in hematocrit[a]	3.9 (1.7–6.6)	3.9 (1.8–6)	.999
Postpartum hemorrhage, n (%)	19 (16)	14 (11.4)	.351
Blood transfusion, n (%)	6 (5)	5 (4.1)	.767
Intensive care unit admission, n (%)	1 (0.8)	0	.494
Uterine rupture, n (%)	0	1 (0.8)	.972
Third or fourth-degree laceration, n (%)	2 (2.6)	5 (5.2)	.226
Episiotomy	2 (2.6)	6 (6.2)	.301
Fetal outcome			
Birthweight (g)[a]	3410 (3030–3741)	3320 (3020–3660)	.680
Apgar score at 5 min <6, n (%)	0	1 (0.8)	1.000
pH <7.1, n (%)	2 (1.8)	6 (5.2)	.281
Shoulder dystocia, n (%)	0	3 (2.4)	.247
Neonatal intensive care unit admission >48 hrs, n (%)	13 (10.8)	7 (5.7)	.166
Neonatal sepsis, n (%)	0	1 (0.8)	1.000

[a] Data are given as median (interquartile range).

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single dose 50 μg of misoprostol before the start of oxytocin for induction of labor. Although their primary outcome was time to vaginal delivery, they performed a subgroup analysis of the group who received misoprostol 25 μg and found an equal rate of vaginal delivery within 24 hours for patients who needed only 1 dose and those who needed additional doses of misoprostol. Apart from a difference in primary objective, this study differed from ours in other ways. It included women with premature rupture of membranes and also had a higher proportion of women who were induced for postdates (72% compared 35.8% in our study). Additionally, it was performed in India with participants who were likely more ethnically homogeneous and reported to have a lean body mass index. A major strength of our study is the inclusion of a higher percentage of women who have risk factors for failed induction, such as nonwhite race/ethnicity and obesity. In fact, our study population was more obese than the 2 recently published studies on induction of labor with the use of misoprostol.[20,21] Compared with the arm that received only misoprostol 25 μg in Levine et al,[20] our study had a lower rate of vaginal delivery within 24 hours. In addition to using a different protocol, the obesity of our study population and the higher rate of diabetes mellitus may explain partly this difference in vaginal delivery rate within 24 hours. Both obesity and diabetes mellitus appear to increase the time to delivery when prostaglandins are used for cervical ripening.[22,23] Our rate of vaginal delivery within 24 hours was, however, similar to that of 2 previously published studies. Ewert et al[24] and Calder et al[25] reported that women who received 25 μg of misoprostol had a vaginal rate within 24 hours of 42% and 43%, respectively.

Our study had additional strengths. It was a large, randomized controlled clinical trial. It excluded only intrauterine growth restriction and premature rupture of membranes, which increased the generalizability of our findings. Our study had some limitations. Because of the nature of the study, neither healthcare providers nor participants were blinded to the assigned medication

regimen. Providers in our institution typically prefer to repeat the dose of misoprostol until the cervix is ripe. For this reason, there was some hesitancy against the use of a single misoprostol and then starting oxytocin if the repeat Bishop score was ≤6 in nulliparous women. This hesitancy appears to have contributed to the 6.2% crossover rate between the 2 study groups. Another limitation of our study was the use of cervical Foley in >20% of the cases. However, the rate of cervical Foley use was statistically similar in both study groups. Finally, although there was no difference in the maternal and neonatal outcomes between treatment groups, our study was not powered to detect these differences. In a post hoc analysis, 4279 women would be required in each group to determine whether the difference that we noted in the rate of vaginal delivery within 24 hours between the 2 groups was statistically significant.

In conclusion, the single-dose misoprostol appears to be an acceptable alternative to a multiple dose regimen for cervical ripening before the induction of labor in multiparous women with an unripe cervix. In light of the increased risk of cesarean birth, we would recommend consideration for repeating the dose of misoprostol in nulliparous women if the Bishop score is <4 at 6 hours after the initial dose of misoprostol. Further research should assess the optimal interval between misoprostol administration and start of oxytocin for timely vaginal delivery. Additionally, more data are needed to validate the use of a Bishop score cut-off before the start of oxytocin to decrease the risk of cesarean delivery. ■

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