Title:

Misoprotol vaginal insert and time to vaginal delivery

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Misoprostol Vaginal Insert and Time to Vaginal Delivery

A Randomized Controlled Trial

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OBJECTIVE: To compare the efficacy and safety of a 200-microgram misoprostol vaginal insert with a 10-mg dinoprostone vaginal insert for reducing the time to vaginal delivery.

METHODS: In a phase III, double-blind, multicenter study, women being induced with a modified Bishop score of 4 or less were randomly assigned to receive either a 200-microgram misoprostol vaginal insert or a 10-mg dinoprostone vaginal insert. Coprimary end points were time to vaginal delivery and rate of cesarean delivery. Secondary end points included time to any delivery mode, time to onset of active labor, and oxytocin use.

RESULTS: A total of 1,358 women were randomized to receive the 200-microgram misoprostol vaginal insert (n=678) or dinoprostone vaginal insert (n=680). Women receiving the misoprostol vaginal insert had a significantly shorter median time to vaginal delivery compared with patients receiving the dinoprostone vaginal insert (21.5 hours compared with 32.8 hours, $P<.001$). Cesarean delivery occurred in 26.0% and 27.1% of women receiving the misoprostol vaginal insert and dinoprostone vaginal insert, respectively. A significant reduction in time to any delivery (18.3 hours compared with 27.3 hours), time to onset of active labor (12.1 hours compared with 18.6 hours), and proportion of women requiring predelivery oxytocin (48.1% compared with 74.1%) was observed with the misoprostol vaginal insert compared with dinoprostone vaginal insert ($P<.001$ for each). Uterine tachysystole requiring intervention occurred in 13.3% and 4.0% of participants receiving the misoprostol vaginal insert and dinoprostone vaginal insert, respectively ($P<.001$).

CONCLUSION: Use of a 200-microgram misoprostol vaginal inset significantly reduced times to vaginal delivery and active labor with reduced need for oxytocin compared with the dinoprostone vaginal insert. Cesarean delivery rates were similar with both treatments. Tachysystole was more common in women receiving the 200-microgram misoprostol vaginal insert.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01127581.

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More than 23% of pregnant women in the United States undergo induction of labor, a rate that has more than doubled since 1990.[1,2] Many methods to promote labor induction are used, including mechanical methods (eg, membrane stripping or sweeping, Foley catheter insertion, and amniotomy) and pharmacologic agents (eg, oxytocin and prostaglandins).[3] Prostaglandin E_2, or dinoprostone, is the only prostaglandin approved by the U.S. Food and Drug Administration for cervical

ripening in pregnant women at or near term with a medical or obstetric need for labor induction (Prepidil package insert, Pharmacia & Upjohn Company, 2010; Cervidil package insert, Forest Pharmaceuticals, Inc, 2010; Propess package insert, Ferring Läkemedel AB, 2008).

Misoprostol is a synthetic prostaglandin E_1 analog approved for reducing the risk of gastric ulcers produced by nonsteroidal anti-inflammatory drug use (Cytotec package insert, G.D. Searle, LLC, 2009). Tablets containing either 100 micrograms or 200 micrograms, split into approximately 25-microgram or 50-microgram fragments, have been extensively studied for the induction of labor. Several different dosing regimens administered by oral as well as vaginal routes have been used by the obstetric community.[3,4]

The present trial evaluates a controlled-release, removable vaginal insert with a 200-microgram reservoir of misoprostol. The insert consists of a hydrogel polymer delivery system contained in a polyester retrieval system. After insertion into the vagina, the hydrogel polymer delivery system releases misoprostol at a controlled rate for up to 24 hours.[5] Women undergoing induction of labor with modified Bishop scores of 4 or less were randomly assigned to receive a 200-microgram misoprostol vaginal insert or a 10-mg dinoprostone vaginal insert. The purpose of this study was to compare the safety and efficacy of the two products.

MATERIALS AND METHODS

This was a phase III, double-blind, randomized, multicenter study of EXogenous Prostaglandin comparing the Efficacy and safety of the Misoprostol Vaginal Insert 200 micrograms with the Dinoprostone vaginal Insert for reducing Time to vaginal delivery in pregnant women at tErm. For a list of other investigators involved in the trial, see the Appendix online at http://links.lww.com/AOG/A403. Participants were at least 18 years of age, of parity three or less with singleton pregnancies, and at least 36 weeks 0 days of gestation. Women were included if they had an unfavorable cervix (baseline modified Bishop score of 4 or less) and a body mass index (calculated as weight (kg)/[height (m)]^2) of 50 or less. Women were excluded if they were in active labor or if they had any of the following: uterine or cervical scarring or other uterine abnormality; severe preeclampsia with central nervous system involvement or hemolysis, elevated liver enzymes, and low platelet count; fetal malpresentation; a diagnosed fetal abnormality; any evidence of fetal compromise at baseline (eg, category II or III fetal heart rate pattern or meconium staining); having ruptured membranes 48 hours or longer before the start of treatment; suspected chorioamnionitis; amnioinfusion or other treatment of nonreassuring fetal status before induction; fever 37.5°C or higher; any condition in which vaginal delivery was contraindicated; allergy to prostaglandins; unexplained bleeding after 24 weeks of gestation; any condition urgently requiring delivery; or inability to comply with the protocol. Women were also excluded if they had received oxytocin or any cervical ripening or labor-inducing agents or a tocolytic drug within 7 days before enrollment. All participants were informed and provided written consent before participation in the study.

The study was conducted at 35 institutions within the United States. Sites were evenly split between university-affiliated and community-based sites. The study protocol was reviewed and approved by the institutional review boards of the participating institutions.

Patients received either a 200-microgram misoprostol vaginal insert or a 10-milligram dinoprostone vaginal insert that were identical in appearance. Enrollment was stratified by parity to ensure a population of approximately 60% nulliparous and 40% parous women. The study drug was placed in the posterior vaginal fornix using water-soluble gel as needed. Patients remained in bed for at least 30 minutes after insertion and were continually monitored for uterine and fetal heart rate activity, except for toileting and short periods of ambulation.

The vaginal insert was removed at onset of active labor (defined as three or more contractions in 10 minutes, lasting 45 seconds or longer, and of moderate or better quality resulting in cervical change or reaching 4-cm dilatation with any frequency of contractions); at the completion of the 24-hour dosing period; at the occurrence of any intrapartum adverse event; or at maternal request. Oxytocin administration was permitted 30 minutes after removal of the insert if the patient was not in active labor and had reassuring fetal status.

Uniform definitions were used for fetal heart rate activity patterns and uterine contractile abnormalities using the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development categorizations.[6,7] Treatment interventions, including tocolysis and amnioinfusion, used to treat tachysystole, fetal heart rate abnormality, or both, were applied, where appropriate, at the discretion of the managing physician. Tachysystole was defined as five or more contractions in 10 minutes averaged over three consecutive 10-minute periods.

Baseline demographics and characteristics collected included maternal race, height, weight, and

body mass index (obtained when the patient was admitted for induction); medical and pregnancy history; and obstetric characteristics (parity, membrane status, gestational age). Each patient underwent at least 15 minutes of cardiotocographic assessment to ensure fetal status and confirm no uterine pattern indicative of active labor. An examination was performed to confirm vertex fetal presentation and determine baseline modified Bishop score. The reason for labor induction was also recorded.

After study drug insertion, vaginal examinations were performed at 6, 12, 18, and 24 hours (if delivery had not occurred). The modified Bishop score was recorded at each time point. These examinations occurred even if the insert had been removed, the woman was in active labor, or a cesarean delivery was planned. The time and mode of delivery of the neonate and reason for cesarean delivery or reason for instrumented vaginal delivery (if applicable) were recorded.

Incidences of intrapartum, maternal postpartum, and neonatal adverse events were recorded. Women and neonates were observed for adverse events through hospital discharge; information was also collected on neonatal admissions and emergency room visits within 1 month of birth. A category III fetal heart rate pattern was to be reported as an intrapartum adverse event as well as all incidences of a category II fetal heart rate pattern that required intervention. Fetal heart rate patterns that qualified as category II or category III patterns were also to be specified (eg, tachycardia, decelerations). Tachysystole was reported as an adverse event if it occurred with fetal heart rate category II or category III patterns or when treatment (eg, amnioinfusion or tocolysis) was required. Retrospective review of cardiotocographic tracings by the investigator was mandated to ensure that fetal heart rate abnormalities and events of tachysystole were captured and consistently reported.

The primary efficacy measure was the time from study drug administration to vaginal delivery of the neonate. The primary safety measure was the rate of cesarean delivery. Secondary efficacy end points included time to any delivery (vaginal or cesarean), time to onset of active labor, and proportion of women requiring predelivery oxytocin. The proportion of women with vaginal delivery and any delivery within 12–24 hours was also assessed. In addition to the rate of cesarean delivery, safety was assessed by comparing rates of adverse events during the intrapartum, postpartum (maternal), and neonatal periods. A data and safety monitoring board was established to independently oversee the progress and safety of the study and review periodic safety reports throughout the study period, blinded as to treatment. There were no interim analyses conducted.

Sample size for both coprimary end points was based on assumptions derived from the time to vaginal delivery and cesarean delivery rates demonstrated in previous studies.[8,9] A sample size of 675 participants per group provided 90% power to detect an improvement of at least 320 minutes (5.3 hours) from time of administration of 200-microgram misoprostol vaginal insert compared with dinoprostone vaginal insert for time to vaginal delivery of the neonate, assuming a median time to vaginal delivery of 1,600 minutes (26.7 hours) for dinoprostone vaginal insert with a 34% dropout rate based on a 5% two-sided test. The study was also prospectively powered for the coprimary safety end point, the rate of cesarean delivery during the first hospitalization. Noninferiority of the 200-microgram misoprostol vaginal insert with respect to cesarean delivery rate assumed a 30% rate of cesarean delivery for the dinoprostone vaginal insert and a 26% rate for the misoprostol vaginal insert and was based on a two-sided α level of 5% and 80% power using a 10% noninferiority limit relative to the dinoprostone vaginal insert rate as requested by the U.S. Food and Drug Administration. A 95% asymptotic confidence interval was used to assess noninferiority.

Descriptive statistics were tabulated for quantitative variables. Baseline demographic, clinical, and obstetric characteristics were compared between treatment groups using one-way analysis of variance for quantitative variables and Fisher's exact test for qualitative variables; χ^2 tests were used to compare treatment groups by race and reason for induction.

Efficacy analyses were performed using the intent-to-treat population, which included all randomized women who received the study drug. The time to vaginal delivery, time to any delivery, and time to onset of active labor were evaluated using log-rank tests with the survivor function calculated using the Kaplan-Meier estimator. Time-to-delivery data were also analyzed by parity and compared between treatment groups. Time-to-event analyses were based on the initial induction attempt (first hospitalization). Women who had cesarean deliveries or did not deliver after the first induction attempt were censored in the time-to-event analyses using times that equaled the longest time to cesarean delivery or longest time to discharge from the labor and delivery suite of any participant in the study independent of treatment group, respectively. Safety data are reported for the

safety population, which includes all women who received the study drug and their neonates.

Statistical analyses were conducted using SAS 9.1 or higher.

RESULTS

A total of 1,358 women were enrolled in this study between September 10, 2010, and March 15, 2012. All randomized participants were included in the intent-to-treat and safety populations (200-microgram misoprostol vaginal insert, n=678; dinoprostone vaginal insert, n=680). Fourteen women did not deliver after their first induction attempt (first hospitalization) (Fig. 1). No significant differences were observed between treatment groups in the demographic or baseline obstetric characteristics of study participants (Table 1).

The Kaplan-Meier estimate of the median time from study drug administration to vaginal delivery for women of any parity was 21.5 hours (95% confidence interval [CI] 20.0–23.4) for the 200-microgram misoprostol vaginal insert and 32.8 hours (95% CI 30.2–34.9) for the dinoprostone vaginal insert ($P<.001$) (Fig. 2). The time to vaginal delivery was also significantly shorter for women receiving the 200-microgram misoprostol vaginal insert compared with women receiving the dinoprostone vaginal insert in both the nulliparous (29.2 hours compared with 43.1 hours, $P<.001$) and parous (13.4 hours compared with 20.1 hours, $P<.001$) subpopulations (Fig. 2). All three key secondary efficacy end points also demonstrated a significant improvement in results for the 200-microgram misoprostol vaginal insert compared with the dinoprostone vaginal insert (Table 2).

The cesarean delivery rates were 26.0% for patients in the 200-microgram misoprostol vaginal insert group (95% CI 22.7–29.4) and 27.1% (95% CI 23.8–30.6) for patients in the dinoprostone vaginal insert group (Table 3). These rates represented a treatment difference of −1.10 percentage points (95% CI −5.79 to 3.59). The upper bound of the 95% CI of the treatment difference of 3.59 percentage points exceeded the prespecified noninferiority margin. Therefore, although the rates of cesarean delivery were not significantly different ($P=.65$), the upper bound of the treatment difference CI exceeded the prespecified 10% margin of the dinoprostone vaginal insert rate of 2.71 percentage points, and noninferiority could not be concluded.

The most common reasons for cesarean delivery in women treated with the 200-microgram misoprostol vaginal insert and dinoprostone vaginal insert were adverse events (25.1% compared with 24.7%), elective procedure (0.1% compared with 0.9%), and lack of efficacy (0.7% compared with 1.5%) (Table 3). Although the majority of adverse events leading to cesarean delivery were reported at similar rates in both groups and considered unrelated to the study drug, there were some differences between treatment groups in the adverse events leading to cesarean delivery. These include category II and III fetal heart rate patterns and uterine tachysystole with late decelerations, bradycardia, or prolonged decelerations, all of which occurred more frequently in the 200-microgram misoprostol vaginal insert arm. Arrest of dilation or descent leading to cesarean delivery were more common within the dinoprostone vaginal insert group.

There were no significant differences between treatment groups in the overall proportions of women or neonates who experienced adverse events. Adverse event rates were 55.5% compared with 54.6% ($P=.74$)

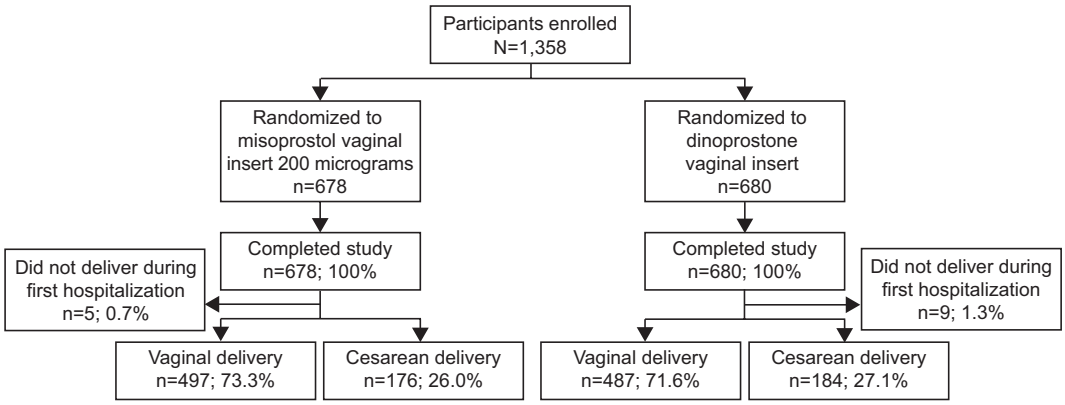

Fig. 1. Participant disposition.

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Table 1. Participant Demographics and Baseline Characteristics

Parameter	200-Microgram Misoprostol Vaginal Insert (n=678)	Dinoprostone Vaginal Insert (n=680)
Age (y)	26.2±6.0	25.9±5.9
	25.0 (18–46)	25.0 (18–46)
Race		
Native American or Alaskan native	12 (1.8)	7 (1.0)
Asian	17 (2.5)	14 (2.1)
African American	221 (32.6)	212 (31.2)
Native Hawaiian or other Pacific Islander	2 (0.3)	2 (0.3)
Hispanic	148 (21.8)	138 (20.3)
White	262 (38.6)	297 (43.7)
Other*	16 (2.4)	10 (1.5)
BMI (kg/m^2) at time of study drug administration	(n=677)	(n=680)
	33.8±6.5	34.1±6.6
	33.0 (20–63)	33.0 (19–54)
Parity		
Nulliparous women	441 (65.0)	451 (66.3)
Parous women	237 (35.0)	229 (33.7)
Gestational age at study drug administration (wk)	39.5±1.3	39.6±1.3
	39.6 (36.1–42.3)	39.9 (36.0–42.1)
Modified Bishop score at baseline	(n=677)	(n=679)
	2.0 (0–5)	2.0 (0–6)

BMI, body mass index.
Data are mean±standard deviation, median (range), or n (%).
Comparisons between treatment groups were not significantly different ($P>.05$) for any parameter.
* If more than one race was checked, participants were counted in the "other" category.

in the intrapartum period, 21.4% compared with 21.2% ($P=.95$) in the postpartum period, and 53.4% compared with 58.1% ($P=.09$) in the neonatal period for the 200-microgram misoprostol vaginal insert and dinoprostone vaginal insert treatment groups, respectively. Overall rates of fetal heart rate category II (24.9% compared with 25.7%) and category III (1.3% compared with 0.7%) adverse events were not significantly different between the misoprostol and dinoprostone inserts ($P=.76$ and $P=.30$, respectively). The adverse event "tachysystole requiring intervention" occurred in significantly more women receiving 200-microgram misoprostol vaginal inserts than in women receiving dinoprostone vaginal inserts (13.3% compared with 4.0%, $P<.001$). These and other safety outcomes of special interest are presented in Table 4. There were no fetal, maternal, or neonatal deaths.

DISCUSSION

This large, double-blind, multicenter, randomized, phase III study demonstrated that use of a 200-microgram misoprostol vaginal insert reduced the median time to vaginal delivery by 11.3 hours compared with the dinoprostone vaginal insert in women undergoing labor induction. Efficacy was further demonstrated by significant improvements in the key secondary efficacy outcomes, including reduced time to any delivery (vaginal or cesarean), reduced time to active labor, and reduced need for oxytocin. There was also a reduction in protracted time to delivery (longer than 24 hours). These efficacy improvements were consistent in both nulliparous and parous women.

Decreasing time to delivery may have several benefits. Prolonged labors are associated with higher infection rates, greater use of antibiotics, increased maternal distress, more use of oxytocin, and more demands on staff and hospital resources. From a maternal satisfaction point of view, Shetty et al[10] have reported that the time to delivery is important to women undergoing induction of labor. In response to a postdelivery questionnaire, 40% of women stated that the speed of induction was the most important aspect they would like to change if they were to undergo another induction.[10] Moreover, labor inductions with long durations are often perceived as traumatic by women.[11]

An increased relative risk of tachysystole is an expected outcome with the use of misoprostol as demonstrated in previous studies of misoprostol vaginal inserts and in a recent Cochrane review of

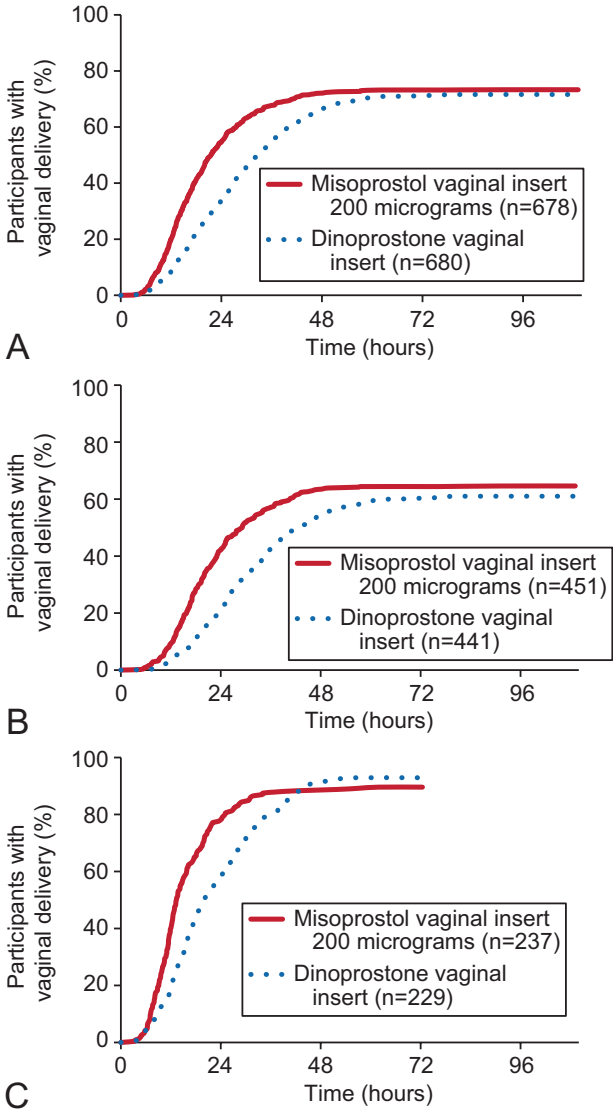

Fig. 2. Median time to vaginal delivery in women treated with either 200-microgram misoprostol vaginal insert or dinoprostone vaginal insert based on Kaplan-Meier estimates ($P<.001$ [two-sided log-rank test]). The y-axis is less than 100% reflecting those participants who failed to achieve vaginal delivery. **A.** Women of all parity. **B**. Nulliparous women. **C**. Parous women.

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misoprostol tablets.[8,12] Uterine activity characterized as tachysystole occurred in almost 50% of women receiving the 200-microgram misoprostol vaginal insert, approximately twice as frequently as the rate of occurrence in the dinoprostone vaginal insert group. The rate of tachysystole with fetal heart rate changes or tachysystole requiring intervention was three times higher with 200-microgram misoprostol vaginal inserts (13.3% compared with 4.0%). The use of the 200-microgram misoprostol vaginal insert therefore requires careful monitoring with timely recognition of tachysystole affecting the fetus and implementation of appropriate intervention, which may range from removal of the insert, to tocolytic treatment, to cesarean delivery.

It is important to evaluate neonatal outcomes to weigh the benefits of reduced time to delivery and reduction of protracted labor against the higher incidence of tachysystole demonstrated with the 200-microgram misoprostol vaginal insert. Similar rates of overall neonatal adverse events, neonatal intensive care unit admissions, and cesarean deliveries were observed with both treatments. In addition, there were similar rates of category II and III fetal heart rate adverse events (Table 4). The incidence of some important neonatal events was too low to allow for statistical comparison, including Apgar score less than 7 at 5 minutes, fetal acidosis, and neonatal encephalopathy. Therefore, these events were evaluated by having an independent, blinded expert panel conduct a post hoc review of the details of each case. The panel consisted of a board-certified perinatologist and a board-certified neonatologist. The assessors reviewed the cases, taking into account all available information, and concluded that none of the cases had plausible links between these specific adverse events and the study drugs. Therefore, despite the higher incidence of tachysystole seen with the 200-microgram misoprostol vaginal insert, neonatal outcomes do not appear to have been different between treatment groups.

Although this was a large randomized, blinded, controlled study, several limitations exist, among them, the mentioned inability to identify rare, drug-related events. Furthermore, the inclusion and exclusion criteria may limit the generalizability of these data, particularly the stringent requirement for cervical unfavorability (modified Bishop score 4 or less) and the exclusion of any fetus with evidence of fetal compromise at baseline. Tachysystole was sometimes identified post hoc based on cardiotocographic tracing review; thus, its identification in this study may be overestimated or underestimated compared with the rate of identification experienced in actual practice. Finally, the dinoprostone vaginal insert was allowed to remain in place for up to 24 hours, beyond the approved 12-hour use in the United States[5]; therefore, these results may not reflect actual U.S. practice regarding dinoprostone vaginal insert use.

Table 2. Efficacy Outcomes in Women Treated With a 200-Microgram Misoprostol Vaginal Insert or Dinoprostone Vaginal Insert

Outcome	200-Microgram Misoprostol Vaginal Insert (n=678)	Dinoprostone Vaginal Insert (n=680)	*P**
Median time to vaginal delivery (h)	21.5 (20.0–23.4)	32.8 (30.2–34.9)	<.001
Nulliparous women	29.2 (25.4–32.7)	43.1 (37.9–48.8)	<.001
Parous women	13.4 (12.5–14.8)	20.1 (17.8–22.8)	<.001
Median time to any delivery (h)	18.3 (17.2–19.5)	27.3 (26.2–28.9)	<.001
Median time to active labor (h)	12.1 (12.0–12.9)	18.6 (18.1–22.5)	<.001
Women requiring predelivery oxytocin	324/674 (48.1)	497/671 (74.1)	<.001†
Incidence of vaginal delivery in 12 h	134 (19.8)	57 (8.4)	<.001
Incidence of vaginal delivery in 24 h	370 (54.6)	231 (34.0)	<.001
Incidence of any delivery within 12 h	157 (23.2)	63 (9.3)	<.001
Incidence of any delivery within 24 h	459 (67.7)	277 (40.7)	<.001
Incidence of vaginal delivery	497 (73.3)	487 (71.6)	.50

Data are hours (95% confidence interval) or n (%) unless otherwise specified.
* *P* values obtained from log-rank test. Multiplicity corrections were made for the first three secondary end points.
† *P* values obtained from Fisher's exact test for women who delivered and received oxytocin during the first hospitalization.

In summary, use of a 200-microgram misoprostol vaginal insert significantly reduced the time to vaginal delivery and reduced need for oxytocin in women with an unfavorable cervix (modified Bishop score 4 or less) compared with the dinoprostone vaginal insert. The rate of cesarean delivery was similar for patients who received either treatment, but noninferiority of the 200-microgram misoprostol

Table 3. Cesarean Delivery Rates and Reasons for Cesarean Delivery

	200-Microgram Misoprostol Vaginal Insert (n=678)	Dinoprostone Vaginal Insert (n=680)	Treatment Difference [% (95% CI)]
All parity	176/678 (26.0)	184/680 (27.1)	−1.10* (−5.79 to 3.59)†
Nulliparous women	152/441 (34.5)	168/451 (37.3)	−2.78 (−9.08 to 3.51)†
Parous women	24/237 (10.1)	16/229 (7.0)	3.14* (−1.93 to 8.20)†
Reasons for cesarean delivery			
Adverse event	170 (25.1)	168 (24.7)	
Category II fetal heart rate pattern	62 (9.1)	42 (6.2)	
Arrest of dilatation or failure to dilate	58 (8.6)	85 (12.5)	
Arrest of descent or failure to descend	24 (3.5)	28 (4.1)	
Uterine tachysystole with late decelerations, bradycardia, or prolonged decelerations	13 (1.9)	0	
Fetal malpresentation	4 (0.6)	2 (0.3)	
Category III fetal heart rate pattern	3 (0.4)	2 (0.3)	
Chorioamnionitis	2 (0.3)	7 (1.0)	
Uterine rupture	1 (0.1)	0	
Placental rupture‡	1 (0.1)	0	
Uterine tachysystole requiring treatment	1 (0.1)	0	
Hypertension or worsening hypertension	1 (0.1)	0	
Preeclampsia or worsening preeclampsia	0	1 (0.1)	
Supraventricular tachycardia	0	1 (0.1)	
Elective	1 (0.1)	6 (0.9)	
Lack of efficacy	5 (0.7)	10 (1.5)	

CI, confidence interval.
Data are n/N (%) or n (%) unless otherwise specified.
Prespecified noninferiority margins were 10% relative to the dinoprostone vaginal insert rates and were 2.71 percentage points for women of any parity, 3.73 percentage points for nulliparous women, and 0.70 percentage points for parous women.
* Did not meet the upper bound of the prespecified 10% relative noninferiority margin.
† $P>.05$ from two-sided $\chi 2$ tests.
‡ MeSH term for placental abruption.

Table 4. Outcomes and Adverse Events of Special Interest

	Participants		
	200-Microgram Misoprostol Vaginal Insert (n=678)	Dinoprostone Vaginal Insert (n=680)	Relative Risk (95% CI) or *P*
Any category II fetal heart rate pattern (adverse event and nonadverse event*)	506 (74.6)	490 (72.1)	1.04 (0.97–1.10)
Category II fetal heart rate patterns (adverse event)	169 (24.9)	175 (25.7)	0.97 (0.81–1.16)
Category III fetal heart rate patterns (adverse event)	9 (1.3)	5 (0.7)	1.81 (0.61–5.36)
Uterine tachysystole (adverse event)	90 (13.3)	27 (4.0)	3.34 (2.20–5.07)†
Without fetal heart rate involvement (requiring treatment)	25 (3.7)	9 (1.3)	2.79 (1.31–5.92)†
With fetal heart rate involvement (late decelerations, bradycardia, or prolonged decelerations)	70 (10.3)	18 (2.6)	3.90 (2.35–6.48)†
Intrapartum resuscitation	85 (12.5)	66 (9.7)	1.29 (0.95–1.75)
Tocolysis use	83 (12.2)	28 (4.1)	2.97 (1.96–4.50)†
Meconium in amniotic fluid	120 (17.7)	92 (13.5)	1.31 (1.02–1.68)†
Arrested labor (dilation or descent)	96 (14.2)	128 (18.8)	0.75 (0.59–0.96)†
Any tachysystole (adverse event and nonadverse event)	333 (49.1)	167 (24.6)	2.00 (1.72–2.33)†
Chorioamnionitis	38 (5.6)	59 (8.7)	0.65 (0.44–0.96)†
Intrapartum IV or IM antibiotic use	38 (5.6)	59 (8.7)	0.65 (0.44–0.96)†
Cesarean delivery during first hospitalization	176 (26.0)	184 (27.1)	0.96 (0.80–1.15)
Instrumented vaginal delivery during first hospitalization	43 (6.3)	35 (5.1)	1.23 (0.80–1.90)
Postpartum IV or IM antibiotic use	31 (4.6)	57 (8.4)	0.55 (0.36–0.83)†
Postpartum hemorrhage	42 (6.2)	40 (5.9)	1.05 (0.69–1.60)
Neonatal birth weight (kg)	3.3±0.49	3.3±0.49	
	3.3 (2–5)	3.3 (2–5)	.128
One-min Apgar score low (less than 7)	80 (11.8)	79 (11.6)	1.02 (0.76–1.36)
Five-min Apgar score low (less than 7)	14 (2.1)	7 (1.0)	2.01 (0.81–4.94)
Fetal acidosis	8 (1.2)	4 (0.6)	2.01 (0.61–6.63)
Neonatal metabolic acidosis	1 (0.1)	0	—
Neonatal encephalopathy	4 (0.6)	1 (0.1)	4.01 (0.45–35.80)
Neonatal ICU admissions	61 (9.0)	71 (10.4)	0.86 (0.62–1.19)
Neonatal IV or IM antibiotic use	47 (6.9)	66 (9.7)	0.71 (0.50–1.02)
Neonatal respiratory events	57 (8.4)	61 (9.0)	0.97 (0.68–1.37)
Neonatal brain disorder	0	1 (0.1)	—

CI, confidence interval; IV, intravenous; IM, intramuscular; ICU, intensive care unit.
Data are n (%), mean±standard deviation, or median (range) unless otherwise specified.
* Nonadverse events did not require treatment.
† $P<.05$ from two-sided Fisher's exact test. If five or fewer participants experienced an event, *P* values were not calculated.

vaginal insert to the dinoprostone vaginal insert could not be concluded for this coprimary end point based on the prespecified 10% margin relative to dinoprostone vaginal insert. The efficacy of 200-microgram misoprostol vaginal insert was further demonstrated by achievement of the key secondary end points. Tachysystole was more common in women receiving the 200-microgram misoprostol vaginal insert; however, there was no definitive evidence of a difference in maternal and neonatal safety outcomes for this group compared with the dinoprostone vaginal insert group. Infections, use of antibiotics, and cesarean deliveries for prolonged labor were more common with the dinoprostone vaginal insert than with the misoprostol vaginal insert.

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