Original Research

Vaginal Compared With Oral Misoprostol Induction at Term

A Cluster Randomized Controlled Trial

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OBJECTIVE: To evaluate efficacy in achieving vaginal delivery with a standardized vaginal compared with oral misoprostol regimen for labor induction at term.

METHODS: In this single-center, cluster randomized trial, we randomized induction method by week among individuals with gestational age of 37 weeks or more, cervical dilation of 2 cm or less, intact membranes, and indication for delivery to either oral (100 micrograms every 4 hours for up to two doses), or vaginal (25 micrograms every 3 hours for up to five doses) misoprostol regimens, followed by a standardized oxytocin protocol. Individuals with an antepartum stillbirth, major fetal anomalies, malpresentation, ruptured membranes, nonreassuring fetal status, or contraindication to prostaglandin were excluded. The primary outcome was vaginal delivery at first induction attempt. Secondary outcomes included time to delivery, need for oxytocin, chorioamnionitis, and adverse maternal and neonatal outcomes. Outcomes were recorded at the individual level and adjusted for clustering, with analysis by intention to treat.

RESULTS: Between May 24, 2021, to September 19, 2022, 1,322 women were randomized to vaginal misoprostol in 33 clusters and 1,224 to oral misoprostol in 37 clusters. Demographic characteristics or initial cervical dilation did not differ between groups. The primary outcome did not differ between induction regimens and occurred in 1,032 (78.1%) of the vaginal misoprostol arm and 945 (77.2%) of the oral misoprostol arm (adjusted relative risk [RR] 1.01, 95% CI, 0.97–1.05). Tachysystole with fetal heart rate changes occurred less frequently with vaginal compared with oral misoprostol (3.5% vs 5.9%, adjusted RR 0.59, 95% CI, 0.40–0.87). Time to delivery did not differ between groups. Oxytocin was less frequently required before delivery in the vaginal misoprostol group (68.8% vs 78.4%, adjusted RR 0.88, 95% CI, 0.84–0.92).

CONCLUSION: Induction of labor with vaginal compared with oral misoprostol protocols did not increase the frequency of vaginal delivery at term but did reduce the need for oxytocin use before delivery.

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Induction of labor is associated with increased cesarean delivery compared with spontaneous labor, especially in those with an unfavorable cervix.[1] Over the past decades, studies comparing pharmacologic and mechanical methods for cervical ripening and labor induction have differed in the population studied (gestational age and membrane status), indication (elective vs indicated), and primary outcome (time to delivery vs delivery mode). Recommendations for induction agent depend on health care professional experience, individual patient characteristics, and institutional environment rather than a clear evidence base, and there is no single best method to achieve vaginal delivery.

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With chronic staffing shortages experienced by many institutions since the start of the coronavirus disease 2019 (COVID-19) pandemic and recommendations for 1:1 nurse staffing ratio for patients receiving oxytocin for induction of labor,[2] even a small reduction in need for oxytocin use before delivery would be meaningful. Thus, we were motivated to examine induction practices that may be associated not only with increased vaginal delivery but also with decreased oxytocin use. The purpose was to determine whether implementation of a vaginal misoprostol protocol would increase vaginal delivery compared with oral misoprostol when both study arms received standardized labor management, including oxytocin dosing and amniotomy. A secondary objective was to determine whether a vaginal misoprostol protocol reduced the need for oxytocin or time to delivery compared with an oral misoprostol protocol.

METHODS

This was a single-center, pragmatic, cluster randomized trial conducted in accordance with the published CONSORT (Consolidated Standards of Reporting Trials) 2010 guidelines for reporting cluster randomized trials.[3] This study was approved by the IRB at University of Texas Southwestern and by the Office of Research Administration at Parkland Health, the clinical site. This trial was registered on ClinicalTrials.gov (NCT04755218). Our institution is a large academic center where induction practice is uniform across health care professionals and patients using standardized protocols for induction and labor augmentation to maintain quality assurance. The IRB waived written informed consent on the basis that 1) women undergoing induction are informed about all induction methods considered standard practice at our institution, including both oral and vaginal misoprostol; 2) there was equipoise in determining a preferred method of induction; and 3) risks and benefits of labor induction are discussed as part of routine clinical care.

Eligible participants included nulliparous and multiparous women at 37 or more weeks of gestation with a living fetus and indication for induction. We excluded individuals with an antepartum stillbirth, major fetal anomalies, malpresentation, ruptured membranes, nonreassuring fetal status, or contraindication to prostaglandin administration.

Cluster randomization methods have been previously described.[4] Briefly, a computer-generated scheme generated by the biostatistician was used to randomly assign the protocol for induction each week, which was the unit of randomization. Clusters were block randomized, with block size varying randomly. Randomization assignment was revealed each Monday at 8 AM on the labor and delivery unit and was concealed until this time. This was a pragmatic trial integrated into clinical practice such that physicians, midwives, nurses, and patients were not blinded to the protocol after weekly assignment was revealed. Our vaginal misoprostol protocol allowed up to five tablets of 25 micrograms misoprostol every 3 hours, placed in the posterior vaginal fornix. Our oral misoprostol induction protocol allowed up to two doses of 100 micrograms oral misoprostol 4 hours apart. Transition to oxytocin with attending physician approval occurred in the setting of nonreassuring fetal heart rate tracing, meconium-stained amniotic fluid, four or more painful contractions in 10 minutes, or *active labor* (defined as cervical dilation of 4 cm or more). If a contraction pattern of three to five contractions in 10 minutes was not achieved with misoprostol, oxytocin was initiated 3 or 4 hours after the last dose of either vaginal or oral misoprostol, respectively. The oxytocin protocol was a standardized high-dose intravenous oxytocin protocol titrated to achieve a goal of 200 Montevideo units in 10 minutes as previously described.[4]

The attending physician staffing the labor and delivery unit approved all inductions initiated within the framework of established hospital protocols. Before trial initiation, education and in-service training were conducted for nurses, house staff, certified nurse midwives, and attending physicians on the labor and delivery unit. For deliveries with more than a single induction episode, cluster allocation was specific to the initial induction attempt. This occurred among individuals with indications for induction such as mild gestational hypertension without severe features of preeclampsia and reassuring fetal status who had no evidence of labor or ruptured membranes after 12–24 hours of induction. In these select cases, we allowed a period of rest overnight in the hospital followed by repeat trial of induction. For the purposes of this study, these individuals were considered to have not met the primary outcome of vaginal delivery at the first induction attempt regardless of eventual mode of delivery.

Baseline demographic and clinical characteristics were recorded, including race and ethnicity to examine diversity in the groups and the potential generalizability of results. Outcomes, determined at the individual level, were abstracted from the medical record after delivery by a team of research nurses. The primary outcome was vaginal delivery at the initial induction attempt. Secondary maternal

outcomes included time to delivery, need for oxytocin, labor epidural use, cesarean delivery indication, *clinical chorioamnionitis* (defined as a temperature of 38°C or higher during labor, with or without fundal tenderness, without other identified cause), *uterine tachysystole* (six or more contractions in 10 minutes) accompanied by fetal heart rate decelerations, *excess estimated blood loss* (estimated visually by the health care professional to include blood loss greater than 500 mL for vaginal delivery or greater than 1,000 mL for cesarean delivery), transfusion, *endometritis* (defined as a temperature of 38°C or higher with or without fundal tenderness more than 24 hours after delivery after exclusion of other causes), uterine rupture, unplanned hysterectomy, and surgical site infection. Neonatal outcomes included umbilical artery pH less than 7.0, 5-minute Apgar score, neonatal intensive care, intubation in the delivery room, and culture-proven neonatal sepsis.

Data-encounter forms for this study were initiated for all inductions and recorded in an Obstetric Quality Database, an ongoing quality-assurance database tracking maternal and neonatal health outcomes. Quality checks are conducted by a team of research nurses for all deliveries at more than 20 weeks of gestation. Additional labor induction variables were obtained through review of the maternal medical record by trained research nurses who recorded the specific induction agents used for each patient, independently of the labor induction assignment. This process allowed determination of mismatch for treatment assignment on an individual level.

We calculated a sample size of approximately 2,154 (1,077 per arm) women to provide 80% power to detect a 5% relative increase in the vaginal delivery rate from 76% to 81% with a type I error rate of 5% (two sided). A 5% difference was chosen because it was perceived to be achievable and clinically meaningful after review of the literature (Appendix 1, available online at http://links.lww.com/AOG/D505). We estimated that 30 inductions would occur per week, assumed an intracluster correlation coefficient of 0.0004 (95% CI, 0–0.06), and adjusted for the design effect for cluster randomization[5] to determine a necessary sample of 1,077 in each arm or 2,154 total enrolled. With an additional margin to allow for ongoing delivery data reconciliation for approximately 3 weeks, we estimated 2,244 enrolled. A planned interim analysis for safety, futility, and efficacy occurred at 50% accrual to determine whether there was any evidence of harm from either standard induction protocol, any significant benefit to either protocol that would mandate consideration of stopping, or whether continuation would yield little useful information. The trial was stopped when enrollment goals were met for both arms. To preserve the overall type I error rate of 0.05, we applied the Lan–DeMets spending function with O'Brien–Fleming-type boundaries, which reduced the ultimate error rate to 0.049.

We also determined a priori that the sample size would provide sufficient power for evaluating secondary outcomes of 1) a 2-hour difference in time to delivery (n=446 per arm, 892 total for 90% power) and 2) oxytocin use at a 10% relative reduction from 84% (n=478 per arm, 956 total for 90% power).

Primary and secondary outcomes were analyzed at an individual level and according to an intent-to-treat principle. Univariable analyses were performed with the Pearson χ^2 test for categorical outcomes and Student *t* test or Wilcoxon rank-sum test (when appropriate) for continuous measures. Effect sizes were estimated from the relative risk (RR) for binary outcomes and mean difference estimated from the Student *t* distribution for continuous outcomes (Hodges–Lehman when Wilcoxon rank-sum test is applied). All estimates were reported with 95% CIs. To adjust for clustering effect on individual outcomes, we used generalized estimating equations under the hierarchy of deliveries nested within cluster. For binary outcomes, this translated to log binomial regression for estimation of RRs and mixed-effects modeling for continuous outcomes. Analyses are presented as unadjusted and adjusted for clustering.

We planned subgroup analyses for two separate factors: nulliparity (yes or no) and dilation at initiation of induction (as closed or not and separately 2 cm dilated or not). These paralleled the primary analysis, adding an interaction term for the subgroup assignment crossed with the treatment assignment (along with the main effects). If the interaction was significant, the estimates at each of the subgroups were presented. Statistical analysis was performed with SAS 9.4.

A post hoc sensitivity analysis was performed to examine differences in the number of individuals with category 2 fetal heart rate tracing who received vaginal misoprostol (n=22 or 1.7%) compared with oral misoprostol (n=2 or 0.2%). In addition, to maintain throughput and limit prolonged inductions on a high-volume labor unit, we allowed up to 18 hours of intravenous oxytocin after 15 hours of vaginal misoprostol (total induction time 33 hours) compared with 24 hours of oxytocin after 8 hours of oral misoprostol (total induction time 32 hours). A Kaplan-Meier curve was constructed to evaluate the time (hours) from the

start of induction with either oral or vaginal misoprostol to oxytocin initiation, with censuring once delivery occurred or oxytocin was terminated.

RESULTS

Between May 24, 2021, to May 19, 2022, 3,946 individuals underwent induction of labor (Fig. 1). Of these, 1,400 were excluded for one or more of the following reasons (not exclusive): gestational age less than 37 weeks (n=262), major fetal anomalies (n=38), antepartum stillbirth (n=47), malpresentation (n=50), cervical dilation greater than 2 cm (n=365), or prelabor rupture of membranes (n=898). Of the 2,546 inductions with singleton pregnancies meeting inclusion criteria for misoprostol induction, 1,322 were randomized to vaginal misoprostol in 33 clusters, and 1,224 were randomized to oral misoprostol in 37 clusters (Fig. 1). Among women induced during weeks randomized to vaginal misoprostol, 450 (34.0%) received one dose, 428 (32.4%) received two doses, 226 (17.1%) received three doses, 173 (13.1%) received four doses, and 44 (3.3%) received five doses. One patient (0.1%) randomized to vaginal misoprostol received oral misoprostol (1 dose) as the initial induction agent. Among women induced during weeks randomized to oral misoprostol, 759 (62.0%) received one dose and 458 (37.4%) received two doses. An additional seven patients randomized to oral misoprostol received vaginal misoprostol as the initial induction agent, with six (0.5%) receiving two doses and one (0.1%) receiving four doses. The primary outcome, vaginal delivery at the initial induction attempt, was analyzed according to intention to treat with 99% of the study cohort receiving the intended per-protocol medication.

There were no differences in baseline demographic characteristics among women in either group, with racial and ethnic distribution reflecting the overall patient population.[6] Approximately half of the individuals were nulliparous, and approximately 95% were classified as having overweight or obesity, with median body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 31 at the first prenatal visit (Table 1). Pregestational diabetes was present in approximately 5% of individuals undergoing induction. Median gestational age at delivery did not differ between groups. Induction characteristics are shown in Table 2. More individuals in the vaginal misoprostol arm were induced after recognition of category 2 fetal heart rate tracing at term (22 [1.7%] vs 2 [0.2%] respectively, $P<.001$). Cervical dilation at induction start did not differ between groups and was 1 cm for 39.9% and 40.3% of individuals in the vaginal and oral misoprostol group, respectively. Internal monitor (intrauterine pressure catheter or fetal scalp electrode) use was less frequent for the vaginal misoprostol group compared with the oral misoprostol group (964 [72.9%] vs 938 [76.6%], respectively, $P=.03$).

The primary outcome did not differ between groups, with vaginal delivery occurring in 1,032 (78.1%) in the vaginal misoprostol group and 945 (77.2%) in the oral misoprostol group (RR 1.01, 95% CI, 0.97–1.05; adjusted RR 1.01, 95% CI, 0.97–1.05) (Table 3). Tachysystole with fetal heart rate changes occurred less frequently with vaginal misoprostol protocol, in 46 (3.5%) of vaginal and 72 (5.9%) of oral misoprostol inductions (adjusted RR 0.59, 95% CI, 0.40–0.87). The need for oxytocin before delivery was significantly decreased with a vaginal misoprostol protocol (909 [68.8%] vs 960 [78.4%], respectively [adjusted RR 0.88, 95% CI, 0.84–0.92]). Mean±SEM time to delivery did not differ between groups (19.7±0.32 hours for vaginal vs 19.7±0.33 hours for oral, adjusted difference in means 0.58, 95% CI, −0.32 to 1.49). The risks of clinical chorioamnionitis and other secondary maternal outcomes were not different between the groups. Among neonatal outcomes, there was no difference in neonatal 5-minute Apgar score, umbilical cord blood pH less than 7.0, or sepsis. Neonatal intensive care unit admission was more frequent in the vaginal misoprostol group (27 [2.0%] vs 12 [1.0%], adjusted RR 2.08, 95% CI, 1.06–4.09), although outcome frequency was low.

In prespecified subgroup analysis, the effect of vaginal misoprostol on primary or secondary outcomes was not statistically significantly different according to nulliparity or initial cervical dilation after adjustment for cluster randomization (Appendix 1, http://links.lww.com/AOG/D505).

Post hoc sensitivity analysis revealed no difference in primary or secondary outcomes after the exclusion of individuals who received misoprostol for category 2 fetal heart rate tracing in each group. Kaplan–Meier curve of time to oxytocin (with censuring for delivery) demonstrated that individuals in the oral misoprostol arm required oxytocin sooner after induction start (median [interquartile range] 9.7 hours [6.3–12.3 hours] in the oral compared with 13.4 hours [8.9–18.3 hours] in the vaginal misoprostol arm) (Appendix 2, available online at http://links.lww.com/AOG/D505).

DISCUSSION

We demonstrate in this single-center, cluster randomized labor induction trial that use of a vaginal

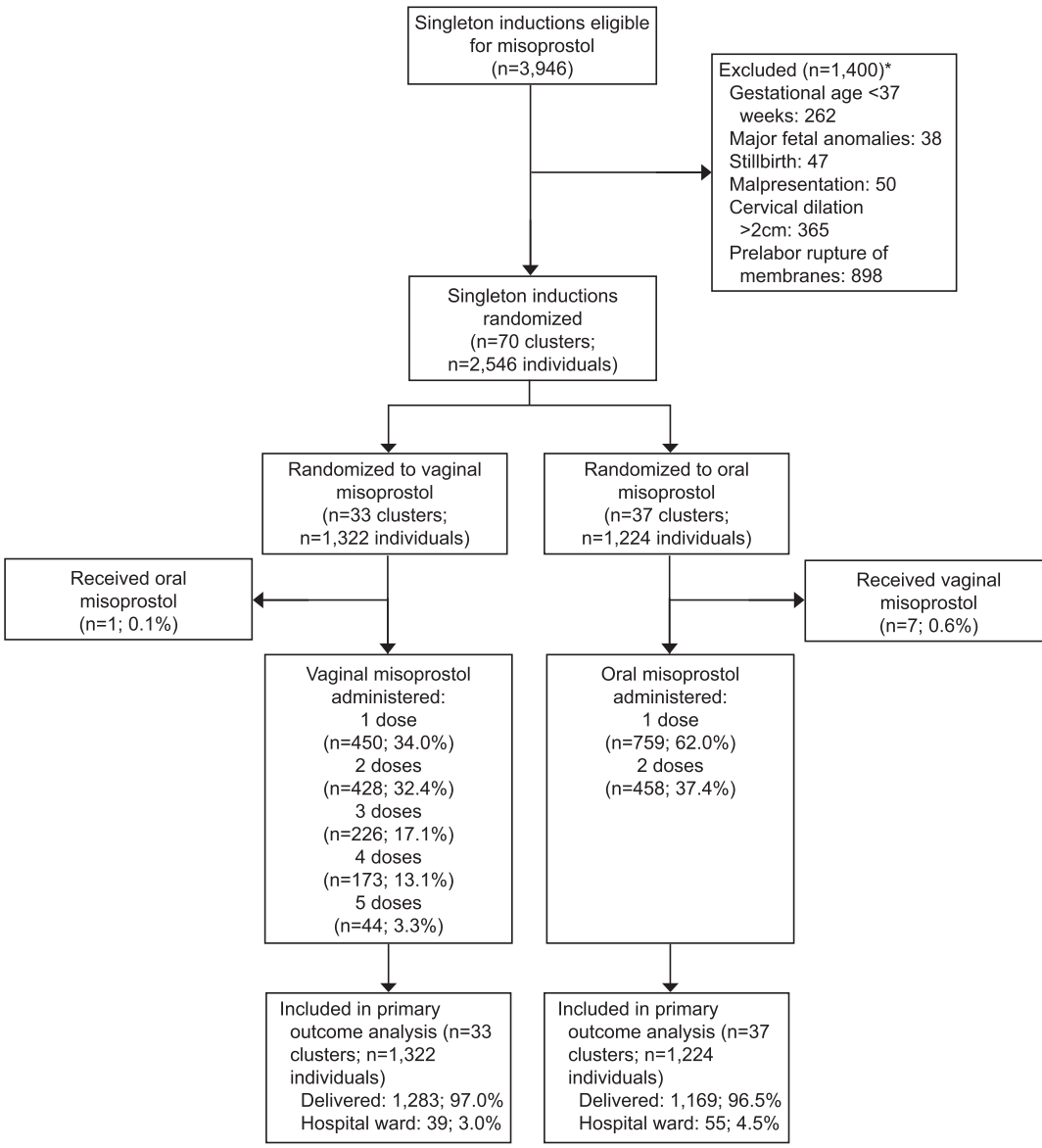

Fig. 1. Flow diagram of eligibility, randomization, intervention, and analysis in a cluster randomized trial of vaginal vs oral misoprostol induction at term. *Not mutually exclusive.

Adhikari. Vaginal vs Oral Misoprostol Induction. Obstet Gynecol 2024.

misoprostol compared with an oral misoprostol protocol for induction of labor in term gravid patients with intact membranes and cervical dilation of 2 cm or less did not result in increased vaginal delivery. Use of a vaginal misoprostol protocol decreased oxytocin requirement before delivery and was associated with less uterine tachysystole with associated fetal heart rate abnormalities. There was no significant difference in time to delivery, duration of first or second stage, or clinical chorioamnionitis. Use of vaginal misoprostol led to a statistically significant increase in neonatal intensive care (representing neonatal assisted ventilation or urgent pediatric surgical intervention), although overall frequency of this outcome was low for both groups, and no differences in other adverse neonatal outcomes were statistically significant.

Our interpretation of the results from the current study, consistent with results from a previous trial from our institution of oral misoprostol plus Foley balloon compared with oral misoprostol alone,[4] is that the frequency of vaginal delivery after labor induction at term, with active management according to standardized protocols, is fairly consistent at approximately 78%, regardless of the method used. In the

Table 1. Demographic Characteristics

Characteristic	Vaginal Misoprostol (33 Clusters, n=1,322)	Oral Misoprostol (37 Clusters, n=1,224)
Age (y)	26.6±6.5	26.9±6.3
Race		
Black, non-Hispanic	212 (16.0)	168 (13.7)
Hispanic	1,017 (76.9)	965 (78.8)
White, non-Hispanic	64 (4.8)	62 (5.1)
None of the above	29 (2.2)	29 (2.4)
Parity		
0	707 (53.5)	617 (50.4)
1	255 (19.3)	234 (19.1)
2	188 (14.2)	191 (15.6)
More than 2	172 (13.0)	182 (14.9)
BMI at 1st prenatal visit (kg/m^2)	30.7±7.5	30.6±7.2
Diabetes		
None	1,143 (86.5)	1,031 (84.2)
Gestational	131 (9.9)	135 (11.0)
Pregestational	48 (3.6)	58 (4.7)
Gestational age at delivery (wk)	39.4±1.4	39.4±1.4

BMI, body mass index.
Data are mean±SD or n (%).

current trial, we found that internal monitor use (either fetal scalp electrode or intrauterine pressure catheter) was lower in the vaginal misoprostol group, which we hypothesize is related to lower use of oxytocin in this group. Our institutional high-dose oxytocin protocol requires that infusion be titrated to attain three to five firm contractions or 200 Montevideo units in 10 minutes, which may be more challenging

Table 2. Labor Induction Characteristics

Characteristic	Vaginal Misoprostol (33 Clusters, n=1,322)	Oral Misoprostol (37 Clusters, n=1,224)	*P*
Before induction			
Indication for induction			<.001
Oligohydramnios	490 (37.1)	429 (35.0)	
Gestational hypertension or preeclampsia	485 (36.7)	435 (35.5)	
Term or postterm	125 (9.5)	144 (11.8)	
Diabetes	102 (7.7)	116 (9.5)	
Other maternal medical condition	60 (4.5)	68 (5.6)	
Decreased fetal movement	27 (2.0)	28 (2.3)	
Category 2 fetal heart rate tracing	22 (1.7)	2 (0.2)	
Clinical chorioamnionitis	1 (0.1)	0 (0.0)	
Prior stillbirth	10 (0.8)	2 (0.2)	
Cervical dilation at induction start			.16
Closed	428 (32.4)	429 (35.0)	
1 cm	527 (39.9)	493 (40.3)	
2 cm	367 (27.8)	302 (24.7)	
After induction			
No. of induction trials			.03
1	1,286 (97.3)	1,171 (95.7)	
More than 1	36 (2.7)	53 (4.3)	
Disposition at 1st induction			
Delivered	1,283 (97.0)	1,169 (95.5)	.04
Rest overnight in the hospital	39 (3.0)	55 (4.5)	
Epidural analgesia during labor	1,151 (87.1)	1,083 (88.5)	.28
Internal monitor use	964 (72.9)	938 (76.6)	.03

Data are n (%) unless otherwise specified.

Table 3. Primary Analysis of Maternal and Neonatal Outcomes, Unadjusted and Adjusted for Clustering

Outcome	Vaginal Misoprostol (33 Clusters, n=1,322)	Oral Misoprostol (37 Clusters, n=1,224)	Unadjusted [RR or Difference in Means (95% CI)]*	Adjusted for Cluster Randomization [aRR or Adjusted Difference in Means (95% CI)]*
Primary outcome				
Vaginal delivery at 1st induction	1,032 (78.1)	945 (77.2)	1.01 (0.97–1.05)	1.01 (0.97–1.05)
Secondary outcomes, maternal				
Tachysystole with fetal heart rate changes	46 (3.5)	72 (5.9)	0.59 (0.41–0.85)	0.59 (0.40–0.87)
Need for oxytocin	909 (68.8)	960 (78.4)	0.88 (0.84–0.92)	0.88 (0.84–0.92)
Clinical chorioamnionitis†	181 (13.7)	162 (13.2)	1.03 (0.85–1.26)	1.03 (0.85–1.26)
Time to delivery (h)‡	19.7±0.32	19.7±0.33	0.58 (−0.26 to 1.42)	0.58 (−0.32 to 1.49)
Time from ruptured membranes to delivery (h)‡	6.67±0.18	6.98±0.19	−0.31 (−0.82 to 0.20)	−0.31 (−0.83 to 0.20)
Labor duration (h)§				
1st stage	18.90±0.36	17.86±0.38	0.63 (−0.27 to 1.53)	0.63 (−0.39 to 1.66)
2nd stage	0.70±0.03	0.64±0.03	0.12 (0.004–0.24)	0.05 (−0.03 to 0.13)
Cesarean indication‖				
Labor dystocia	93 (7.0)	92 (7.5)	0.94 (0.71–1.24)	0.94 (0.71–1.24)
Abnormal fetal heart rate tracing	147 (11.1)	132 (10.8)	1.03 (0.83–1.29)	1.03 (0.82–1.31)
Excess estimated blood loss¶	223 (16.9)	193 (15.8)	1.07 (0.90–1.28)	1.07 (0.90–1.28)
Transfusion within 12 h of delivery	49 (3.7)	40 (3.3)	1.13 (0.75–1.71)	1.13 (0.75–1.71)
Endometritis#	7 (0.5)	6 (0.5)	1.08 (0.36–3.21)	1.08 (0.36–3.21)
Wound infection	8 (0.6)	3 (0.2)	2.47 (0.66–9.29)	2.43 (0.61–9.75)
Uterine rupture	1 (0.1)	1 (0.1)	0.93 (0.06–14.79)	0.93 (0.06–14.79)
Unplanned hysterectomy	3 (0.2)	3 (0.2)	0.93 (0.19–4.58)	0.93 (0.19–4.58)
Secondary outcomes, neonatal				
Meconium-stained amniotic fluid	306 (23.1)	266 (21.7)	1.07 (0.92–1.23)	1.07 (0.92–1.23)
5-min Apgar score less than 4	6 (0.5)	4 (0.3)	1.39 (0.39–4.91)	1.39 (0.39–4.91)
Umbilical cord blood pH less than 7.0**	10 (0.8)	8 (0.7)	1.14 (0.45–2.87)	1.30 (0.49–3.45)
Intubation in delivery room	3 (0.2)	1 (0.1)	2.78 (0.29–26.67)	2.78 (0.29–26.67)
Intensive care	27 (2.0)	12 (1.0)	2.08 (1.06–4.09)	2.08 (1.06–4.09)
Sepsis	4 (0.3)	2 (0.2)	1.85 (0.34–10.09)	1.85 (0.34–10.09)

RR, relative risk; aRR, adjusted relative risk.
Data are n (%) or mean±SEM unless otherwise specified.
* Ratios are vaginal to oral misoprostol. RR, relative risk indicating outcome more (more than 1) or less (less than 1) frequent in the vaginal misoprostol arm.
† Clinical chorioamnionitis defined as maternal temperature of 38°C or higher during labor with or without fundal tenderness, without other identified cause.
‡ Among individuals who delivered on first induction (n=1,283 for the vaginal misoprostol arm and n=1,169 for the oral misoprostol arm).
§ Among individuals who delivered on first induction and who reached second stage or complete cervical dilation (n=929 for the vaginal misoprostol arm and n=827 for the oral misoprostol arm).
‖ Denominator is total number of cesarean deliveries.
¶ Estimated blood loss greater than 500 mL for vaginal deliveries and greater than 1,000 mL for cesarean deliveries.
# Fever with or without fundal tenderness more than 24 hours after delivery, after the exclusion of other causes.
** Denominator is 1,249 for the vaginal misoprostol arm and 1,132 for the oral misoprostol arm (*P*=.06).

in patients with high BMI, leading to more intrauterine pressure catheter use when oxytocin is required.[7,8]

Despite decades of labor induction studies, no single best recipe for induction of labor has been determined, and the hospital setting, patient characteristics, and labor induction practices vary widely. Prior studies directly comparing vaginal with oral misoprostol for induction in gravid patients with intact membranes were published primarily between 1998 and 2010 (Appendix 3, available online at http://links.lww.com/AOG/D505).[9-26] Most included term gravid patients with unfavorable cervices measured with the Bishop score. The majority were powered to detect a difference in time to delivery[9–17] or vaginal delivery within 24 hours[18–20] or 12 hours,[21] and some measured time to vaginal delivery,[22,26] censuring individuals who delivered by cesarean. In most but not all, use of vaginal misoprostol (doses varied widely) was associated with decreased time to delivery compared with oral misoprostol but increased uterine tachysystole with and without fetal heart rate changes and cesarean delivery for fetal distress. After 2010, induction trials generally shifted toward comparing the use of mechanical methods such as Foley balloon with and without pharmacologic agents, including our own recently published study.[4]

Strengths of the study include the large number of participants, randomized design, consistency in study adherence with few crossovers, and pragmatic integrated trial design. Limitations include a single-center study and majority of patients with obesity, which reflects national trends but may reduce generalizability. Although planned subgroup analysis did not detect a significant difference in the association between vaginal misoprostol and vaginal delivery among nulliparous compared with multiparous individuals, the study did not have sufficient power to prevent a type II error. The study was underpowered to detect differences in rare maternal and neonatal outcomes, limiting conclusions that can be made from these data.

In summary, we found no significant improvement in achieving vaginal delivery with use of a vaginal compared with oral misoprostol protocol, reduced need for oxytocin with a vaginal misoprostol protocol, and no difference in time to delivery. We believe the primary outcome of vaginal delivery remains the most clinically relevant to patients, obstetricians, and labor unit staff when assessed within the context of standardized labor management.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *Not available.*

What other documents will be available? *Not available.*

When will data be available (start and end dates)? *Not applicable.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Not applicable.*

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