Original Research

Cervical Ripening Efficacy of Synthetic Osmotic Cervical Dilator Compared With Oral Misoprostol at Term

A Randomized Controlled Trial

Rachana Gavara, MD, Antonio F. Saad, MD, Ronald J. Wapner, MD, George Saade, MD, Anne Fu, MD, MPH, Ruth Barrow, MD, Swapna Nalgonda, MD, Sabine Bousleiman, RN, MPH, Cassandra Almonte, MD, Sarah Alnafisee, MD, Anita Holman, MD, Anna Burgansky, MD, and Pekka Heikkila, MSc

OBJECTIVE: To evaluate whether a synthetic osmotic cervical dilator is noninferior to oral misoprostol for cervical ripening.

METHODS: In an open-label, noninferiority randomized trial, pregnant women undergoing induction of labor at 37 weeks of gestation or more with Bishop scores less than 6 were randomized to either mechanical cervical dilation or oral misoprostol. Participants in the mechanical dilation group underwent insertion of synthetic osmotic cervical dilator rods, and those in the misoprostol group received up to six doses of 25 micrograms orally every 2 hours. After 12 hours of ripening, oxytocin was initiated, with artificial rupture of membranes. Management of labor was at the physician's discretion. The primary outcome was the proportion of women achieving vaginal delivery within 36 hours of initiation of study intervention. Secondary outcomes included increase in Bishop score, mode of delivery, induction-to-delivery interval, total length of hospital stay, and patient satisfaction. On the basis of a noninferiority margin of 10%, an expected primary outcome frequency of 65% for misoprostol and 71% for mechanical methods, and 85% power, a sample size of 306 participants was needed.

RESULTS: From November 2018 through January 2021, 307 women were randomized, with 151 evaluable participants in the synthetic osmotic cervical dilator group and 152 in the misoprostol group (there were four early withdrawals). The proportion of women achieving vaginal delivery within 36 hours was higher with mechanical cervical dilation compared with misoprostol (61.6% vs 59.2%), with an absolute difference of 2.4% (95% CI −9% to 13%), indicating noninferiority for the prespecified margin. No differences were noted in the mode of delivery. Tachysystole was more frequent in the misoprostol group (70 [46.4%] vs 35 [23.3%]; P=.01). Participants in the synthetic osmotic cervical dilator group reported better sleep, less unpleasant abdominal sensations, and lower pain scores (P<.05).

CONCLUSION: Synthetic osmotic cervical dilator is noninferior to oral misoprostol for cervical ripening. Advantages of synthetic osmotic cervical dilator include a better safety profile and patient satisfaction, less tachysystole, lower pain scores, and U.S. Food and Drug Administration approval.

From the Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, New York; the Department of Obstetrics and Gynecology, University of Texas Medical Branch at Galveston, Galveston, Texas; and NEOX s.r.o., Prague, Czech Republic.

Presented at the American College of Obstetricians and Gynecologists' Annual Clinical and Scientific Meeting, held virtually, April 30–May 2, 2021.

The authors thank the following individuals who were instrumental in executing the aims of this trial, advancing the science, and pulling the manuscript together. Without their help, this work would not have been possible: Michelle Divito, MSN, Columbia University Irving Medical Center; Caroline Torres, MD, MS, Columbia University Irving Medical Center; Ester Godbold, RN, University of Texas Medical Branch at Galveston; Ashley Salazar, MSN, WHNP-BC, University of Texas Medical Branch at Galveston; and Ronald Loosen Andrade, BS, Columbia University Irving Medical Center.

Each author has confirmed compliance with the journal's requirements for authorship.

Corresponding author: Rachana Gavara, MD, Department of Obstetrics and Gynecology, Lawrence Hospital, Bronxville NY; email: rg2460@cumc.columbia.edu.

Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/22

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT03670836.

FUNDING SOURCE: Medicem Technology s.r.o., Czech Republic.

(Obstet Gynecol 2022;00:1–9)

DOI: 10.1097/AOG.0000000000004799

In developed countries, approximately 25% of pregnant women undergo induction of labor.[1] This number is expected to rise in the future.[2] The majority of women undergoing induction of labor present with an unfavorable cervix.[2,3] Preinduction cervical ripening has been shown to reduce the induction-to-delivery interval.[1,2,4–6] An optimal agent is one that is readily available, safe, and effective and has a predictable response with minimal side effects. Two commonly used methods for cervical ripening are prostaglandin analogs and mechanical devices.

Misoprostol is a prostaglandin E1 analog approved for treatment and prevention of gastric ulcers.[7] In addition, misoprostol acts on the intracellular matrix of the cervix and causes breakdown of the collagen fibrils, leading to cervical softening. The American College of Obstetricians and Gynecologists has indicated that misoprostol appears to be safe and effective for induction of labor when used in low doses.[3] Compared with mechanical methods, misoprostol may lead to unwanted side effects such as uterine tachysystole with or without abnormal fetal heart rate changes, hence needing continuous fetal heart rate tracing during the cervical ripening period.[6–10] Oral misoprostol in a dose of 25 micrograms to be given every 2 hours was chosen based on less likelihood of causing uterine tachysystole compared with higher doses. The pharmacokinetics of misoprostol vary with route of administration.[11] The half-life of oral misoprostol is 30 minutes, compared with 90 minutes for vaginal misoprostol, requiring it to be administered every 2 hours compared with 4 hours for the vaginal route. This difference is due to a rapid metabolism of oral misoprostol by first-pass mechanism. In our institution, administration of vaginal misoprostol can be done only by physicians, whereas oral misoprostol can be given by nurses; this allowed better adherence to the dosing schedule for the study.

Dilapan-S (synthetic osmotic cervical dilator) is a U.S. Food and Drug Administration–approved mechanical method for cervical ripening that is made of a hydrogel (Aquacryl). The synthetic osmotic cervical dilator is available in 3- and 4-mm diameter rods that are inserted into the cervical canal in such a way that they cross the internal os. Within 6–8 hours, these rods expand up to four times their original diameter by absorbing fluids from the surrounding cervical and vaginal tissue to create a radial force inside the cervical canal, causing it to dilate. Another mechanism of action is activation of endogenous prostaglandins leading to cervical softening and shortening.[12] This response occurs at a predictable rate. Studies done in the 1990s and other, more recent, ongoing national and international trials have established the safety of synthetic osmotic cervical dilator for use in pregnant women at term.[13–17]

Currently, published clinical trials comparing this novel device with other methods of cervical ripening in term pregnancies are limited. The objective of this trial was to determine whether synthetic osmotic cervical dilator is noninferior to oral misoprostol in accomplishing a vaginal delivery within 36 hours of initiation of study intervention.

METHODS

This was a prospective, open-label, randomized controlled trial conducted at two medical centers in the United States. Our clinical trial was approved by the Institutional Review Boards at Columbia University Medical Center, New York, and the University of Texas Medical Branch at Galveston, Texas. This study was reported according to CONSORT (Consolidated Standards of Reporting Trials) guidelines[18] and was registered at ClinicalTrials.gov on September 12, 2018 (NCT03670836), before the first participant was enrolled on November 15, 2018.

Patients aged 18 years or older presenting for induction of labor at 37 weeks of gestation or more with an established plan for preinduction cervical ripening were screened for eligibility. Women with an *unfavorable cervix*, defined as having Bishop scores less than 6, with no contraindication for vaginal delivery were eligible for the trial. Participants were excluded if there was fetal death, prior uterine scar, major fetal congenital anomaly, nonreassuring fetal heart rate tracing, premature rupture of membranes, severe preeclampsia, chorioamnionitis, or active vaginal bleeding.

Randomization was created independently using a computer-generated sequence and concealed from the research staff responsible for recruiting and enrolling participants. Enrolled participants were randomly assigned in a 1:1 ratio to either synthetic osmotic cervical dilator insertion or oral misoprostol, using stratification for 1) parity (nulliparous vs multiparous women) and 2) gestational age (39 weeks or less vs more than 39 weeks).

Owing to the nature of the interventions, blinding of participants and health care professionals was not possible. All enrolled participants underwent fetal heart rate tracing for at least 20 minutes before the planned intervention.

Patients randomized to asynthetic osmotic cervical dilator were placed in the lithotomy position, and a sterile speculum examination was performed to visualize the cervix, which was then cleaned with betadine. Cervical dilator rods were inserted by trained physicians either digitally or using a sponge forceps, ensuring that the rods crossed the internal os as per the manufacturer's recommendations. A moist gauze was placed inside the vagina. Patients were allowed to ambulate, shower, and have light meals as long as they met the criteria for intermittent fetal monitoring based on institutional guidelines. Patients were instructed to report any pain, bleeding, and loss of fluid from the vagina. *Failed insertion* was defined as failure to place the synthetic osmotic cervical dilator rods for any reason.

For participants randomized to the misoprostol group, after the baseline assessment and a reassuring fetal heart rate tracing for 20 minutes, 25 micrograms misoprostol was administered orally every 2 hours, to a maximum of six doses. All participants had continuous fetal heart rate monitoring. A dose was held if the patient was noted to have uterine tachysystole, fetal heart rate tracing abnormalities, or three or more painful uterine contractions over a period of 10 minutes, averaged over a period of 30 minutes (indicating onset of labor). Participants in both groups remained in the labor and delivery department.

Management of participants with onset of labor was directed by the findings of examination. Otherwise, all study participants were re-examined after 12 hours of receiving study intervention. Bishop score was reassessed, and oxytocin was initiated at 1–2 milliunits/minute and increased by 1–2 milliunits/minute every 15 minutes until a desired response was obtained. The maximum dose was limited to 40 milliunits/minute. Amniotomy was performed as soon as clinically feasible. Management of labor was left to the managing physician's discretion. *Failed induction* was defined as failure of onset of active labor after oxytocin for 24 hours with artificial rupture of membranes. All participants had the option to receive epidural anesthesia for pain management.

Data points including demographics, complete medical history, physical examination, and maternal and fetal outcomes were extracted from the medical records by trained research staff and entered into a secure electronic database. Satisfaction surveys pertaining to participants' experience with cervical ripening were obtained after delivery. Research staff contacted study participants by phone 2 weeks after their discharge from the hospital to ascertain whether there had been unscheduled postpartum visits for the neonate or the participant.

The primary outcome was the rate of vaginal delivery within 36 hours of the study intervention. Prespecified secondary outcomes were a change in the Bishop score after 12 hours of study intervention; the overall rates of vaginal delivery, operative vaginal delivery, and cesarean delivery; induction-to-delivery interval, and total length of hospital stay. Maternal and fetal safety outcomes were also collected.

According to the noninferiority hypothesis, we conducted primary analyses on both the intention-to-treat (ITT) and per-protocol populations.[19] The ITT population included participants who were analyzed in accordance with their randomized study treatment (ie, the treatment group to which they were originally allocated, regardless of the treatment that was actually received). The per-protocol population comprised participants who received the treatment to which they were originally allocated, with complete adherence to the protocol. Demographics, baseline characteristics, and secondary outcomes were analyzed in the ITT population. The safety population comprised all participants in whom a synthetic osmotic cervical dilator was inserted or who received at least one dose of misoprostol. This population was based on the actual treatment received, in case it differed from that to which the participant was randomized.

We used the Cochran-Armitage test for trend analysis of the patient survey.[20] Student test, Pearson's χ^2 test, and Mantel Hanzal test were used as indicated. $P<.05$ was considered statistically significant. Delivery time was presented using Kaplan-Meier curves, with censoring for cesarean delivery. The sample size calculation used assumptions based on prior published data.[10,14] Using a noninferiority margin of 10%, a total of 306 participants were needed to evaluate the primary outcome with 85% power to confirm noninferiority with a one-sided confidence level of 97.5%. We predefined the primary outcome for the statistical analysis. This outcome was adjusted for stratification factors–gestational age and parity.

A total of 307 patients were enrolled, with four early withdrawals from the study. The remaining 303 participants were eligible for evaluation of the primary outcome, keeping the study well-powered to detect the prespecified noninferiority margin and preserving the conclusion and findings. The data were reviewed once by the Data and Safety Monitoring

Board to ensure the safety aspects of the study. Data were presented without revealing the randomization group.

ROLE OF THE FUNDING SOURCE

Medicem Technology s.r.o., located in the Czech Republic, provided the funding for the study and supplied the Dilapan-S rods. The study was investigator-initiated, and the principal investigators designed the protocol, managed data collection, and wrote the manuscript. Medicem performed source data verification on behalf of the sponsor and provided editorial input into the final manuscript. An independent third-party statistician, funded by Medicem, received password-protected data directly from the sponsor and performed the data analysis. The authors had access to relevant aggregated study data and other information required to understand and report the research findings. The authors take public responsibility for all aspects of the work including publication of the research findings and have been fully involved during all stages of publication development. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication development are listed appropriately. The role of the funder in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or nonfinancial, relating to this research and its publication have been disclosed.

RESULTS

From November 2018 to January 2021, 307 women were randomized, 154 in the synthetic osmotic cervical dilator group and 153 in the misoprostol group (Fig. 1). There were three withdrawals in the synthetic osmotic cervical dilator group and one in the misoprostol group.

Demographics and baseline characteristics were analyzed in the ITT population, and no significant differences were noted (Table 1). Of a total of 303 evaluable participants, 191 (63.0%) had gestational age greater than 39 weeks and 112 (37.0%) had gestational age 39 weeks or less. All inductions at less than 39 weeks of gestation were medically indicated. Multiparous and nulliparous participants were equally distributed between the two groups. The most common indication for induction of labor was postterm pregnancy, followed by elective induction.

Vaginal delivery within 36 hours of initiation of study intervention was more common in the synthetic osmotic cervical dilator group compared with the misoprostol group (ITT analysis; synthetic osmotic cervical dilator: 93 [61.6%] vs misoprostol: 90 [59.2%], with an absolute difference with respect to the misoprostol of 2.4% [95% CI −9% to 13%]),

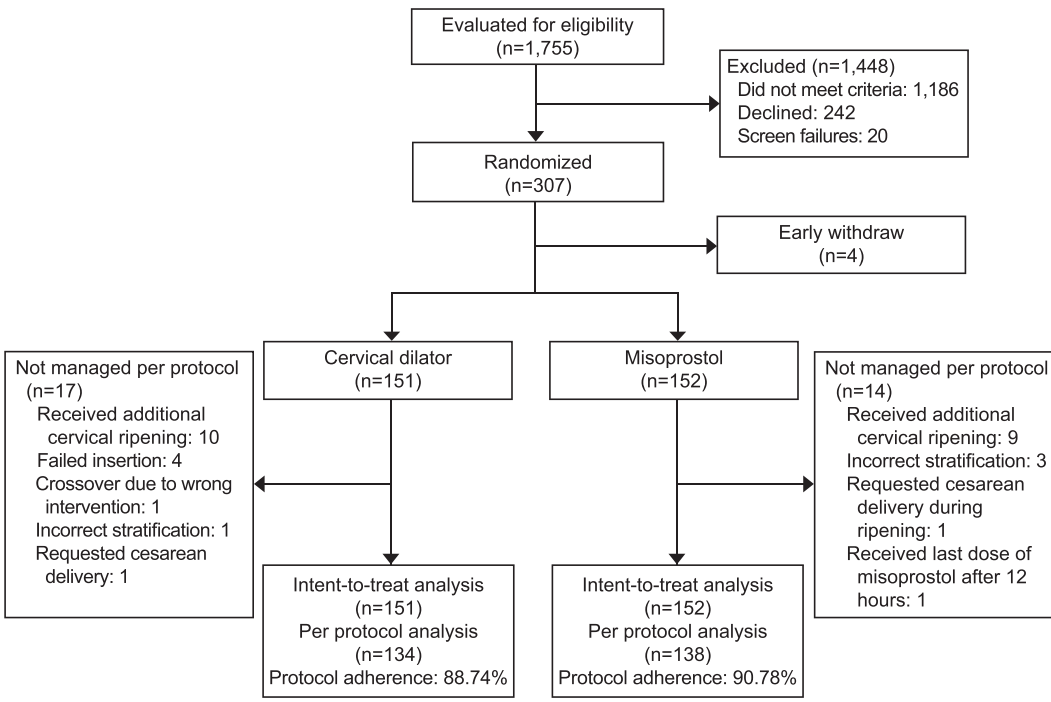

Fig. 1. Flow chart describing patient enrollment for the study.
Gavara. Efficacy of Synthetic Osmotic Cervical Dilator. Obstet Gynecol 2022.

Table 1. Demographic and Baseline Characteristics of the Study Population*

Characteristic	Synthetic Osmotic Cervical Dilator Group (n=151)	Misoprostol Group (n=152)
Age (y)	27.2±5.94	27.7±5.9
Gestational age at randomization (wk)		
39 or less	57 (37.7)	55 (36.2)
More than 39	94 (62.3)	97 (63.8)
Parity at randomization		
Multiparous	70 (46.4)	71 (46.7)
Nulliparous	81 (53.6)	81 (53.3)
BMI at randomization (kg/m^2)	33.1±5.02	33.1±4.83
GBS positive	60 (39.7)	52 (34.2)
Indication for induction		
Diabetes	15 (9.9)	7 (4.6)
Postterm pregnancy	47 (31.1)	40 (26.3)
Hypertensive disease of pregnancy	14 (9.3)	20 (13.2)
Cholestasis of pregnancy	1 (0.7)	2 (1.3)
Intrauterine growth restriction	9 (6)	16 (10.5)
Oligohydramnios	14 (9.3)	22 (14.5)
Elective	37 (24.5)	32 (21.1)
Other	24 (15.9)	20 (13.2)

BMI, body mass index; GBS, group B streptococcus.
Data are mean±SD or n (%).
* Demographics and baseline characteristics were analyzed in the intention-to-treat population, and no significant differences were noted among the two groups.

indicating noninferiority for the prespecified margin (Table 2 and Fig. 2). The primary outcome did not change after adjusting for parity and gestational age (data not shown). A Kaplan-Meier curve (Fig. 3) did not show any difference in the distribution of vaginal deliveries over time in the two groups after censoring for cesarean deliveries.

Secondary outcomes did not differ between groups (Table 3). There was no difference in vaginal delivery rate, cesarean delivery rate, or change in Bishop score. There was no difference in mean initiation of cervical ripening–to–delivery interval in the two groups. Total mean duration of hospitalization was similar.

Both interventions demonstrated similar safety profiles, with only tachysystole showing a significant difference (Tables 3 and 4). Uterine tachysystole during cervical ripening occurred in 53.6% (81/152) of the participants receiving misoprostol, which was significantly more frequent than the 25.7% (39/151) in the synthetic osmotic cervical dilator group ($P<.01$). Only 41.4% of patients in the misoprostol group had no complications and received all six doses. Similarly, tachysystole during labor with nonreassuring fetal heart rate changes was statistically greater in the misoprostol group ($P=.03$) (Table 3). In the synthetic osmotic cervical dilator group, the most common complication was failed insertion in 4 of 151 (2.6%) patients. None of the complications were severe enough to require significant interventions or emergent delivery. Patients who received the synthetic osmotic cervical dilator reported lower pain scores ($P=.02$), had less abdominal discomfort ($P=.04$), and

Table 2. Primary Outcome: Vaginal Delivery Within 36 Hours

Vaginal Delivery within 36 h	Synthetic Osmotic Cervical Dilator Group	Misoprostol Group	Difference in Proportions (95% CI)*	RR (95% CI)
Population				
Intention-to-treat	93 (61.6)	90 (59.2)	2.4 (−9.0 to 13.0)	1.04 (0.9–1.2)
Per-protocol	86 (64.2)	86 (62.3)	1.9 (−1 to 13)	1.03 (0.9–1.2)

RR, relative risk.
Data are n (%) unless otherwise specified.
* Difference in proportions expressed as the rate in the synthetic osmotic cervical dilator group minus the rate in the misoprostol group (95% CI).

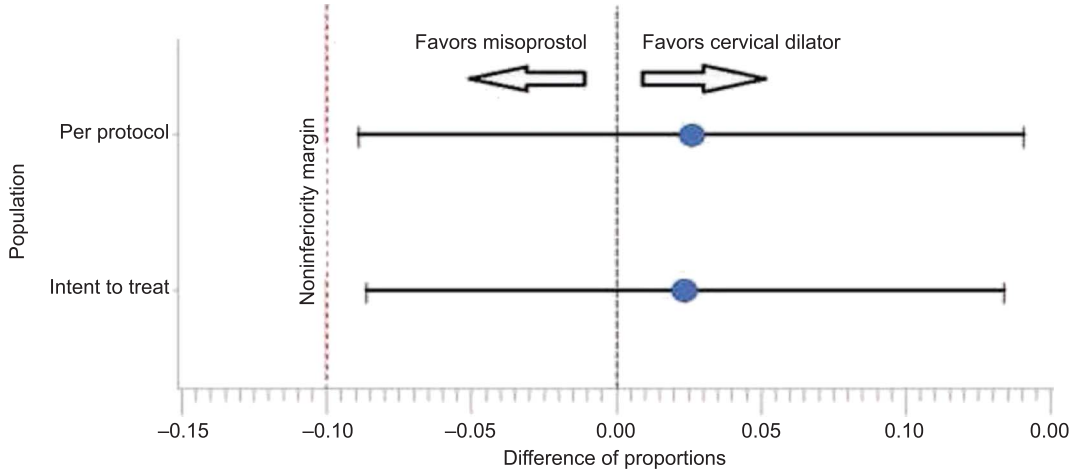

Fig. 2. Primary outcome: vaginal delivery within 36 hours. Absolute difference in vaginal delivery rate (with 95% CI) between cervical dilator and misoprostol in the intention-to-treat and per-protocol analysis. The 95% CI spans 0 but lies wholly above the Δ margin, indicating noninferiority.

Gavara. Efficacy of Synthetic Osmotic Cervical Dilator. Obstet Gynecol 2022.

were able to sleep more (P=.03) during cervical ripening (Fig. 4).

DISCUSSION

We found that the synthetic osmotic cervical dilator is noninferior to oral misoprostol for cervical ripening. Our findings were consistent between the ITT and per-protocol populations, confirming the robustness of our results. Uterine tachysystole was observed more frequently in the misoprostol group. Women in the synthetic osmotic cervical dilator group had lower pain scores, reported less abdominal discomfort, and were able to sleep better and ambulate more, consistent with prior published trials.[14,21,22]

Secondary outcomes such as rate of vaginal delivery within 24 and 48 hours, change in Bishop score, rate of cesarean delivery, operative vaginal delivery, induction-to-delivery interval, and total length of hospital stay were not different between groups. Neonatal and maternal outcomes and infectious morbidity were similar with both methods. These findings are consistent with other recent clinical trials evaluating synthetic osmotic cervical dilators.[14–17]

In the DILAFOL (Dilapan-S vs Foley balloon for preinduction cervical ripening) clinical trial conducted by Saad et al,[14] use of a synthetic osmotic cervical dilator was found to be as safe and efficacious as a

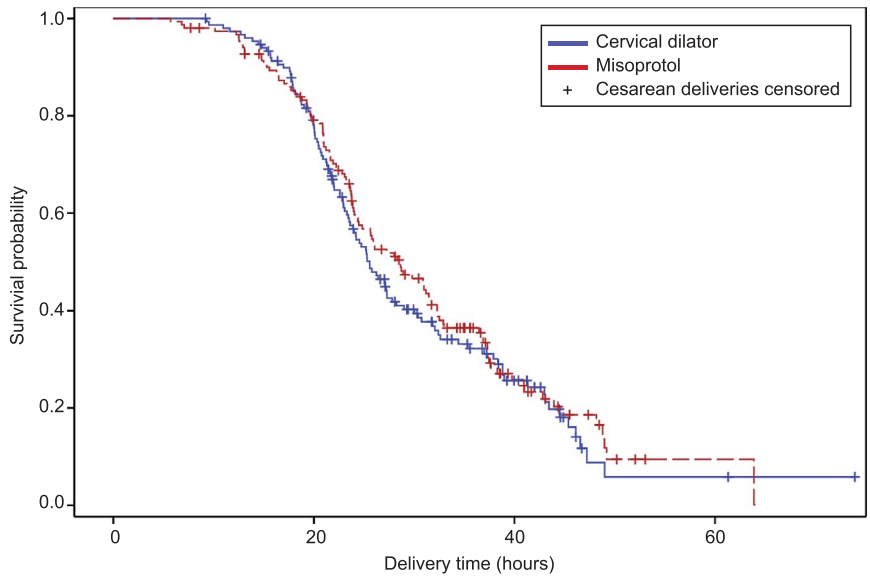

Fig. 3. Kaplan-Meier curve showing vaginal deliveries over time in the two groups, with censoring for cesarean deliveries.

Gavara. Efficacy of Synthetic Osmotic Cervical Dilator. Obstet Gynecol 2022.

Table 3. Secondary Outcomes by Intervention Method in the Intention-to-Treat Population

Outcome	Synthetic Osmotic Cervical Dilator Group (n=151)	Misoprostol Group (n=152)	RR (95% CI)
Change in Bishop score	2 (0–11)	3 (0–11)	—
Change in modified Bishop score	2 (0–8)	2 (0–8)	—
Cesarean delivery	41 (27.2)	42 (27.6)	0.98 (0.68–1.42)
Spontaneous vaginal delivery	104 (68.9)	104 (68.4)	1.01 (0.86–1.17)
Operative vaginal delivery	6 (3.9)	6 (3.9)	1.01 (0.33–3.05)
Chorioamnionitis	12 (7.9)	10 (6.6)	1.21 (0.54–2.71)
Postpartum fever	3 (2.0)	3 (2.0)	1.01 (0.21–4.91)
Postpartum hemorrhage*	1 (0.7)	3 (2.0)	0.34 (0.04–3.19)
Nonreassuring FHR tracing during labor	18 (12.1)	27 (17.6)	0.67 (0.38–1.17)
2nd round of cervical ripening	5 (3.3)	8 (5.3)	0.63 (0.21–1.88)
Duration from initiation of cervical ripening to vaginal delivery (h)	24.9±8.98	25.8±10.19	—
Duration from initiation of cervical ripening to any delivery (h)	27.2±10.68	27.9±10.96	—
Hospital stay (h)	80.5±21.8	84±22.6	—

RR, relative risk; FHR, fetal heart rate.
Data are median (range), n (%), or mean±SD unless otherwise specified.
* Estimated blood loss greater than 1,000 mL.

Foley catheter for cervical ripening. Higher satisfaction scores were reported with synthetic osmotic cervical dilator compared with Foley catheter, even though both are mechanical methods. Clinical trials comparing the synthetic osmotic cervical dilator with other methods of cervical ripening, such as dinoprostone gel, extra amniotic saline infusion, and misoprostol, have shown that the synthetic osmotic cervical dilator has similar efficacy and a similar safety profile.[15–17]

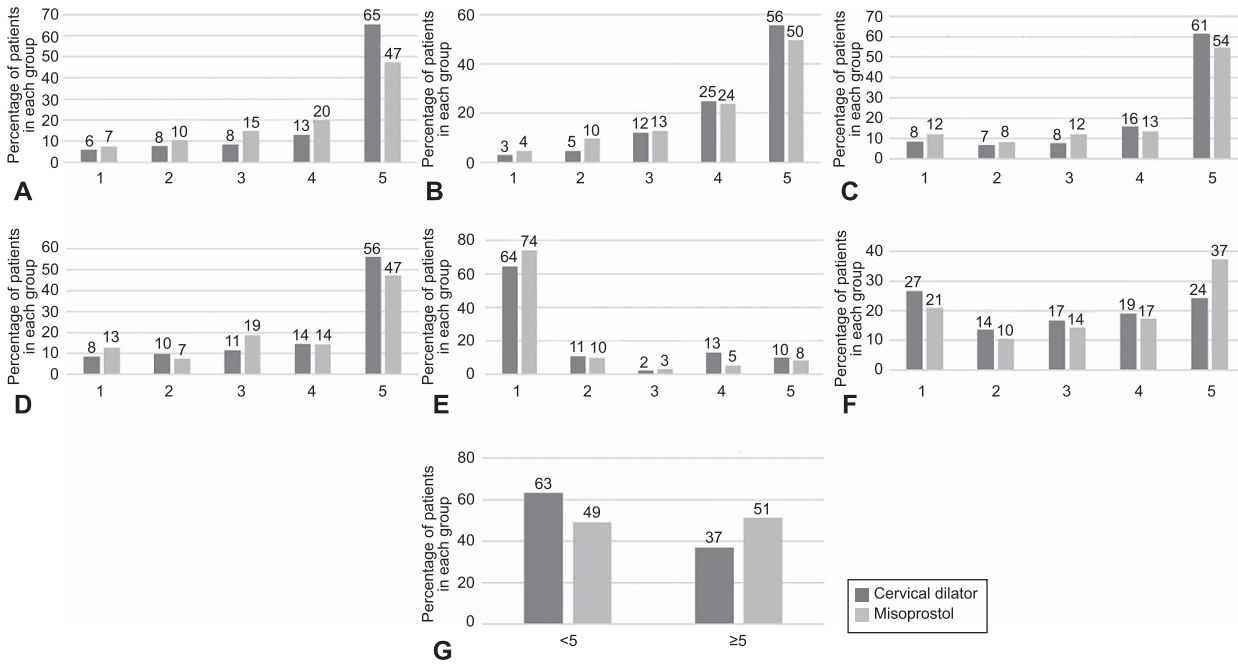

Fig. 4. Maternal satisfaction graph. **A**. "I was able to sleep" (P=.03). **B**. "I am pleased with my overall cervical ripening experience" (P=.12). **C**. Preference of alternative method (P=.14). **D**. "I was able to walk, eat, and shower…" (P=.15). **E**. "I experienced unpleasant side effects" (P=.08). **F**. "I experienced unpleasant sensations" (P=.04). **G**. Pain level experienced during ripening (P=.019). 1, strongly disagree; 5, strongly agree.

Gavara. Efficacy of Synthetic Osmotic Cervical Dilator. Obstet Gynecol 2022.

Table 4. Maternal and Neonatal Complications in the Intention-to-Treat Population

Complications of the Method	Synthetic Osmotic Cervical Dilator Group (n=151)	Misoprostol Group (n=152)	RR (95% CI)
Failed insertion	4 (2.6)	0 (0)	N/C
Cervical laceration during cervical ripening	0 (0)	0 (0)	
Vasovagal reaction during insertion	0 (0)	0 (0)	
Cesarean delivery during cervical ripening	1 (0.7)	2 (1.3)	0.50 (0.05–5.49)
ROM during cervical ripening	1 (0.7)	0 (0)	N/C
Uterine tachysystole*	35 (23.3)	70 (46.4)	0.50 (0.36–0.71)
Uterine tachysystole with nonreassuring FHR tracing†	4 (2.6)	11 (7.3)	0.37 (0.12–1.12)
Uterine hypertonus‡	8 (5.3)	11 (7.3)	0.73 (0.30–1.77)
Failed induction	11 (7.3)	13 (8.6)	0.85 (0.39–1.84)
Arrest of 1st stage	12 (7.9)	12 (7.9)	1.01 (0.47–2.17)
Arrest of 2nd stage	1 (0.7)	3 (2.0)	0.34 (0.04–3.19)
Nonreassuring FHR tracing in labor	18 (12.1)	27 (17.6)	0.67 (0.39–1.17)
Intrapartum maternal fever	15 (9.9)	17(11.2)	0.89 (0.46–1.71)
Uterine tachysystole*	14 (9.3)	12 (7.9)	1.17 (0.56–2.45)
Uterine tachysystole with nonreassuring FHR tracing†	1 (0.7)	7 (4.6)	0.14 (0.018–1.15)
Uterine hypertonus‡	8 (5.3)	7 (4.6)	1.15 (0.43–3.09)
5-min Apgar score less than 7	0	1 (0.7)	N/C
Cord pH less than 7.1	0	4 (2.6)	N/C
Neonatal sepsis	1 (0.7)	3 (2.0)	0.34 (0.04–3.19)
NICU admission	9 (6.0)	8 (5.3)	1.13 (0.45–2.86)
Intubation	0 (0)	0 (0)	
Hypoglycemia	4 (2.6)	3 (2.0)	1.34 (0.31–5.90)
Apnea	0	1 (0.7)	N/C
Meconium aspiration	1 (0.7)	0	N/C
Neonatal jaundice	13 (8.6)	11 (7.3)	1.19 (0.55–2.57)
Antibiotics used	5 (3.3)	4 (2.6)	1.26 (0.34–4.60)

RR, relative risk; N/C, noncalculable; ROM, rupture of membranes; FHR, fetal heart rate; NICU, neonatal intensive care unit.
Data are n (%) unless otherwise specified.
* More than five contractions per 10-minute period, averaged over 30 minutes.
† More than five contractions per 10-minute period, with abnormal fetal heart rate changes.
‡ A uterine contraction lasting more than 2 minutes.

Our study compares oral misoprostol with a cervical dilator for cervical ripening at term pregnancy. The strengths of this study are a large sample size, prespecified outcomes, and enrollment at two geographically different academic centers–one hospital system in the Northeast and one in the South–thus including a diverse population. Another strength of our study is the use of a single cervical ripening agent that was randomly assigned for the same period of time in both groups, thereby eliminating confounding from use of other ripening agents during the process of labor induction. Statistical analysis was performed on ITT and per-protocol populations that were prespecified before data analysis.

One limitation of our study was the inability to blind the participants and investigators owing to the nature of the intervention. The likelihood of bias is minimal, because the outcomes were prespecified and not affected by subjective interpretation. This study was not powered to detect the differences in secondary outcomes and rare adverse effects. However, the relative similarity of these outcomes among the two groups makes a clinically significant difference unlikely. Another limitation of our study is the generalizability of the results. Even though enrollment was done at two geographically different locations, multiple physicians managing labor and unique differences in each institution's labor-management protocols could have affected the outcomes.

In summary, we present level 1 evidence that synthetic osmotic cervical dilator is an efficacious mechanical method for cervical ripening at term. Patient satisfaction was higher compared with oral misoprostol, with lower rates of tachysystole in the synthetic osmotic cervical dilator group. In addition, the safety profile of the synthetic osmotic cervical dilator makes it an optimal method for cervical ripening in the outpatient setting among low-risk women undergoing induction of labor, providing potential cost savings compared with ripening

approaches requiring inpatient monitoring. We are presently completing a randomized controlled trial comparing inpatient with outpatient cervical ripening with synthetic osmotic cervical dilator in women with low-risk pregnancies.

REFERENCES

1. Orr L, Reisinger-Kindle K, Roy A, Levine L, Connolly K, Visintainer P, et al. Combination of Foley and prostaglandins versus Foley and oxytocin for cervical ripening: a network meta-analysis. Am J Obstet Gynecol 2020;223:743.e1–17. doi: 10.1016/j.ajog.2020.05.007
2. Migliorelli F, De Oliveira SS, Martínez de Tejada B. The ARRIVE trial: towards a universal recommendation of induction of labour at 39 weeks? Eur J Obstet Gynecol Reprod Biol 2020;244:192–5. doi: 10.1016/j.ejogrb.2019.10.034
3. Society of Maternal-Fetal Medicine (SMFM) Publications Committee. SMFM statement on elective induction of labor in low-risk nulliparous women at term: the ARRIVE trial. Am J Obstet Gynecol 2019;221:B2–4. doi: 10.1016/j.ajog.2018.08.009
4. Induction of labor. ACOG Practice Bulletin No. 107. American College of Obstetricians and Gynecologists. Obstet Gynecol 2009;114:386–97. doi: 10.1097/AOG.0b013e3181b48ef5
5. Talaulikar VS, Arulkumaran S. Failed induction of labor: strategies to improve the success rates. Obstet Gynecol Surv 2011; 66:717–28. doi: 10.1097/OGX.0b013e31823e0c69
6. Levine LD, Downes KL, Elovitz MA, Parry S, Sammel MD, Srinivas SK. Mechanical and pharmacologic methods of labor induction: a randomized controlled trial. Obstet Gynecol 2016; 128:1357–64. doi: 10.1097/AOG.0000000000001778
7. Hofmeyr GJ, Gülmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. The Cochrane Database of Systematic Reviews 2003, Issue 1. Art. No.: CD000941. doi: 10.1002/14651858.CD000941
8. Kerr RS, Kumar N, Williams MJ, Cuthbert A, Aflaifel N, Haas DM. Low-dose oral misoprostol for induction of labour. The Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD014484. doi: 10.1002/14651858.CD014484
9. Weeks AD, Navaratnam K, Alfirevic Z. Simplifying oral misoprostol protocols for the induction of labour. BJOG 2017;124: 1642–5. doi: 10.1111/1471-0528.14657
10. ten Eikelder MLG, Oude Rengerink K, Jozwiak M, de Leeuw JW, de Graaf IM, van Pampus MG, et al. Induction of labour at term with oral misoprostol versus a Foley catheter (PROBAAT-II): a multicentre randomized controlled non-inferiority trial. Lancet 2016;387:1619–28. doi: 10.1016/S0140-6736(16)00084-2
11. Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. Int J Gynaecol Obstet 2007;99(suppl 2):S160–7. doi: 10.1016/j.ijgo.2007.09.004
12. Drunecký T, Reidingerová M, Plisová M, Dudič M, Gdovinová D, Stoy V. Experimental comparison of properties of natural and synthetic osmotic dilators. Arch Gynecol Obstet 2015;292: 349–54. doi: 10.1007/s00404-015-3623-3
13. Gilson GJ, Russell DJ, Izquierdo LA, Qualls CR, Curet LB. A prospective randomized evaluation of a hygroscopic cervical dilator, Dilapan, in the preinduction ripening of patients undergoing induction of labor. Am J Obstet Gynecol 1996; 175:145–9. doi: 10.1016/S0002-9378(96)70264-8
14. Saad AF, Villarreal J, Eid J, Spencer N, Ellis V, Hankins GD, et al. A randomized controlled trial of Dilapan-S vs Foley balloon for preinduction cervical ripening (DILAFOL trial). Am J Obstet Gynecol 2019;220:275.e1–9. doi: 10.1016/j.ajog.2019.01.008
15. Baev OR, Babich DA, Prikhodko AM, Tysyachniy OV, Sukhikh GT. A comparison between labor induction with only Dilapan-S and a combination of mifepristone and Dilapan-S in nulliparous women: a prospective pilot study. J Matern Fetal Neonatal Med 2021;34:2832–7. doi: 10.1080/14767058.2019.1671340
16. Kashanian M, Eshraghi N, Sheikhansari N, Eshraghi N. Comparing the efficacy of Dilapan with extra-amniotic saline infusion and oral misoprostol for cervical ripening in term pregnancies. J Matern Fetal Neonatal Med 2021 Feb 23 [Epub ahead of print]. doi: 10.1080/14767058.2021.1888912
17. Gupta J, Chodankar R, Baev O, Bahlmann F, Brega E, Gala A, et al. Synthetic osmotic dilators in the induction of labour–an international multicentre observational study. Eur J Obstet Gynecol Reprod Biol 2018;229:70–5. doi: 10.1016/j.ejogrb.2018.08.004
18. Moher D, Schulz KF, Altman DG; CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Clin Oral Investig 2003;7:2–7. doi: 10.1007/s00784-002-0188-x
19. Macaya F, Ryan N, Salinas P, Pocock SJ. Challenges in the design and interpretation of noninferiority trials. J Am Coll Cardiol 2017;70:894–903. doi: 10.1016/j.jacc.2017.06.039
20. Buonaccorsi JP, Laake P, Veierød MB. On the power of the Cochran–Armitage test for trend in the presence of misclassification. Stat Methods Med Res 2014;23:218–43. doi: 10.1177/0962280211406424
21. Walker KF, Wilson P, Bugg GJ, Dencker A, Thornton JG. Childbirth experience questionnaire: validating its use in the United Kingdom. BMC Pregnancy Childbirth 2015;15:86. doi: 10.1186/s12884-015-0513-4
22. Thong ISK, Jensen MP, Miró J, Tan G. The validity of pain intensity measures: what do the NRS, VAS, VRS, and FPS-R measure? Scand J Pain 2018;18:99–107. doi: 10.1515/sjpain-2018-0012

Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No. At present we do not plan to share any deidentified participant data for this study. We are working on a timeline to determine when we can share information related to study protocol and statistical analysis plan.*

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.*

PEER REVIEW HISTORY

Received November 3, 2021. Received in revised form January 5, 2021. Accepted January 13, 2022. Peer reviews and author correspondence are available at http://links.lww.com/AOG/C696.