OBSTETRICS

Induction of labor at term with vaginal misoprostol or a prostaglandin E2 pessary: a noninferiority randomized controlled trial

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BACKGROUND: Induction of labor is among the most common procedures for pregnant women. Only a few randomized clinical trials with relatively small samples have compared misoprostol with dinoprostone. Although their efficacy seems similar, their safety profiles have not been adequately evaluated, and economic data are sparse.

OBJECTIVE: This study aimed to test the noninferiority of vaginal misoprostol (prostaglandin E1) (25 μg) to a slow-release dinoprostone (prostaglandin E2) pessary (10 μg) for induction of labor with an unfavorable cervix at term.

STUDY DESIGN: This was an open-label multicenter randomized noninferiority trial at 4 university hospitals of the Research Group in Obstetrics and Gynecology between 2012 and 2015. We recruited women who underwent induction of labor for medical reasons, those with a Bishop score of $\leq$5 at $\geq$36 weeks' gestation, and those with a cephalic-presenting singleton pregnancy with no previous cesarean delivery. Women were randomly allocated to receive either vaginal misoprostol at 4-hour intervals (25 μg) or a 10-mg slow-release dinoprostone pessary. The primary outcome was the total cesarean delivery rate. Noninferiority was defined as a difference in the cesarean delivery rates between the groups of no more than 5%. Secondary outcomes included neonatal and maternal morbidity, vaginal delivery at <24 hours after starting the induction of labor process, and maternal satisfaction.

RESULTS: The study included 1674 randomized women. The per-protocol analysis included 790 women in each group. The total cesarean delivery rates were 22.1% (n=175) in the misoprostol group and 19.9% (n=157) in the dinoprostone group, a difference of 2.2% (with an upper-bound 95% confidence limit of 5.6%) (P=.092). Results in the intention-to-treat analysis were similar. Neonatal and maternal morbidity rates were similar between groups. Vaginal delivery within 24 hours was significantly higher in the misoprostol group (59.3% vs 45.7%; P<.001) as was maternal satisfaction, assessed in the postpartum period by a visual analog scale (mean score, 7.1±2.4 vs 5.8±3.1; P<.001).

CONCLUSION: The noninferiority of a 25-μg dose of vaginal misoprostol every 4 hours to the dinoprostone pessary for cesarean delivery rates after induction of labor at term could not be demonstrated, although the confidence limit of the difference barely exceeded the noninferiority margin. Nonetheless, given the small difference between these cesarean delivery rates and the similarity of neonatal and maternal morbidity rates in this large study, the clinical risk-to-benefit ratio justifies the use of both drugs.

Key words: dinoprostone, induction of labor, misoprostol, prostaglandin E2 pessary, term pregnancy, vaginal

Introduction

Induction of labor (IOL) is among the most common procedures for pregnant women planning a vaginal delivery, performed in approximately 40% of nulliparous and 30% of parous women.[1] It is generally warranted for women with medical indications, and several physicians have begun advocating its use for all women after 39 weeks' gestation to improve the safety of both mothers (lowers the rates of cesarean delivery [CD] and hypertensive disorders) and their children (reduces the need for respiratory support during the first 72 hours of life) during delivery.[2,3] The practice of IOL, which is likely to become more widespread, reinforces the need for studies comparing different methods of inducing labor to determine which is the best for the growing population of pregnant women.

Numerous studies have shown a good risk-to-benefit ratio for dinoprostone (prostaglandin E2 [PGE2]) in its various forms (intravaginal slow-release pessary, intravaginal gel, intracervical gel) for women with an unfavorable cervix. It is the reference method for IOL,[4] with slow-release dinoprostone currently not only the most frequently prescribed medication for this indication but also the most expensive.[5]

Misoprostol, a synthetic analog of prostaglandin E1, has been an alternative medication used for cervical ripening for several years. It is easy to use, inexpensive, and thermostable. Moreover, several studies have sought to define its optimal dose and route of administration.[6,7] Although oral misoprostol is increasingly studied, the administration of misoprostol via the vaginal route remains the most thoroughly documented.[8] Currently, low-dose (25 μg) vaginal misoprostol is recommended as a first-line medication for IOL by the American College of Obstetricians and Gynecologists,[9] the International Federation of Gynecology and Obstetrics,[10] and the World Health Organization.[11]

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AJOG at a Glance

Why was this study conducted?

As induction of labor (IOL) is likely to be considered for all women after 39 weeks' gestation to improve the safety of both mothers and their children during delivery, studies are needed to compare different methods and determine which is the best.

Key findings

The total cesarean delivery (CD) rates were 22.1% in the group receiving 25 μg of vaginal misoprostol every 4 hours and 19.9% in the dinoprostone pessary group, a difference of 2.2% (P=.092).

What does this add to what is known?

The noninferiority of a 25-μg dose of vaginal misoprostol every 4 hours to the dinoprostone pessary for CD rates after IOL at term could not be demonstrated. Nonetheless, given the small difference between the CD rates and the similarity of neonatal and maternal morbidity rates, the clinical risk-to-benefit ratio justifies the use of both drugs.

Few randomized clinical trials (RCTs) have compared low-dose vaginal misoprostol to dinoprostone.[12–15] Although their efficacy seems similar, their safety profiles have not been adequately evaluated, and the relatively small samples in these studies limit their validity.

The CYTOPRO (CYTOtec® versus PROpess®) trial was designed to test the hypothesis that a 25-μg dose of vaginal misoprostol every 4 hours would not be inferior to a 10-mg slow-release dinoprostone pessary, assessed by CD rates in women who underwent IOL and a Bishop score of ≤5, and would have similar side effect profiles for the mother and child.

Materials and Methods

Study design and patients

The CYTOPRO trial was an open-label, multicenter, randomized, noninferiority trial conducted from September 2012 to June 2015 in 4 French centers participating in the Groupe de Recherche en Obstétrique et Gynécologie. It compared a 25-μg dose of intravaginal misoprostol every 4 hours to a 10-mg slow-release dinoprostone pessary (PGE2). This study was supported by a grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique, June 18, 2010) and promoted by the Departement of Clinical Research of the Toulouse University Hospital Center.

Information about the trial was first given when a medical indication for IOL arose. Informed consent was asked for and provided right before IOL took place. We enrolled women aged 18 years or older with a viable singleton fetus in cephalic presentation, a gestational age of 36 weeks or more, an unfavorable cervix (Bishop score of ≤5), and uterine contractions of ≤3 per 10 minutes, as recorded by electronic fetal monitoring (EFM) for 30 minutes at admission for a medically indicated IOL. Women with ruptured membranes were eligible for inclusion. Noninclusion criteria included a previous CD, history of myomectomy, suspected fetal distress on EFM at admission, unexplained bleeding, suspected chorioamnionitis, fetopelvic disproportion, estimated fetal weight of >4500 g, placenta previa, active herpes infection (primary infection or recurrence within 7 days), any known allergy or intolerance to prostaglandin agents, and any contraindication to vaginal delivery.

The French National Agency for Medicine and Health Product Safety (2011-000933-35, A110414-12) and the committee for the protection of people participating in biomedical research (CPP, 1.11.08) approved the trial, registered on ClinicalTrials.gov (NCT01765881).

Randomization

Eligible women were randomly assigned in a 1:1 ratio to receive either misoprostol capsules or a dinoprostone pessary. Sealed envelopes were used for allocation according to a permuted block method (20 women per block), stratified by center and parity (nulliparous or parous).

Study drugs and procedures

Misoprostol was manufactured by the Toulouse hospital pharmacy and consisted of 200-μg misoprostol tablets pulverized with microcrystalline cellulose to achieve the volume needed for 100 capsules of 25 μg each. Each capsule contained between 23.5 and 27.5 μg misoprostol. High-performance liquid chromatography showed the standard retention time and that of the sample differed by less than 2.5%.

Every 4 hours, the clinical care provider placed a 25-μg capsule into the posterior vaginal fornix of women allocated to the vaginal misoprostol group, with a maximum of 4 capsules per day, that is, 100 μg. Before the administration of each capsule, fetal well-being and uterine activity were checked by EFM. If the fetal heart rate (FHR) trace was nonreassuring, or the woman had at least 2 painful contractions in 10 minutes, the planned capsule was not placed.

For women allocated to the slow-release dinoprostone (10 mg) group (Propess; Ferring SAS; Gentilly, France), the pessary was placed by the care provider in the posterior vaginal fornix until labor started or for 24 hours maximum. In cases of nonreassuring FHR or uterine tachysystole, the pessary was removed. If the removal occurred in the first 12 hours of IOL, another pessary was placed after normalization of EFM. Women in both groups were monitored identically, with a one-hour-long EFM analysis every 4 hours.

IOL was continued until either there was an adequate response (Bishop score of ≥7 or cervical dilation of ≥3 cm) or 24 hours had passed since cervical ripening began. The pessary was then removed from women in that group, and all women were asked not to reveal

their allocation group. They were then transferred to the delivery room and managed by a midwife and/or obstetrician blinded to the method used to induce labor.

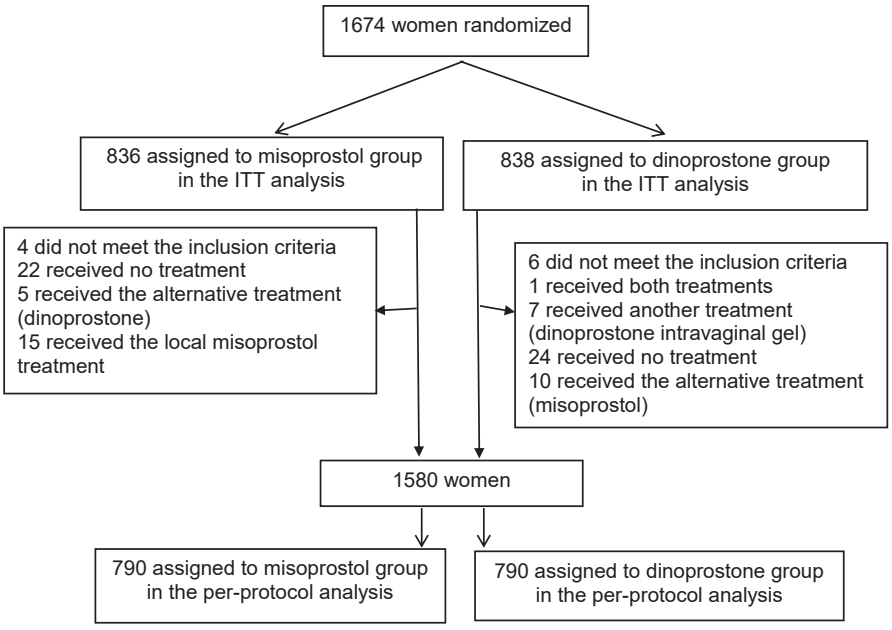
In both groups, except women with preterm premature rupture of membranes, the first procedure in the delivery room was an amniotomy, performed at least 30 minutes after the removal of the dinoprostone pessary or 4 hours after the last misoprostol administration, as recommended. Epidural analgesia was provided at maternal request, and EFM was monitored continuously from entry into the delivery room. If uterine activity was deemed insufficient (as evaluated by the midwife and/or the obstetrician, depending on FHR, uterine activity, and progression of dilation) or if amniotomy was not possible, oxytocin was continuously infused until at least 3 contractions per 10 minutes were achieved or progression of labor was considered adequate. The protocol used for oxytocin infusion was standardized with an initial dose of 2 mIU/min, increased if needed by 2 mIU every 20 to 30 minutes.

Indications for CD were decided by the care provider, based on the French guidelines on CD for lack of progress in labor.[16] In the active phase of the first stage of labor, a CD could be considered after 2 hours with no change in dilation and was necessary after 3 hours. The use of fetal blood sampling was uncommon in all 4 centers, and management was identical in both groups.

Trial outcomes

The primary outcome was the total CD rate. Secondary outcomes related to neonatal mortality and morbidity included neonatal death, neonatal seizure, admission to the neonatal intensive care unit (NICU), arterial umbilical cord pH of <7.05, 5-minute Apgar score of <7, meconium-stained amniotic fluid, and meconium aspiration. Secondary outcomes related to maternal morbidity included uterine rupture, uterine hypertonus (a contraction lasting longer than 2 minutes), tachysystole (more than 5 contractions in 10 minutes on at least 2 occasions), hyperstimulation syndrome (hypertonus or tachysystole associated with abnormal FHR), postpartum hemorrhage (blood loss of >500 mL), fever during labor (temperature of ≥38.5°C), episiotomy, severe perineal lesion (third- and fourth-degree lacerations), CDs indicated only because of abnormal FHR, and CDs indicated only for lack of progress in labor. Other secondary outcomes were related to efficacy and maternal satisfaction: vaginal delivery within 24 hours, rate of oxytocin use, and satisfaction, assessed by a visual analog scale (VAS) during the postpartum period.

FIGURE 1
Study flowchart: randomization and protocol adherence



ITT, intention to treat.

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Sample size

The sample size was determined to rule out an absolute difference in CD rates of ≥5% (the noninferiority margin) with misoprostol vs dinoprostone if misoprostol is truly not inferior. The noninferiority boundary was based on clinical evidence from previous RCTs.[12,13] Because we assumed a CD rate of 20% for women in the dinoprostone group,[17] with a 1-sided Farrington-Manning test and a 1-sided type I error of 0.025, the study required 1588 patients to have an overall power of 0.80. We planned to randomize 1700 women, assuming that approximately 6.5% of the women might be excluded from the main analysis of the primary endpoint, because of noncompliance with the protocol or attrition.

Statistical analysis

Descriptive statistics included the 25th percentile (Q1), median, 75th percentile (Q3), and number of nonmissing observations for the categorical data and counts and percentages for the continuous data. Percentages were calculated on nonmissing data. The per-protocol (PP) population excluded women with major protocol deviations. The intention-to-treat (ITT) dataset included all women randomized in the study (Figure 1). No missing primary outcome data were reported. Participants were analyzed according to their randomization group.

The primary outcome was estimated as the difference in the CD rates between the misoprostol and dinoprostone arms. The primary analysis was performed in the PP population

TABLE 1
Baseline characteristics of women in the CYTOPRO trial

Characteristic	Misoprostol (n=836)	Dinoprostone (n=838)
Maternal age (y)	31.0 (27.2–35.3)	30.8 (27.0–34.6)
Nulliparous	503 (60.2)	502 (59.9)
BMI (kg/m^2)	26.7 (22.6–31.2)	26.4 (22.8–30.5)
Gestational age (wk)[a]	39.7 (38.6–41.1)	39.7 (38.6–41.3)
≥41[b]	284 (44.6)	282 (43.9)
Bishop score	3 (2.0–4.0)	3 (2.0–4.0)
Indication for induction[c]		
Prolonged and postterm pregnancy	225 (26.9)	249 (29.7)
Premature rupture of membranes	201 (24.0)	192 (22.9)
Diabetes mellitus	142 (17.0)	141 (16.8)
Hypertensive disorders	114 (13.6)	101 (12.1)
Fetal growth restriction	47 (5.6)	48 (5.7)
Nonreassuring fetal heart rate	36 (4.3)	33 (3.9)
Other	143 (8.5)	155 (9.3)

Data are presented as number (percentage) or median (interquartile range).

BMI, body mass index; *IOL*, induction of labor.

[a] Available for 1279 women; [b] Prolonged pregnancy alone was not a systematic indication for IOL; [c] Indications for IOL were not mutually exclusive.

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(Figure 1) and repeated as a sensitivity analysis in the ITT population. Confidence intervals (CIs) were calculated with the Wald method, and additional *P* values were calculated with the noninferiority Dunnet and Gent chi-square test.[18,19] To take the trial design into account (randomization stratified by center and parity), we further estimated the treatment effect, adjusted for center and parity, in a logistic regression model. Safety outcomes were analyzed by randomization group in the ITT population.

The cumulative incidence rates of these CDs were estimated with the Fine-Gray model[20] to describe their occurrence over time. The cumulative incidence curve represented the probability of CD owing to each cause in turn, before time t. Lastly, efficacy outcomes were analyzed with superiority 2-sided tests with an alpha value of 5% and 95% CI in the ITT population. No corrections were made for multiple comparisons.

All statistical analyses were performed with the Statistical Analysis System software (version 9.4; SAS Institute Inc, Cary, NC) and RStudio software (version 1.1.383; RStudio, Boston, MA).

Results

Between September 2012 and June 2015, the 4 centers randomized 1674 women, 836 allocated to the misoprostol group and 838 allocated to the dinoprostone group; furthermore, of the 1674 women, 1005 (60.0%) were nulliparous and 669 (40.0%) parous (Figure 1). After 94 women were excluded from the PP analysis (46 in the misoprostol group and 48 in the dinoprostone group), 790 remained in each group (Figure 1): 945 (59.8%) nulliparous and 635 (40.2%) parous. Baseline characteristics were comparable between groups (Table 1). The most common indications for IOL were postterm pregnancy, premature rupture of membranes, diabetes mellitus, and hypertensive disorders (Table 1).

Primary outcome

Results in the ITT and PP dataset were similar (Table 2). As recommended by methodological guidelines regarding noninferiority design trials,[21–23] results are presented in the PP dataset. The total CD rate was 22.2% (175 of 790) in the misoprostol group and 19.9% (157 of 790) in the dinoprostone group, a difference of 2.3%, with a 95% upper-bound CI limit of 5.6%, which significantly exceeded the limit for noninferiority (*P*=.092) (Figure 2).

Secondary neonatal and maternal safety outcomes

Differences in neonatal and maternal morbidity rates between groups were small. Table 3 presents the neonatal outcomes, and Table 4 presents the maternal outcomes.[24] There were 4 neonatal deaths and 38 admissions to NICU. The most important differences observed among neonatal outcomes concerned meconium aspiration: 1.0% of neonates in the misoprostol group compared with 0.3% in the dinoprostone group. The CD rate for abnormal FHR as the only indication for CD was slightly higher in the misoprostol group (risk difference of 2.2; 95% CI, −0.3 to 4.6), whereas the CD rates for lack of progress in labor were more similar (risk difference of −0.8; 95% CI, −0.3 to 1.6).

The cumulative incidence of CDs for abnormal FHR as the only indication for CD seemed to differ slightly between groups, and the incidence of CDs was higher in the misoprostol than in the dinoprostone group (Figure 3).

Efficacy and maternal satisfaction (ITT population)

Vaginal delivery within 24 hours after starting the IOL process was more frequent in the misoprostol group than in the dinoprostone group: 484 of 816 women (59.3%) vs 370 of 809 (45.7%) (*P*<.001). At the same time, oxytocin use during labor was less frequent in the misoprostol group: 484 of 825 women (58.7%) vs 545 of 811 (67.2%) (*P*<.001).

Most patients (52.1%) needed 2 misoprostol capsules, 25.5% 3 capsules, and 22.4% 4 capsules. In the dinoprostone group, 118 (15.2%) had the pessary removed before 24 hours. Maternal satisfaction, evaluated during the postpartum period, was available for 1297 women, 80.4% in the misoprostol group

TABLE 2
Primary outcome

Mode of delivery	Per-protocol analysis			ITT analysis		
	Total (N=1580)	Misoprostol (n=790)	Dinoprostone (n=790)	Total (N=1674)	Misoprostol (n= 836)	Dinoprostone (n=838)
Cesarean delivery	332 (21.0)	175 (22.2)	157 (19.9)	350 (20.9)	184 (22.0)	166 (19.8)
Instrumental delivery	288 (18.2)	137 (17.3)	151 (19.1)	310 (18.5)	148 (17.7)	162 (19.3)
Spontaneous delivery	960 (60.8)	478 (60.5)	482 (61.0)	1014 (60.6)	504 (60.3)	510 (60.9)
	5% limit for noninferiority: +0.056			Limit of 5% for noninferiority: +0.055		

Data are presented as number (percentage).

ITT, intention to treat.

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and 74.9% in the dinoprostone group. Women allocated to the misoprostol arm reported a significantly higher level of satisfaction (mean VAS score, 7.1±2.4) than those in the dinoprostone arm (mean VAS score, 5.8±3.1) ($P<.001$). Notably, 78% of the women in the misoprostol group stated that they would choose the same method should they require IOL again vs 63% in the dinoprostone group ($P<.001$).

Comment

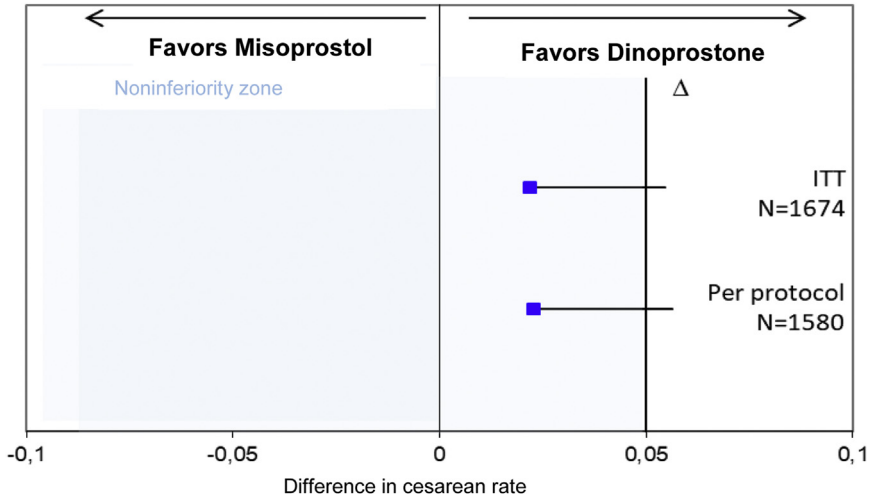
Principal findings

In this multicenter randomized trial, the CD rates of 22.1% in the misoprostol group and 19.9% in the dinoprostone group failed to meet the noninferiority criterion for misoprostol ($P=.092$). Nonetheless, neonatal or maternal outcomes did not differ between groups. Moreover, both rates of vaginal delivery within 24 hours and maternal satisfaction were significantly higher in the misoprostol group.

Results

To our knowledge, only 2 RCTs have compared vaginal misoprostol (25 μg) every 4 hours with the 10-mg slow-release dinoprostone pessary.[13,15] The trial by Wing et al[13] randomized 200 women and found no significant difference in their modes of delivery, neonatal outcomes, or rates of delivery within 24 hours, whereas tachysystole was significantly less frequent in the misoprostol group than in the dinoprostone group (7.1% vs 18.4%; $P=.020$). In our trial, the lower frequency of tachysystole in our misoprostol group was not significant (8.0% vs 10.2%; $P=.1$). A recent RCT compared these treatments for IOL in 198 nulliparous women after the 41st week of gestation[15] and did not find a difference in the primary outcome of successful vaginal delivery within 24 hours (49.5% for misoprostol and 42.4% for dinoprostone; $P=.400$) or the CD rates (22.2% for misoprostol and 26.3% for dinoprostone; $P=.500$). Neonatal outcomes (ie, admission to the NICU, umbilical cord pH, and Apgar score) did not differ between the groups, but abnormal FHR during active labor was

FIGURE 2
Forest plot: difference in the cesarean delivery rate and the noninferiority zone in the analyses



The *vertical line* represents the noninferiority margin (5%); the noninferiority zone is colored in *blue*. The *squares* represent the estimated differences in cesarean delivery rates between the misoprostol and dinoprostone groups. The *horizontal lines* represent the upper 95% confidence limit of the difference.

ITT, intention to treat.

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TABLE 3
Neonatal outcomes in the intention-to-treat population by randomization group

Outcome	Misoprostol (n=836)	Dinoprostone (n=838)	Risk difference (95% CI)	*P* value
Neonatal death	1/836 (0.1)	3/838 (0.4)	−0.2 (−0.7 to 0.2)	.625[a]
Neonatal seizure[b]	0/824 (0.0)	0/810 (0.0)	—	—
Admission to the NICU[b]	17/824 (2.1)	21/810 (2.6)	−0.5 (−2.0 to 1.0)	.478
Arterial umbilical cord pH<7.05[b]	10/776 (1.3)	12/762 (1.6)	−0.3 (−1.5 to 0.9)	.637
5-min Apgar score of <7[b]	30/836 (3.6)	41/837 (4.9)	−1.3 (−3.3 to 0.7)	.184
Meconium-stained amniotic fluid	34/811 (4.2)	31/799 (3.9)	0.3 (−1.6 to 2.3)	.750
Meconium aspiration[b]	8/825 (1.0)	2/809 (0.3)	0.7 (0.0−1.5)	.061

Data are presented as number/total number (percentage), unless otherwise indicated.

CI, confidence interval; *NICU*, neonatal intensive care unit.

[a] The Fisher exact test was used; [b] Stillbirths were excluded.

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less frequent in the misoprostol group (44.4% vs 58.6%; *P*=.047).

Clinical implications

In high-resource countries today, approximately 25% of women have IOL. A Randomized Trial of Induction Versus Expectant Management (ARRIVE) trial[2,3,25] demonstrated that in low-risk nulliparous women at 39 weeks' gestation, routine IOL, compared with expectant management, was not associated with more adverse neonatal effects, and it benefited mothers, by decreasing the rates of both CDs and hypertensive disorders of pregnancy.[2] Therefore, the Society for Maternal-Fetal Medicine recently stated that IOL is a reasonable option for low-risk nulliparous women at or after 39 weeks' of gestation.[26] The increase in the IOL rate likely to result makes our trial especially interesting by providing additional information about the drugs used for it. Our trial showed that both 25 μg of vaginal misoprostol every 4 hours and a slow-release dinoprostone pessary are safe options for IOL. Furthermore, 2 meta-analyses have confirmed the benefit of low-dose misoprostol for both efficacy and safety, both vaginally and orally, compared with dinoprostone.[8,27] Misoprostol as a less expensive thermostable drug seems to have especially great advantages over dinoprostone in low-resource settings.

Strengths and limitations

This study had several strengths. With 1674 women included, it is to our knowledge the largest RCT comparing low-dose vaginal misoprostol with the

TABLE 4
Maternal outcomes in the intention-to-treat population by randomization group

Outcome	Misoprostol	Dinoprostone	Risk difference % (95% CI)	*P* value
Uterine rupture	0/825 (0.0)	0/811 (0.0)	—	—
Uterine hypertonus	70/836 (8.4)	88/838 (10.5)	−2.1 (−5.1 to 0.8)	.136
Tachysystole	65/836 (7.8)	83/838 (9.9)	−2.1 (−5.0 to 0.7)	.125
Hyperstimulation syndrome	25/836 (3.0)	27/838 (3.2)	−0.2 (−2.0 to 1.5)	.785
Postpartum hemorrhage of >500 mL	51/825 (6.2)	48/811 (5.9)	0.3 (−2.1 to 2.6)	.823
Fever during labor	10/836 (1.2)	18/838 (2.2)	−1.0 (−2.2 to 0.3)	.129
CD for abnormal FHR[a]	65/836 (7.8)	47/838 (5.6)	2.2 (−0.3 to 4.6)	.076
CD for lack of progress in labor	51/836 (6.1)	58/838 (6.9)	−0.8 (−3.3 to 1.6)	.476
Episiotomy	165/824 (20.0)	185/809 (22.9)	−2.8 (−7.3 to 1.7)	.162
Severe perineal lacerations	11/823 (1.3)	6/808 (0.7)	0.6 (−0.4 to 1.6)	.238

Data are presented as number/total number (percentage), unless otherwise indicated.

CD, cesarean delivery; *CI*, confidence interval; *FHR*, fetal heart rate.

[a] Adapted from FIGO.[24]

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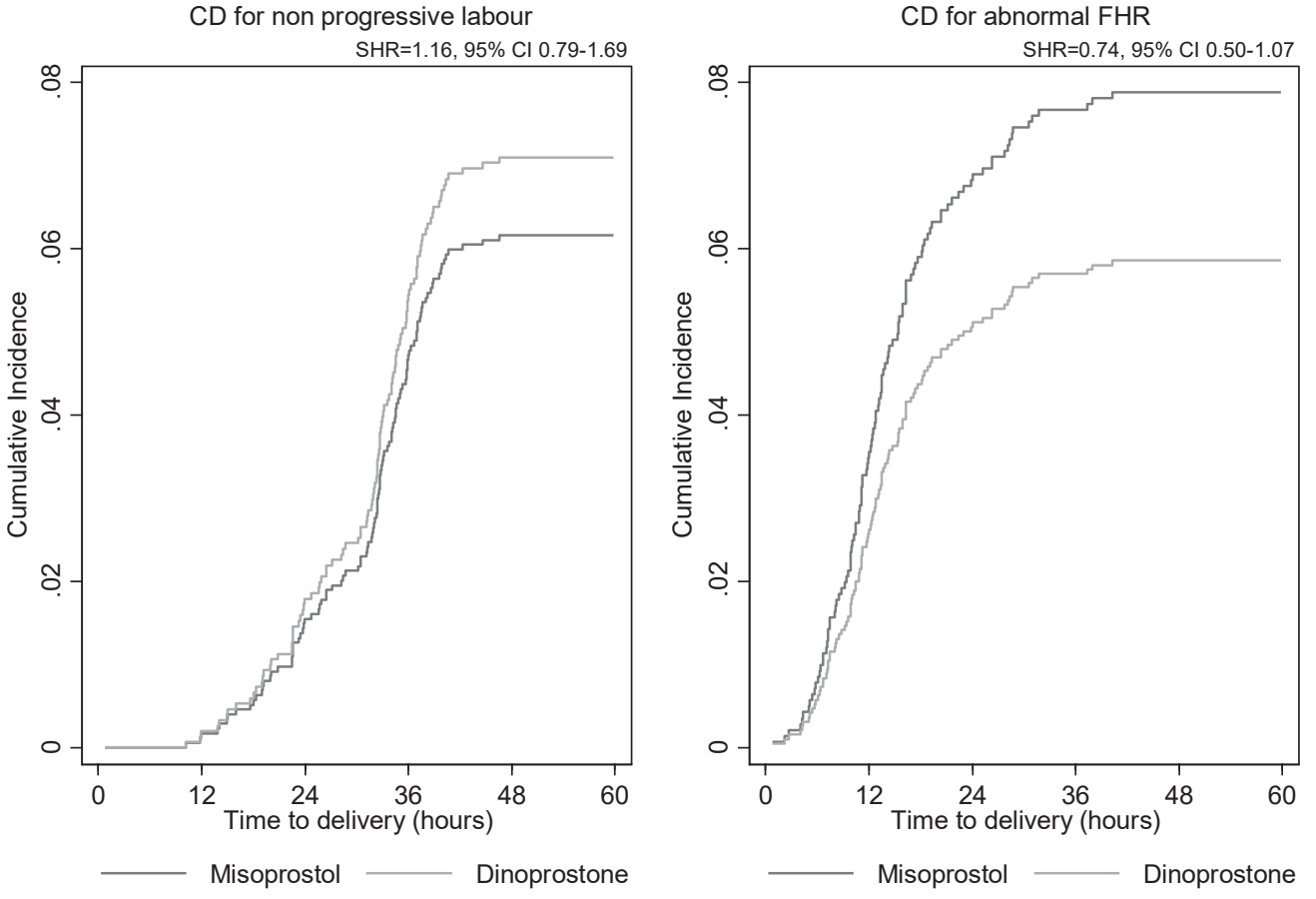
FIGURE 3
Cumulative incidence of cesarean delivery rate by randomization group, in the ITT population and estimations for Fine-Gray model in the presence of competing risks



CD, cesarean delivery; *CI*, confidence interval; *FHR*, fetal heart rate; *ITT*, intention-to-treat; *SHR*, subdistribution hazard ratio.

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slow-release dinoprostone pessary. Moreover, because misoprostol is an off-label drug for this indication, the French drug agency inspected each center during the study. For the same safety reasons, we double verified all neonatal outcome data. This has delayed the publication process but reinforced the reliability of these results.

In addition, this study has several limitations. First, because the pharmaceutical presentation was different for each drug (capsule vs pessary), a double-blinded study was not feasible and was not attempted. This bias was limited by ensuring that the delivery room staff was blinded to the allocation group or IOL method; IOL was managed by different obstetricians and midwives. Moreover, it has recently been suggested that the benefits of blinding may be exaggerated.[28] Misoprostol had to be manufactured by the hospital pharmacy. This was a limitation as additional techniques are required to transform 200-μg tablets into 25-μg capsules. Hospitals unable to do so cannot use our protocol. Second, the noninferiority study design might be seen as a limitation, although it seemed appropriate for the comparison of an off-label drug with the dinoprostone pessary that is the reference drug for cervical ripening. The noninferiority boundary (5%) was determined on clinical grounds as a difference small enough to have no clinical impact. Although the noninferiority of misoprostol to the dinoprostone pessary could not be demonstrated with a risk of error of 5%, the CIs showed that the maximum difference did not exceed 5.6%. In terms of clinical relevance, this does not seem very different from the predefined 5.0%. This point should also be interpreted in light of misoprostol's superior ease of use and greater patient satisfaction. This trial has illustrated the difficulty of the arbitrary choice, based on a clinical value judgment, of the maximum tolerated difference in noninferiority trials and raised questions about the distinction between statistical significance and clinical relevance.

Conclusions

In our large multicenter trial, the noninferiority of a 25-μg dose of vaginal misoprostol every 4 hours to the dinoprostone pessary for CD rates after IOL at term could not be demonstrated, although the confidence limit of the difference barely exceeded the noninferiority margin. Because the neonatal morbidity rates were similar and the CD rates were very close to one another, both methods can be considered when IOL is indicated in singleton pregnancies without a previous CD. Women should be counseled about the benefits, side effects, and specificity of each method to be able to choose the appropriate procedure for themselves. ■

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