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A. TITLE PAGE

Induction of Labor at Term With Vaginal Misoprostol or a PGE2 Pessary: a Noninferiority RCT

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55 **Condensation:**

56 The noninferiority of 25- μ g vaginal misoprostol every four hours to the dinoprostone
57 pessary for cesarean delivery rates after induction of labor at term was not
58 demonstrated.

59

60 **Short title:** Induction of labor with vaginal misoprostol versus a PGE2 pessary

61

62 **AJOG at a Glance:**

63 A. Why was this study conducted?

64 As induction of labor is likely to be considered for all women after 39 weeks'
65 gestation to improve safety, studies are needed to compare different methods and
66 determine which is best.

67 B. What are the key findings?

68 The total CD rate in the group receiving 25- μ g vaginal misoprostol every 4 hours
69 was 22.1% and in the dinoprostone pessary group, 19.9%, for a difference
70 between the groups of 2.2%, $P=.092$.

71 C. What does this study add to what is already known?

72 The noninferiority of 25- μ g vaginal misoprostol every four hours to the
73 dinoprostone pessary for CD rates after IOL at term could not be demonstrated.

74 Nonetheless, in view of the small difference between the cesarean rates and the

75 similarity of neonatal and maternal morbidity rates, the clinical risk-benefit ratio
76 justifies the use of both drugs.

77

78

Abstract

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

Objective: To test the noninferiority of vaginal misoprostol (PGE1) (25 µg) to a slow-release dinoprostone (PGE2) pessary (10 µg) for induction of labor with an unfavorable cervix at term.

Study Design: Open-label multicenter randomized noninferiority trial at 4 university hospitals of the Research Group in Obstetrics and Gynecology (GROG) between 2012 and 2015. We recruited women with labor induced for medical reasons, a Bishop score ≤ 5 at ≥ 36 weeks, and a cephalic-presenting singleton pregnancy with no prior 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 < 24 hours after starting the induction process, and maternal satisfaction.

Results: The study included 1674 randomized women. The per-protocol analysis included 790 in each group. The total cesarean delivery rate in the misoprostol group was 22.1% (n=175) and in the dinoprostone group, 19.9% (n=157), for a difference between the groups 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 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 (SD 2.4) vs 5.8 (3.1), $P<.001$.

Conclusion: The noninferiority of 25- μ g vaginal misoprostol every four 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. Nonetheless, given the small difference between these cesarean rates and the similarity of neonatal and maternal morbidity rates in this large study, the clinical risk-benefit ratio justifies the use of both drugs.

Clinical Trial Registration: ClinicalTrials.gov: NCT01765881

Key words: dinoprostone, labor induction, misoprostol, PGE2 pessary, term pregnancy, vaginal

118 INTRODUCTION

119 Induction of labor (IOL) is among the most common procedures for pregnant women
120 planning vaginal delivery, performed for about 40% of nulliparous and 30% of parous
121 women.¹ It is generally warranted for women with medical indications, and some
122 have begun advocating considering its use for all women after 39 weeks of gestation
123 to improve safety for both mothers (lower rates of cesarean delivery and of
124 hypertensive disorders) and children (reduced need for respiratory support during the
125 first 72 hours of life).^{2,3} This use of IOL, which is likely to become more widespread,
126 reinforces the need for studies comparing different methods of inducing labor to
127 determine which is best for this growing population of pregnant women.

128 Numerous studies have shown a good risk-benefit ratio for dinoprostone (PGE₂) in
129 its various forms (intravaginal slow-release pessary, intravaginal gel, intracervical
130 gel) for women with an unfavorable cervix. It is the reference method for induction,⁴
131 with slow-release dinoprostone currently the substance most frequently prescribed
132 for this indication, but also the most expensive.⁵

133 Misoprostol, a synthetic analog of prostaglandin E₁ (PGE₁) has been an alternative
134 method used for cervical ripening for several years. It is easy to use, inexpensive,
135 and thermostable. Several studies have sought to define its optimal dose and route
136 of administration.^{6,7} Although oral misoprostol is increasingly studied, the vaginal
137 route remains the most thoroughly documented.⁸ Currently, low-dose vaginal (25 µg)
138 misoprostol is recommended as a first-line substance for IOL by the American
139 College of Obstetricians and Gynecologists (ACOG),⁹ the International Federation of
140 Gynecology and Obstetrics,¹⁰ and the World Health Organization.¹¹

141 Few randomized clinical trials (RCTs) have compared low-dose vaginal misoprostol
142 to dinoprostone.¹²⁻¹⁵ Although their efficacy appears similar, their safety profiles have

not been adequately evaluated and the relatively small samples in these studies limit their validity.

The CYTOPRO trial was designed to test the hypothesis that a 25- μ g dosage of vaginal misoprostol every four hours would not be inferior to a 10-mg slow-release dinoprostone pessary, assessed by cesarean delivery (CD) rates in women with IOL and a Bishop score ≤ 5 , and would have similar side-effect profiles for 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 four French centers participating in the Groupe de Recherche en Obstétrique et Gynécologie (GROG). It compared intravaginal misoprostol (25 μ g) every four hours to a 10-mg slow-release dinoprostone pessary (PGE₂). The French Ministry of Health (Programme Hospitalier de Recherche Clinique, 2010, 18-08) supported this study, which was sponsored by Toulouse University Hospital Center (UHC).

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 ≤ 5), and ≤ 3 uterine contractions 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. Non-inclusion criteria

168 included a previous CD, history of myomectomy, suspected fetal distress on EFM at
169 admission, unexplained bleeding, suspected chorioamnionitis, fetopelvic
170 disproportion, estimated fetal weight > 4500 g, placenta previa, active herpes
171 infection (primary infection or recurrence within 7 days), any known allergy or
172 intolerance to prostaglandin agents, and any contraindication to vaginal delivery.

173 The French national agency for medicine and health product safety (ANSM) (2011-
174 000933-35, A110414-12) and the committee for the protection of people participating
175 in biomedical research (CPP, 1.11.08) approved the trial, registered at
176 clinicaltrials.gov (NCT 01765881).

178 *Randomization*

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

184 *Study drugs and procedures*

185 Misoprostol was manufactured by the Toulouse hospital pharmacy and consisted of
186 200-µg misoprostol tablets pulverized with microcrystalline cellulose to achieve the
187 volume needed for 100 capsules of 25 µg each. Each capsule contained between
188 23.5 and 27.5 µg misoprostol. High-performance liquid chromatography showed the
189 standard retention time and that of the sample differed by less than 2.5%.

190 Every four hours, the clinical care provider placed a 25-µg capsule into the posterior
191 vaginal fornix of the women allocated to vaginal misoprostol, with a maximum of 4
192 capsules per day, that is, 100 µg. Before the administration of each capsule, fetal

193 well-being and uterine activity were checked by EFM. If the fetal heart rate (FHR)
194 trace was nonreassuring, or the woman had at least two painful contractions in 10
195 minutes, the planned capsule was not placed.

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

203 IOL continued until there was either adequate response (Bishop score ≥ 7 or cervical
204 dilation ≥ 3 cm) or 24 hours had passed since cervical ripening began. The pessary
205 was then removed from women in that group, and all women were asked not to
206 reveal their allocation group. They were then transferred to the delivery room to a
207 midwife and/or obstetrician masked to the method used to induce labor.

208 In both groups, except women with PPROM, the first procedure in the delivery room
209 was an amniotomy, performed at least 30 minutes after the removal of the
210 dinoprostone pessary or four hours after the last misoprostol administration, as
211 recommended. Epidural analgesia was provided at maternal request, and EFM
212 monitored continuously from entry into the delivery room. If uterine activity was
213 deemed insufficient (as evaluated by the midwife and/or the obstetrician, depending
214 on FHR, uterine activity, and progression of dilation) or if amniotomy was not
215 possible, oxytocin was continuously infused until at least three contractions per 10
216 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 cesarean delivery for lack of progress in labor.¹⁶ In the active phase of the first stage of labor, a cesarean could be considered indicated 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 of course identical in both groups.

Trial outcomes

The primary outcome was the total CD rate. Secondary outcomes related to neonatal mortality and morbidity comprised neonatal death, neonatal seizure, admission to the neonatal intensive care unit (NICU), arterial umbilical cord pH < 7.05, 5-minute Apgar score < 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 min), tachysystole (more than 5 contractions in 10 min on at least 2 occasions), hyperstimulation syndrome (hypertonus or tachysystole associated with abnormal FHR), postpartum hemorrhage (>500 mL), fever during labor ($\geq 38.5^{\circ}\text{C}$), episiotomy, severe perineal lesion (third and fourth degree), 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 during the postpartum period.

Sample size

The sample size was determined to rule out an absolute difference in CD rates greater than or equal to 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 one-sided Farrington & Manning test and a one-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, supposing that up to 6.5% of them 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 non-missing observations for the categorical data and counts and percentages for the continuous data. Percentages were calculated on non-missing data. The per-protocol (PP) population excluded women with major protocol deviations. The intention-to-treat (ITT) dataset comprised all the 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 (Figure 1) and repeated as a sensitivity analysis in the ITT population. Confidence intervals (CIs) were computed with Wald's method, and additional *P*-values with the noninferiority Dunnett 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.

Cumulative incidence of these CDs were estimated with the Fine and Gray model²⁰ to describe their occurrence over time. The cumulative incidence curve represents the probability of CD due to each cause in turn, before time t.

Lastly, efficacy outcomes were analyzed with superiority 2-sided tests with alpha=5% and 95%CI in the ITT population. No corrections were made for multiple comparisons.

All statistical analyses were performed with SAS software, version 9.4 (Cary, NC, SAS Institute) and R-studio software, version 1.1.383.

RESULTS

Between September 2012 and June 2015, the four centers randomized 1674 women, 836 allocated to the misoprostol and 838 to the dinoprostone group; 1005 (60.0%) were nulliparous and 669 (40.0%) parous (Figure 1).

After 94 women were excluded from the per-protocol 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 post-term pregnancy, premature rupture of membranes, diabetes, and hypertensive disorders (Table 1).

Primary outcome (Table 2)

Results in the ITT and per-protocol dataset were similar. As recommended by methodological guidelines regarding noninferiority design trials,²¹⁻²³ results are presented in the per-protocol dataset. The total CD rate was 22.2% (175/790) in the misoprostol group and 19.9% (157/790) in the dinoprostone group, for a difference between rates 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 between groups in neonatal and maternal morbidity were small (see Table 3 for neonatal outcomes and Table 4 for maternal outcomes). 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 to 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; 4.6), while the CD rates for lack of progress in labor were more similar (risk difference of -0.8, 95% CI -0.3; 1.6). The cumulative incidence of CDs for abnormal FHR as the only indication for CD seemed to differ slightly between groups and was somewhat higher incidence in the misoprostol than the dinoprostone group (Figure 3).

Efficacy and maternal satisfaction (ITT population)

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

Most patients (52.1%) needed two misoprostol capsules, 25.5% three capsules, and 22.4% all four. 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% of the misoprostol and 74.9% of the dinoprostone group. Women allocated to the misoprostol arm reported a significantly higher level of satisfaction (mean VAS score 7.1 (SD 2.4)) than those in the dinoprostone arm (5.8 (3.1); $P<.001$). Notably, 78% of the women in the misoprostol group said that they would choose the same method should they require induction again, vs 63% in the dinoprostone group ($P<.001$).

COMMENT

Principal findings

In this multicenter randomized trial, the CD rate 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, the groups did not differ for either neonatal or maternal outcomes. Moreover, both the rate of vaginal delivery within 24 hours and maternal satisfaction were significantly higher in the misoprostol group.

Results

To our knowledge, only two RCTs have compared vaginal misoprostol (25 µg) every four hours with the 10-mg slow-release dinoprostone pessary.^{13,15} The trial by Wing et al. randomized 200 women and found no significant difference in their modes of delivery, neonatal outcomes, or rates of delivery within 24 hours,¹³ while tachysystole was significantly less frequent in the misoprostol than 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 gestation¹⁵ 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 in the CD rates (respectively, 22.2% and 26.3%, $P=.500$). Neonatal outcomes (that is, admission to the NICU, umbilical cord pH, and Apgar score) did not differ between the groups, but abnormal FHR during active labor was less frequent in the misoprostol group (44.4% vs 58.6%, $P=.047$).

Clinical implications

In high-resource countries today, around 25% of women have labor induced. The ARRIVE trial^{2, 3, 24} demonstrated that in low-risk nulliparous women at 39 weeks, 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 As a result, the SMFM recently issued a statement that IOL is a reasonable option for low-risk nulliparous women at or after 39 weeks.²⁵ 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 vaginal misoprostol 25 µg every four hours and a slow-release dinoprostone pessary are safe options for IOL. Two meta-analyses have confirmed the benefit of low-dose misoprostol for both efficacy and safety, both vaginally and orally, compared to dinoprostone.^{8, 26} Misoprostol as a less expensive thermostable drug appears to have especially great advantages over dinoprostone in low-resource settings.

365

366 *Strengths and limitations*

367 This study had several strengths. With 1674 women included, it is to our knowledge
368 the largest RCT comparing low-dose vaginal misoprostol to the slow-release
369 dinoprostone pessary. Moreover, because misoprostol is an off-label drug for this
370 indication, the French drug agency inspected each center during the study. For the
371 same safety reasons, we double-verified all neonatal outcome data. This has delayed
372 the publication process but also reinforced the reliability of these results.

373

374 This study also has some limitations. First, because the pharmaceutical presentation
375 was different for each drug (capsule vs pessary), a double-blinded study was not
376 feasible and was not attempted. This bias was limited by ensuring that the delivery
377 room staff was masked to the allocation group or IOL method; IOL was managed by
378 different obstetricians and midwives. Moreover, it has recently been suggested that
379 the benefits of blinding may be exaggerated.²⁷ Misoprostol had to be manufactured
380 by the hospital pharmacy. This is clearly a limitation as additional techniques are
381 required to transform 200- μ g tablets into 25- μ g capsules. Hospitals unable to do so
382 cannot use our protocol.

383 Second, the noninferiority study design might be seen as a limitation, although it
384 appears appropriate for the comparison of an off-label drug to the dinoprostone
385 pessary that is the reference drug for cervical ripening. The noninferiority boundary
386 (5%) was determined on clinical grounds as a difference small enough to have no
387 clinical impact. Although the noninferiority of misoprostol to the dinoprostone pessary
388 could not be demonstrated with a risk of error of 5%, the confidence interval showed
389 that the maximum difference did not exceed 5.6%. In terms of clinical relevance, this

does not appear 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 illustrates the difficulty of the arbitrary choice, based on a clinical value judgment, of the maximum tolerated difference in noninferiority trials and raises questions about the distinction between statistical significance and clinical relevance.

Conclusions

In our large multicenter trial, the noninferiority of 25- μ g vaginal misoprostol every four 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 very close to one another, both drugs 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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Figure 1: Study flow chart: randomization and protocol adherence

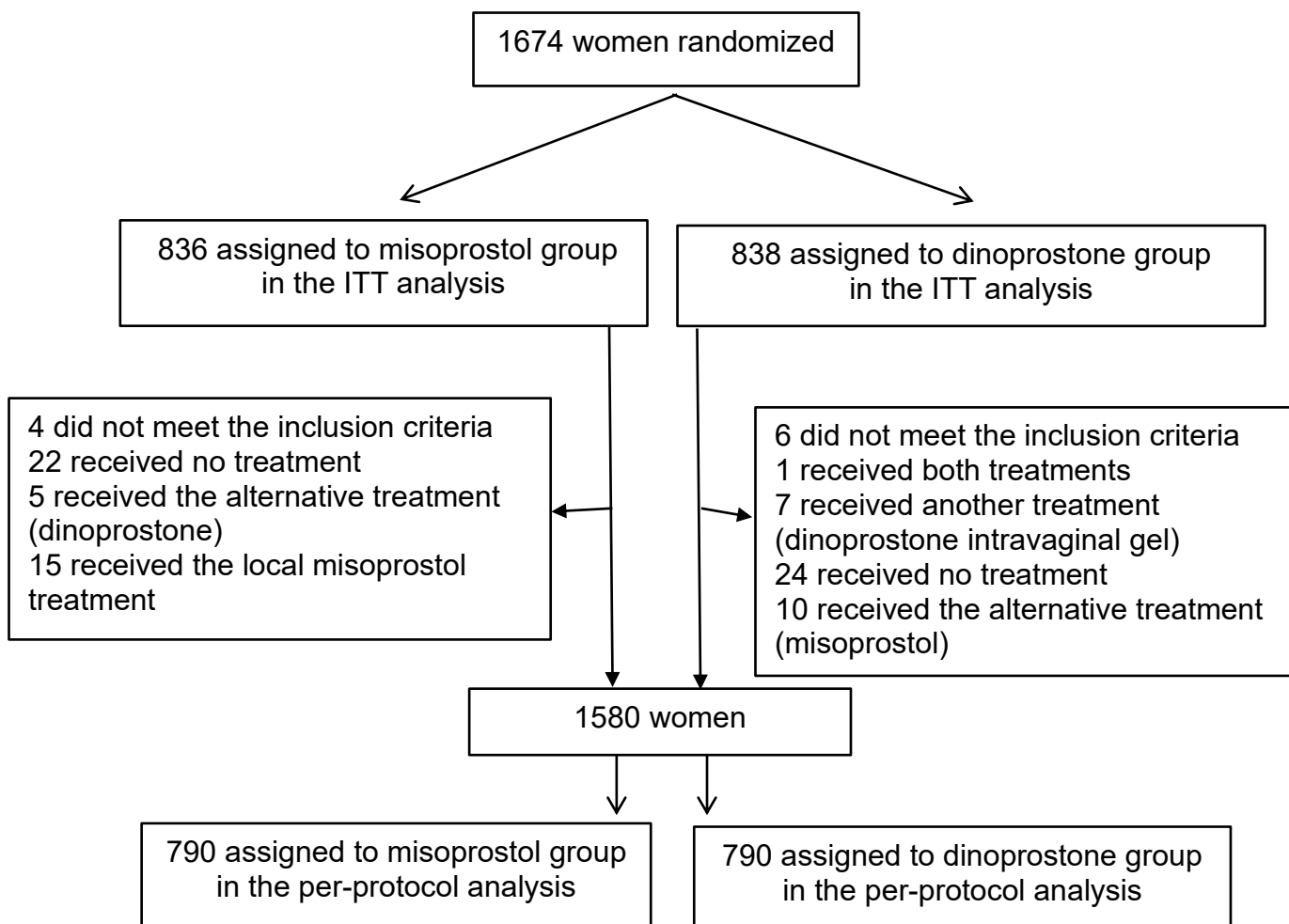
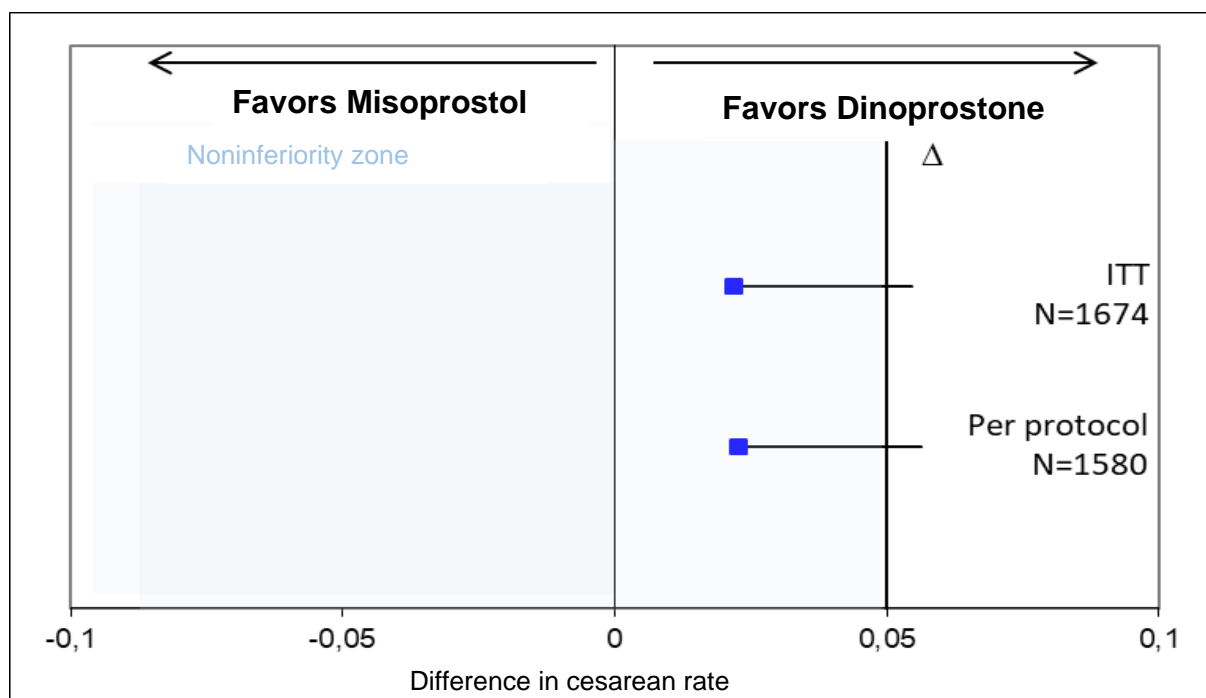
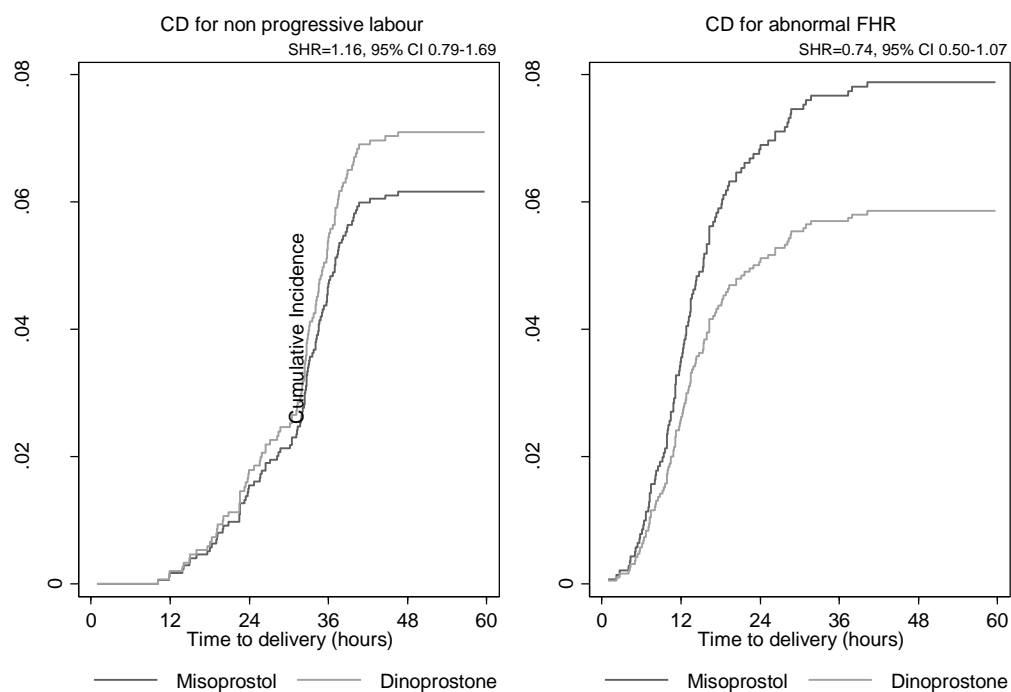


Figure 2: Forest plot of the representation of the difference in the cesarean delivery rate and the noninferiority zone in the per-protocol and ITT analyses*



*Vertical line (□) represents the noninferiority margin (5%); the noninferiority zone is colored in blue. Squares represent the estimated differences in cesarean delivery rates between the misoprostol and dinoprostone groups. Lines represent the upper 95% confidence limit of the difference.

Figure 3 : Cumulative incidence of cesarean delivery rate by randomization group, in the ITT population. Estimations for Fine and Gray model in the presence of competing risks.



SHR: Subdistribution hazard ratio (Fine & Gray model)

95% CI: 95% confidence interval

FHR: Fetal heart rate

CD: Cesarean delivery

Table 1: Baseline characteristics of women in the CYTOPRO trial

	Misoprostol	Dinoprostone
	n= 836	n=838
Maternal age (years; median, IQR)	31.0 (27-35)	31.0 (27-35)
Nulliparous (n, %)	503 (60.2)	502 (59.9)
BMI (kg/m ² ; median, IQR)	26.7 (22.6-31.2)	26.4 (22.8-30.5)
Gestational age* (weeks; median, IQR)	39.7 (38.6-41.1)	39.7 (38.6-41.3)
- Gestational age \geq 41 weeks**	284 (44.6)	282 (43.9)
Bishop score (median, IQR)	3 (2-4)	3 (2-4)
Indication for induction (n, %)**		
- Prolonged and post-term pregnancy	225 (26.9)	249 (29.7)
- Premature rupture of membranes	201 (24.0)	192 (22.9)
- Diabetes	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)

IQR interquartile range

* available for 1279 women

** Prolonged pregnancy alone was not a systematic indication for IOL

***Indications for induction were not mutually exclusive

Table 2: Primary outcome

	Per-Protocol Analysis			ITT Analysis		
Mode of delivery	Total N= 1580 N (%)	Misoprostol n= 790 n (%)	Dinoprostone n=790 n (%)	Total N= 1674 N (%)	Misoprostol n= 836 n (%)	Dinoprostone n=838 n (%)
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		

Table 3: Neonatal outcomes in the ITT population, by randomization group

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

F: Fisher's exact test

*Stillbirths excluded

Table 4: Maternal outcomes in the ITT population, by randomization group

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

* 1987 FIGO classification²⁸