# Results of the RE-DINO multicenter randomized trial on the repeated use of vaginal dinoprostone (Propess®) for labor induction in patients at term

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**BACKGROUND:** Labor is induced in over 25% of women in France. Prostaglandins, especially intravaginal dinoprostone (Propess®), are widely used to initiate cervical ripening. If labor does not start within 24 hours, there is uncertainty about whether to administer a second dinoprostone pessary or to use oxytocin to induce labor in order to achieve a vaginal delivery.

**OBJECTIVES:** Our principal objective was to determine whether placement of a second Propess®, followed by oxytocin (Syntocinon®) if necessary, in pregnant women for whom the first Propess® failed to induce cervical ripening increases the vaginal delivery rate compared to direct oxytocin injection. The vaginal delivery rate was therefore the primary outcome. The secondary outcomes were the cervical ripening failure rate and maternal and fetal morbidity and mortality.

**STUDY DESIGN:** RE-DINO is a prospective, open-label, multicenter, randomized superiority trial with 2 parallel arms running in 7 French hospitals. Patients at > 37 weeks of gestation who had unfavorable cervical conditions (Bishop score < 6) 24 hours after placement of the first Propess® (vaginal patch featuring progressive continuous diffusion of 10 mg dinoprostone), with fetuses in cephalic presentation, were included.

**RESULTS:** 160 pregnant women were randomized, 80 patients in each group, from December 2016 through April 2022. Baseline characteristics such as age, BMI, maternal age at induction and Bishop score at induction were similar between both groups. Vaginal delivery occurred in 76.3% of cases in the 2nd Propess® group and 73.8% of cases in the Syntocinon® group (RR=1.03 [0.86; 1.24], $p$=.715). Although the cesarean section rate was similar in each group, there were significantly more cesarean sections for arrest of dilatation (52.6% vs 19%; $p$=.0262) in the Propess® group and a larger, borderline-significant difference in patients having operative vaginal delivery (24.6% vs 11.9%; $p$=.07) for abnormal fetal heart rate (80% vs 29%; $p$=.05). There was significantly more failure of cervical ripening in the Propess® group (57.1% vs 19%; RR=2.59 ; 95% CI [1.64; 4.11]; $p$<.0001) and the interval between study treatment and delivery was also significantly longer (28.1h vs 9,7h; $p$<.0001). There was a higher incidence of postpartum hemorrhage in the Propess® group, although this was not significant (11.3% vs 5% ; $p$=,15), but also more newborns with acidosis (39.3% vs 27.9% ; $p$=.18) or severe acidosis (8,6% vs 3.4% ; $p$=.27), more meconium fluid (11.3% vs 6.3% ; $p$=.26) and transferred to intensive care (5% vs 2.5% ; $p$=.68).

**CONCLUSION:** Our data showed no superiority of a second dinoprostone pessary over oxytocin in patients not responding to initial prostaglandins E2 maturation for labor induction. Repeated use of Propess® is not useful for induction of labor.

**Key words:** dinoprostone, induction of labor, oxytocin, pregnancy, vaginal delivery

## Introduction

Perinatal surveys indicate that labor is induced in more than 25% of French pregnant women.[1] Labor induction rates are rising around the world and are likely to continue increasing since the publication in 2018 of the randomized trial of Grobman et al. who found a decrease in risk of cesarean section (C-section) with labor induction at 39 weeks of gestation (WG) versus expectant management.[2] Mechanical methods of labor induction are currently in full expansion, but prostaglandins (PGs) [usually intravaginal dinoprostone (Propess®)] remain widely used to initiate cervical ripening,[3] since in 2021 intravaginal PG was the most used cervical preparation method in France (48.7%).[1] According to the manufacturer's instructions, use of a single Propess® is recommended, and the active labor rate following a single Propess®, is 65% to 73%, with more than 80% of subsequent deliveries being vaginal.[4,5] Currently, patients who have not entered labor 24 hours after placement of Propess® are either induced by oxytocin (Syntocinon®)[6–8] or undergo C-section. Alternatively, in several maternity hospitals, a second Propess® is placed.[9] A retrospective single-center study showed that placement of a second Propess® was associated with a vaginal delivery rate of 53.1% and no additional maternal and fetal morbidity or mortality.[10] Antonazzo et al.[11] performed a randomized trial with 94 patients; vaginal delivery rate was higher when a second Propess® was placed versus labor induced by oxytocin. However, in the absence of a marketing authorization for use of a second Propess®, a prospective assessment is required.

Thus, we wished to study whether the use of a second Propess® had a place in obstetric practice, by comparing it with the use of Syntocinon®, for cervical ripening in patients with unfavorable cervix at term, by studying the rates of vaginal delivery, failed cervical ripening and maternal-fetal morbidity.

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## AJOG MFM at a Glance

### Why was this study conducted?

Induction of labor is a daily obstetrical problem. The use of a second Propess® is common practice with no real scientific proof. To improve care for pregnant women.

### Key findings

No increase in vaginal delivery rate with repeated use of dinoprostone pessary. Significant increase in failure to cervical ripening with a second Propess® compared with oxytocin. Significant increase in interval between study treatment and delivery with repeated use of dinoprostone pessary.

### What does this add to what is known?

No superiority of second dinoprostone pessary over oxytocin for labor induction.

## Methods

### Study design

We performed a multicenter (7 French centers: 3 type 3 university maternity units and 4 type 2 maternity units), randomized, open-label, superiority trial with 2 parallel arms, whose study protocol has been previously published.[12]

Our primary objective was to determine whether a second Propess® vaginal pessary featuring progressive continuous diffusion of 10 mg dinoprostone (0.33 mg/h), followed by oxytocin (Syntocinon®) if necessary, in women for whom the first Propess®, placed for 24 hours, failed to induce cervical ripening, increases the vaginal delivery rate compared to direct oxytocin injection.

Our secondary objectives were to compare cervical ripening failure (cervical dilatation still <3 cm), 24 hours after placement of the second Propess® in the experimental group and despite 6 hours of Syntocinon® infusion (one ampoule) in the control group. We also compared maternal-fetal morbidity and mortality between each group.[12]

### Study population

We included patients ≥18 years of age who had already had a first Propess®, within 24 to 36 hours because of medical indications, a term pregnancy (>37 WG), unfavorable cervix (Bishop score <6), and intact membranes 1 hour before inclusion. The fetus had to be in cephalic presentation and the patient affiliated with a French social security scheme.

We excluded:

- multiple pregnancy,
- prior uterine scar (previous cesarean delivery or myomectomy),
- any contraindications to epidural anesthesia, Propess® (a recent history of pelvic inflammatory disease or PG hypersensitivity) or Syntocinon® (oxytocin hypersensitivity, any cardiovascular disorder, or severe toxemia of pregnancy),
- abnormal uterine contractility or an abnormal fetal heart rate (AFHR) triggering the removal of the first Propess®, or any adverse effect while the first Propess® is in place, - induction of premature membrane rupture,
- fetus with intrauterine growth retardation (<3rd percentile) or fetal macrosomia (>97th percentile),
- severe AFHR
- induction due to fetal death in utero, medical termination of pregnancy, or a lethal fetal anomaly
- patients under guardianship or curatorship.

### Procedures

If labor had not begun 24 hours after placement of the first Propess®, patients, after written information and signed consent, were randomized to the control (oxytocin and peridural analgesia if the patient wishes) or experimental (a second 24-hour Propess® prior to oxytocin if necessary and peridural analgesia if the patient wishes) group using the method of minimization. Randomization was 1:1 and performed electronically over a secured internet connection and implemented on the Ennov Clinical software and CSRANDO module on five stratification factors: Bishop's score (<3, 3−5), body mass index (< or ≥30 kg/m$^2$), parity (nulliparous, multiparous), age (< or ≥40), center.

In the control group, 5 IU of oxytocin was diluted in 49 mL of physiological saline and started at 2.5 mIU/min, a flow rate of 1.5 mL/h with an increase of 2.5 mIU every 20 to 30 min up to 12 mL/h. In the case of cervical ripening failure (cervical dilatation remaining <3 cm despite 6 hours of oxytocin = 1 syringe and the presence of regular uterine contractions and amniotomy), the patient had a C-section for failure to induce labor. In total, oxytocin was administered to induce labor for 6 hours and then, if the labor commenced, an additional syringe of oxytocin was administered if uterine contractions were absent or labor stagnated. The FHR was recorded continuously in the delivery room and a cervix examination was performed every hour. In the experimental group, the patient was hospitalized in the maternity unit and Propess® was inserted high in the posterior vaginal fornix. The FHR was monitored within 2 hours from insertion and then every 6 hours. Additional monitoring was performed if uterine contractions were reported or if the patient reported increased frequency or intensity of uterine contractions and in this case, a cervical examination was performed. The second Propess® was removed after 24 hours or earlier if labor began or, in case of abnormal uterine contractions, AFHR or poor maternal tolerance. If oxytocin was needed in the experimental group after 24 hours of the second Propess®, it was delivered in the same way as in the control group. If labor had not begun (cervical dilatation remaining <3 cm despite second Propess® + 6 hours of oxytocin = 1 syringe and

the presence of regular uterine contractions and amniotomy), the patient had a C-section for failed induction. If the second Propess® fell out, we waited 2 hours to see if labor started. If labor had not begun and if the Propess® fell out before 18 hours of use, another Propess® was inserted for a duration not exceeding 24 hours of cumulative exposure. If the Propess® fell out after 18 hours of use, induction of labor was continued using oxytocin. Both treatments were labeled and supplied to the different centers and stored according to the manufacturers' recommendations. Only Risordan (*isosorbide dinitrate*) and Natispray (*nitroglycerin*) were allowed to correct abnormal uterine contractions. No other medical or mechanical labor-inducing means were permitted.

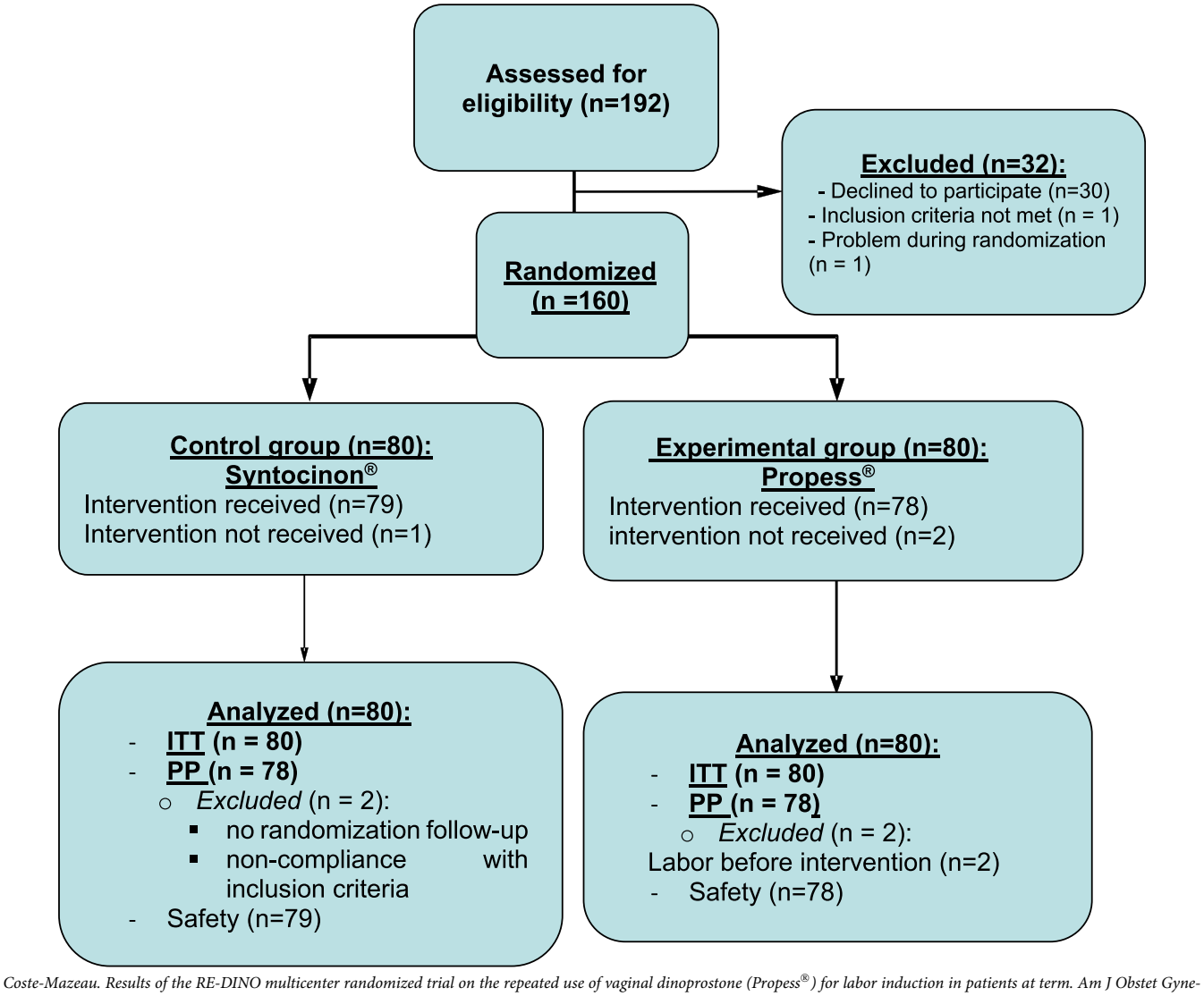
## Safety

All adverse events (AEs) affecting the patient or fetus/newborn from enrollment to 10 days after delivery (end of study) were recorded continuously, regardless of their relation to the intervention. Serious AEs (SAEs) were any medical events that led to death, were life-threatening, caused or prolonged hospital admission, or resulted in persistent/significant disability. Severity was assessed as mild, moderate, or severe based on its impact on daily living activities.

## Sample size and statistical analyses

The number of participants was calculated on the primary outcome for a comparative superiority test. We assumed a 15% difference between groups, meaning that to achieve 80% power to detect a specific difference at the 5% significance level (2-tailed test), 180 patients per group were required in a two-group scenario (nQuery Advisor

FIGURE
**RE-DINO study flowchart**




*Coste-Mazeau. Results of the RE-DINO multicenter randomized trial on the repeated use of vaginal dinoprostone (Propess®) for labor induction in patients at term. Am J Obstet Gynecol MFM 2024.*

TABLE 1
**Baseline characteristics of the population**

| | Total (n=160) n (%) mean ± std (n) [Min; Max] median (Q1; Q3) | Propess® group (n=80) n (%) mean ± std (n) [Min; Max] median (Q1; Q3) | Syntocinon group (n=80) n (%) mean ± std (n) [Min; Max] median (Q1; Q3) |
|---|---|---|---|
| **Age (years)** | 30.2±5.9<br>(N=160) [18; 44]<br>30 (26; 34) | 30.2 ± 5.4<br>(N=80) [20; 43]<br>30 (26.5; 33) | 30.1 ± 6.4<br>(N=80) [18; 44]<br>29 (25.5; 35) |
| **Term at induction of labor (WG)** | 39.2±1.4<br>(N=160)<br>[37; 41.9]<br>39 (38.1; 40.3) | 39.3 ± 1.4<br>(N=80)<br>[37; 41.9]<br>39 (38.3; 40.4) | 39.1 ± 1.4<br>(N=80)<br>[37.1; 41.7]<br>38.8 (38.1; 40.3) |
| **Term at birth (WG)** | 39.5±1.4<br>(N=160)<br>[37.3; 42.1]<br>39.2 (38.4 ; 40.6) | 39.6 ± 1.4<br>(N=80)<br>[37.4; 42.1]<br>39.3 (38.6 ; 40.6) | 39.4 ± 1.4<br>(N=80)<br>[37.3; 42]<br>39 (38.3 ; 40.5) |
| **Parity:** | | | |
| - Primiparity | 103 (64.4%) | 51 (63.8%) | 52 (65%) |
| - Multiparity (≥2 children) | 57 (35.6%) | 29 (36.3%) | 28 (35%) |
| **Weight before inclusion (kg)** | 87.8±15<br>(N=160) [59; 127]<br>88 (76; 98) | 88.2±14.3<br>(N=80) [59; 127]<br>86.5 (78; 98.5) | 87.4±15.8<br>(N=80) [60; 124]<br>88.5 (74.5; 97) |
| **BMI before inclusion (kg/m$^2$)** | 32.4±5.7<br>(N=160)<br>[18.9; 47.6]<br>31.9 (28.4; 35.4) | 32.5±5.4<br>(N=80)<br>[23.8; 47.6]<br>31.9 (28.3; 35.4) | 32.3±6<br>(N=80) [18.9; 47.3]<br>31.6 (28.4; 35.8) |
| **Bishop score at inclusion** | 2.7±1.4<br>(N=160) [0 ; 6]<br>3 (2 ; 4) | 2.7±1.3<br>(N=80) [0 ; 5]<br>3 (2 ; 4) | 2.8±1.6<br>(N=80) [0 ; 6]<br>3 (1.5 ; 4) |
| **PROM during treatment (n=160)** | 36 (22.5%) | 24 (30%) | 12 (15%) |
| **Interval from study treatment to PROM (hours)** | 10.5±9.8<br>(N=34)<br>[-1.3; 39.3]<br>8.2 (2.8; 14.5) | 14.4±9.6<br>(N=23)<br>[0.5; 39.3]<br>13.2 (8; 20.8) | 2.4±2.3<br>(N=11)<br>[-1.3; 6.8]<br>2 (0.7; 4) |

PROM= premature rupture of membranes; WG= weeks of gestation.

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7). Data were analyzed using SAS Enterprise Guide v.7.1 (SAS Institute Cary, NC). *P*-values <.05 were considered statistically significant. Our analysis was conducted using the intention-to-treat principle and reporting followed CONSORT 2010 recommendations. Descriptive statistics of continuous data were reported as means ± standard deviations or medians and interquartile ranges depending on the distribution of the variable. Dichotomous and categorical data were presented by numbers and percentages. The analysis of the primary outcome was carried out by a Chi-square test. The effect size was estimated using relative risk and its 95% confidence interval. Secondary analyses were performed by using a Chi-square or a Fisher's exact test according to the conditions of application and a nonparametric Mann−Whitney test for continuous outcomes as their distributions were not normal (Shapiro-Wilk test). We also performed a subgroup analysis of our primary outcome according to maternal age, BMI, parity and Bishop score at inclusion.

The overall safety analysis was conducted on patients who received the investigational drugs, according to ICH-E9 guidelines.[13] All AEs occurring from administration of the investigational drugs to the end of the trial were included in the safety dataset.

## Ethics

Our trial complied with the Helsinki guidelines, revised in 2013, for human

TABLE 2
**Mode of delivery**

| | Total (n=160) n (%) | Propess® group (n=80) n (%) | Syntocinon group (n=80) n (%) | RR [95% CI] | *P*-value (Test) |
|---|---|---|---|---|---|
| **Mode of delivery:** | | | | | |
| - **Cesarean section** | 40 (25%) | 19 (23.8%) | 21 (26.3%) | 1.03 [0.86 ; 1.24] | .7150 ($X^2$) |
| - **Vaginal delivery** (spontaneous and operative) | 120 (75%) | 61 (76.3%) | 59 (73.8%) | | |
| - **Operative vaginal delivery** | 22 (18.3%) | 15 (24.6%) | 7 (11.9%) | | .0717 ($X^2$) |
| - **Indication for cesarean section** | (n=40) | (n=19) | (n=21) | | |
| - Abnormal fetal heart rate | 19 (47.5%) | 8 (42.1%) | 11 (52.4%) | | .5158 ($X^2$) |
| - Arrest of dilatation | 14 (35%) | 10 (52.6%) | 4 (19%) | | **.0262** ($X^2$) |
| - Arrest of fetal descent | 3 (7.5%) | 2 (10.5%) | 1 (4.8%) | | .5962 (F) |
| - Failed induction | 16 (40%) | 5 (26.3%) | 11 (52.4%) | | .0929 ($X^2$) |
| - **Indication for operative vaginal delivery**<br>- Abnormal fetal heart rate<br>- Arrest of fetal descent<br>- Others | (n=22)<br>14 (63.6%)<br>13 (59.1%)<br>3 (20%) | (n=15)<br>12 (80%)<br>7 (46.7%)<br>3 (20%) | (n=7)<br>2 (28.6%)<br>6 (85.7%)<br>0 | | .0523 (F)<br>.1649 (F)<br>.5227 (F) |

$X^2$= Chi-square test; MW= Mann-Whitney test; F= Fisher test.

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research and was approved by the Committee for the Protection of Personnel of Sud-Ouest Outre-Mer IV on 10 June 2016 (approval no. CPP16−030-PP) and authorized by the "Agence Nationale pour la Sécurité du Médicament et des Produits de Santé" (ANSM) on 21 June 2016. The study was registered in the clinicaltrials.gov website, no. NCT02888041, in September 2016, and the first patient was included in December 2016. URL: https://classic.clinicaltrials.gov/ct2/show/NCT02888041

## Results

### Study population and follow-up

As shown in Figure, 160 pregnant women were randomized, 80 patients in each group, from December 2016 through April 2022. Enrollment was stopped before achieving the planned recruitment due to slower-than-expected recruitment and the failure to obtain additional funding to extend the study. Our analyses of primary and secondary outcomes were conducted on an intention-to-treat (ITT) basis containing all the randomized patients and a per-protocol (PP) basis excluding 2 patients in each group. The baseline characteristics of the study population are shown in Table 1.

The 2 randomization groups were comparable in terms of age, parity, term, BMI, and Bishop score at inclusion. The second Propess® was stopped before 24 hours in 43 patients (55.1%) due to labor in 74.4% of cases (32 patients), AFHR in 4.7% of cases (2 patients), vaginal irritation in 4.7% of cases (2 patients), logistical reasons in 7% of cases (3 patients). According to the protocol, the 4 patients who lost their second Propess® after 18 hours of use continued labor induction with Syntocinon®.

### Outcomes

Vaginal delivery occurred in 76.3% of cases in the 2nd Propess® group and 73.8% of cases in the Syntocinon® group (RR=1.03 [0.86; 1.24], $p$=.715) (Table 2). Although the C-section rate was similar between groups, there were significantly more cesareans for arrest of dilatation, defined by stagnation at the same cervix dilatation for 3 hours, in the Propess® group (52.6% vs 19%; $p$=.0262), as well as a larger, borderline-significant difference in patients having operative vaginal delivery (24.6% vs 11.9%; $p$=.07) for AFHR (80% vs 29%; $p$=.05). In the Syntocinon® group, there were more C-sections for failed induction, although the difference was not significant (52.4% vs 26.3%; $p$=.09). Sometimes, the indications for C-section or operative vaginal delivery were multiple for the same patient (Table 2).

There were significantly more failures of cervical ripening in the Propess® group (57.1% vs 19%; RR=2.59; 95% CI [1.64 ; 4.11]; $p$<.0001) than in the Syntocinon® group (Table 3).

Postpartum hemorrhage (PPH)) occurred more frequently in the Propess® group, although this was not significant (11.3% vs 5% ; $p$=.15). The interval between study treatment and delivery was significantly longer in the Propess® group (28.1h vs 9,7h; $p$<.0001) (Supplementary data Figure 1). There were no statistically significant differences in maternal morbidity between groups.

Among fetuses born after labor induction with a second Propess®, there were more cases of acidosis (umbilical arterial pH <7.15 and/or lactate levels >5) (39.3% vs. 27.9%; $p$=.18), severe acidosis (umbilical arterial pH <7 and/or lactate levels >8) (8.6% vs 3.4%; $p$=.27),

TABLE 3
**Characteristics and complications of delivery, and hospitalization**

| | Total (n=160) n (%) mean±std (n) [Min;Max] median (Q1;Q3) | Propess® group (n=80) n (%) mean±std (n) [Min;Max] median (Q1;Q3) | Syntocinon group (n=80) n (%) mean±std (n) [Min;Max] median (Q1;Q3) | RR [95% CI] | *p*-value (Test) |
|---|---|---|---|---|---|
| **Cervical ripening failure** | 59 (37.8%) | 44 (57.1%) | 15 (19%) | 2.59 [1.64 ; 4.11] | **<.0001 ($X^2$)** |
| **Hypertonia or tachysystole requiring treatment during labor** | 11 (6.9%) | 4 (5%) | 7 (8.8%) | | .3486 ($X^2$) |
| **Care:** | | | | | |
| Manual placenta removal | 13 (8.1%) | 7 (8.8%) | 6 (7.5%) | | .7723 ($X^2$) |
| Manual uterine examination | 21 (13.1%) | 14 (17.5%) | 7 (8.8%) | | .1012 ($X^2$) |
| **Post-partum hemorrhage (> 500 mL) and treatment** | | | | | |
| Post-partum hemorrhage<br>Blood transfusion, uterine artery embolization, vascular ligation, hemostatic hysterectomy | 13 (8.1%)<br>0 | 9 (11.3%)<br>0 | 4 (5%)<br>0 | | .1480 ($X^2$) |
| Use of sulprostone (Nalador) | 2 (1.3%) | 1 (1.3%) | 1 (1.3%) | | 1.0000 (F) |
| **Transfer to intensive care units** | 0 | 0 | 0 | | - |
| **Complete uterine rupture** | 0 | 0 | 0 | | - |
| **Duration of active labor** (minutes from 3 cm cervical dilatation to delivery) | 381.8±233.9<br>(N=145)<br>[0; 1349]<br>347<br>(219; 517) | 392.5±243.6<br>(N=77)<br>[0; 1349]<br>354<br>(233; 511) | 369.7±223.6<br>(N=68)<br>[18; 1040]<br>323.5<br>(213; 518) | | .5536 (MW) |
| **Interval from study treatment to delivery (hours)** | 18.8±12.1<br>(N=157)<br>[0.7; 52]<br>15 (9.2;30.3) | 28.1±10.3<br>(N=78)<br>[6.6; 52]<br>30.4 (19.2;34.8) | 9.7±4.2<br>(N=79)<br>[0.7; 18]<br>9.4 (6.4;12.7) | | **<.0001** (MW) |
| **Maternal hospitalization duration (days)** | 6.5±1.7<br>(N=160)<br>[3 ; 14]<br>6 (5 ;7) | 6.8±1.9<br>(N=80)<br>[3 ;14]<br>7 (6 ; 7) | 6.3±1.5<br>(N=80)<br>[4 ;13]<br>6 (5 ; 7) | | .0945 (MW) |

$X^2$= Chi-square test; MW= Mann-Whitney test; F= Fisher test.

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meconium-stained fluid (11.3% vs. 6.3%; *p*=.26), and transfer to intensive care (5% vs. 2.5%; *p*=.68). However, these differences were not statistically significant (Table 4). No maternal or fetal death occured.

In our subgroup analysis, we did not observe any difference in vaginal delivery according to age, BMI, parity or Bishop score (Table 5).

### Overall safety

One hundred and seventy-seven AEs were recorded (Supplementary data Tables 1 and 2). No patient or fetus/newborn had recurrent events.

For the patients, 47 AEs were recorded, 25 in the Propess® group and 22 in the Syntocinon® group. Ten patients (12.8%) in the 2nd Propess® group had SAEs versus 4 (5.1%) in the Syntocinon® group (*p*=.10). Two patients (2.6%) had severe AEs in the 2nd Propess® group (PPH) versus one (PPH) in the Syntocinon® group.

For newborns, 130 AEs were recorded, 72 in the 2nd Propess® group and 58 in Syntocinon® group. Three newborns in the 2nd Propess® group (3.8%) vs 2 in the Syntocinon® group (2.5%) had SAEs, none was related to the intervention by the investigator. Five newborns (6.4%) had severe AEs (acidosis) in the 2nd Propess® group versus 3 (3.8%) in the Syntocinon® group (2 severe acidosis and 1 umbilical cord prolapse).

## Discussion

### Principal findings

We did not observe a significant increase in the vaginal delivery rate when using a second Propess®

TABLE 4
**Neonatal morbidity**

| | Total (n=160) n (%) mean±std (n) [Min;Max] median (Q1;Q3) | Propess® group (n=80) n (%) mean±std (n) [Min;Max] median (Q1;Q3) | Syntocinon group (n=80) n (%) mean±std (n) [Min;Max] median(Q1;Q3) | *p*-value (test) |
|---|---|---|---|---|
| **Umbilical arterial pH** | 7.2±0.1 (N=131) [6.8; 7.4] 7.3 (7.2 ; 7.3) | 7.2±0.1 (N=65) [6.8; 7.4] 7.3 (7.2 ; 7.3) | 7.3±0.1 (N=66) [7; 7.4] 7.3 (7.2 ; 7.3) | |
| **Cord lactate** | 4.2±2.2 (N=138) [1.4; 14.8] 3.8 (2.6; 5.3) | 4.4±2.4 (N=70) [1.4; 14.8] 4.1 (2.6; 5.7) | 4.1±2.1 (N=68) [1.7; 12.3] 3.5 (2.6; 5) | |
| **Fetal acidosis** umbilical arterial pH < 7.15 and/or lactate levels > 5 | 41 (33.6%) | 24 (39.3%) | 17 (27.9%) | .1797 ($X^2$) |
| **Severe fetal acidosis** umbilical arterial pH < 7 and/or lactate levels > 8 | 7 (6%) | 5 (8.6%) | 2 (3.4%) | .2719 (F) |
| **Meconium amniotic fluid at birth** | 14 (8.8%) | 9 (11.3%) | 5 (6.3%) | .2631 ($X^2$) |
| **3-min Apgar score** | 9.5±1.4 (N=155) [1; 10] 10 (10 ;10) | 9.5±1.4 (N=78) [2; 10] 10 (10 ;10) | 9.4±1.4 (N=77) [1; 10] 10 (10 ;10) | .5347 (MW) |
| **3-min Apgar score < 7** | 8 (5.2%) | 4 (5.1%) | 4 (5.2%) | 1.0000 (F) |
| **5-min Apgar score** | 9.8±1 (N=160) [2; 10] 10 (10 ;10) | 9.8±1 (N=80) [2; 10] 10 (10 ;10) | 9.8±0.9 (N=80) [4; 10] 10 (10 ;10) | .4847 (MW) |
| **5-min Apgar score < 7** | 2 (1.2%) | 1 (1.2%) | 1 (1.2%) | 1.0000 (F) |
| **10-min Apgar score** | 9.9±0.6 (N=160) [5; 10] 10 (10 ;10) | 9.9±0.7 (N=80) [5; 10] 10 (10 ;10) | 9.9±0.3 (N=80) [8; 10] 10 (10 ;10) | .7196 (MW) |
| **10-min Apgar score < 9** | 3 (1.9%) | 2 (2.5%) | 1 (1.3%) | 1.0000 (F) |
| **Admission to neonatal intensive care unit** | 6 (3.8%) | 4 (5%) | 2 (2.5%) | .6815 (F) |

$X^2$= Chi-square test; MW= Mann-Whitney test; F= Fisher test.

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compared to direct injection of Syntocinon®.

## Results

Induction of labor with an unfavorable cervix has been the subject of debate and trials for many years. In recent years, the advent of mechanical methods and the availability of oral misoprostol (Angusta) on the European market have led to a proliferation of studies,[14–17] with disparate results and thus a heterogeneity of practices throughout the world. Nevertheless, PGs remain one of the most widely used methods in the world, and few studies have evaluated the efficacy and safety of applying a second vaginal pessary of dinoprostone (Propess®). We did not find the results previously described in the only randomized trial published to date, with a smaller number of patients.[11] In that study, vaginal deliveries were significantly higher in the repeated dinoprostone group (26/47; 55.3%) than in the oxytocin group (16/47 (34.0%); $p<.05$).[11] In the groups of our study, our vaginal delivery rates were much higher than those described in retrospective studies. Out of 111 and 177 patients, Petrovic et al. and Sun et al. had a vaginal delivery rate of 53.1% and 48.6%, respectively, with second dinoprostone pessary.[10,18] In the study by Gulersen et al.,[19] 149 nulliparous pregnant women continued labor induction with oxytocin alone and 50.3% of them delivered vaginally. We also found no influence of parity, BMI,

TABLE 5
**Subgroup analysis of primary outcome**

| Subgroups | Mode of delivery | Total (n=160) n (%) | Propess® Group (n=80) n (%) | Syntocinon Group (n=80) n (%) | *p*-value (test) |
|---|---|---|---|---|---|
| • According to BMI: | | | | | |
| BMI>30 (n=56) | *Vaginal delivery* | 47 (83.9%) | 23 (82.1%) | 24 (85.7%) | 1.0000 (F) |
| BMI ≥ 30 (n=104) | *Vaginal delivery* | 73 (70.2%) | 38 (73.1%) | 35 (67.3%) | .5201 ($X^2$) |
| BMI < 35 (n=112) | *Vaginal delivery* | 83 (74.1%) | 41 (74.5%) | 42 (73.7%) | .9172 ($X^2$) |
| BMI ≥ 35 (n=48) | *Vaginal delivery* | 37 (77.1%) | 20 (80%) | 17 (73.9%) | .6162 ($X^2$) |
| BMI < 40 (n=145) | *Vaginal delivery* | 111 (76.6%) | 59 (77.6%) | 52 (75.4%) | .7474 ($X^2$) |
| BMI ≥ 40 (n=15) | *Vaginal delivery* | 9 (60%) | 2 (50%) | 7 (63.6%) | 1.0000 (F) |
| • According to parity: | | | | | |
| Nulliparous (n=103) | *Vaginal delivery* | 69 (67%) | 35 (68.6%) | 34 (65.4%) | .7264 ($X^2$) |
| Multiparous (n=57) | *Vaginal delivery* | 51 (89.5%) | 26 (89.7%) | 25 (89.3%) | 1.0000 (F) |
| • According to age: | | | | | |
| Age < 40 (n=146) | *Vaginal delivery* | 109 (74.7%) | 55 (75.3%) | 54 (74%) | .8491 ($X^2$) |
| Age ≥ 40 (n=14) | *Vaginal delivery* | 11 (78.6%) | 6 (85.7%) | 5 (71.4%) | 1.0000 (F) |
| • According to Bishop score at inclusion: | | | | | |
| Bishop <3 (n=62) | *Vaginal delivery* | 37 (59.7%) | 18 (58.1%) | 19 (61.3%) | .7957 ($X^2$) |
| Bishop ≥ 3 (n=98) | *Vaginal delivery* | 83 (84.7%) | 43 (87.8%) | 40 (81.6%) | .4000 ($X^2$) |

$X^2$=Chi-square test; MW= Mann-Whitney test; F= Fisher test.

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age, or Bishop score at inclusion on mode of delivery in the 2 groups. Although the C-section rate was similar between groups, we observed significantly more C-sections for arrest of dilatation ($p$=.03), but also more instrumental vaginal deliveries when a 2nd Propess® ($p$=.07) was used. One possible explanation could be that the uterus, tired by a longer onset of labor in this group, contracted less. These results differ from those of Antonazzo et al. study,[11] where the main indication for C-section was failed induction in the 2nd Propess® group.

We found a significant increase of cervical ripening failure after placement of the second Propess® (57% vs 19%; $p$=.0001). This result is similar to that of Petrovic et al.[10] who found 48.7% of labor induction failures. The use of a 2nd Propess® alone cannot induce labor. A possible biological mechanism explaining this finding might be saturated receptors or intracellular PGE2 transporters in the cervical tissue.[20] Nevertheless, its combination with Syntocinon® could help reduce the risk of induction failure, compared to the use of Syntocinon® alone on an unfavorable, immature cervix (cesarean for failed induction: 26% in Propess® group vs 52% in Syntocinon® group; $p$=.09).

As in the Antonazzo et al. study,[11] we did not observe any increased risk of hypertonia or tachysystole after use of a second Propess®, adverse effects classically described as associated with the use of PGs.[17,21]

As in the Antonazzo et al. study,[11] the interval between study treatment and delivery was significantly longer in the Propess® group, with, nevertheless, in our trial, a similar duration of the active phase of labor and hospitalization in each group. However, the longer duration of labor in the Propess® group may influence patients' tiredness and postpartum experience.

As in the Antonazzo et al. study,[11] we found no significant difference in terms of maternal-fetal morbidity and mortality. Nevertheless, our results show a non-significant increase in morbidity with the iterative use of dinoprostone, with more PPH, neonatal acidosis, admission to neonatal intensive care, SAEs and severe AEs. Our rate of PPH (11.3%) was identical to literature values after cervical ripening with a single Propess®.[22] Our observed high acidosis rates may be explained by the fact that definitions of fetal acidosis vary considerably in the literature, although severe fetal acidosis is consistently defined by an umbilical arterial pH <7. Nevertheless, the rates obtained are close to those we found in a previous trial comparing PGs versus misoprostol induction after premature rupture of membranes in our maternity unit.[23]

## Research implications

In 2022, a meta-analysis of 12 trials and over 5,000 patients found no difference in C-section rates and maternal

morbidity whatever the method of induction used (balloon catheters vs vaginal PGs), but a lower perinatal morbidity after balloon use.[24] These data were confirmed in the De Vaan et al.[16] review in 2023. Recent studies have also demonstrated the efficacy and safety of oral misoprostol in inducing labor.[25,26] These data explain the current enthusiasm for the use of mechanical methods or oral misoprostol in labor induction and further randomized studies are needed to determine which method of labor induction is the most effective and safest.

### Strengths and limitations

The main limitation of our study was lack of power because the trial was prematurely interrupted before reaching the targeted sample size. The power of the primary analysis was 5%. This is particularly low and related to lower than expected sample size combined with an observed primary outcome proportion markedly higher in the control group than a priori estimated. With such sample size (n=80 patients in both groups) and this proportion of vaginal delivery in the control group (73.8%), the study would have been powered to detect a difference of 16.8% between both groups, so a proportion of 90.6% vaginal difference in the Propess® group. We did not conduct a blind trial as the different pharmaceutical forms of the treatments did not allow us to do so. There are no French recommendations defining failure of cervical ripening and failure to induce labor. It is therefore difficult to extrapolate our results, as each country has its own definition and management of labor. Our randomized trial is only the second on the subject with more patients than the previous one and it helps to answer a question that is frequently asked in maternity units.

### Clinical implication

While we thought there might be an interest in using a second Propess®, our results run counter to this thinking. The high risk of PPH and severe neonatal acidosis when using a second Propess® should be considered.

## Conclusion

The use of a second Propess® does not increase the vaginal delivery rate but increase the duration of labor. Overall, the repeated use of a second intravaginal dinoprostone pessary no longer seems legitimate to us. ■

## CRediT authorship contribution statement

**Perrine Coste-Mazeau:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Denis Gallot:** Writing – review & editing, Investigation. **François Siegerth:** Writing – review & editing, Investigation. **Angeline Garuchet-Bigot:** Writing – review & editing, Investigation. **Emmanuel Decroisette:** Writing – review & editing, Investigation. **Julie Blanc:** Writing – review & editing, Investigation. **Muriel Cantaloube:** Writing – review & editing, Investigation. **Sabrina Crépin:** Writing – review & editing, Validation, Methodology, Formal analysis. **Julien Magne:** Writing – review & editing, Validation. **Anais Labrunie:** Writing – review & editing, Formal analysis, Data curation. **Renaud Martin:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Miassa Hessas:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2024.101510.

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