

How Effective Is Cervical Ripening Using the Controlled-Release Dinoprostone Vaginal Delivery System for Primiparas with Unruptured Membranes?

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Abstract

Background: Labor induction has a low success rate, especially in primiparas with unruptured membranes. Previous studies focused on pregnant women with unruptured membranes, but none specifically targeted primiparas. **Aims:** To compare the effectiveness of a controlled-release dinoprostone vaginal delivery system for cervical dilatation (PROPESS) with that of mechanical dilation for labor induction in primiparous women with unruptured membranes. **Materials and Methods:** We retrospectively analyzed the data of 90 primiparas with unruptured membranes (41 and 49 in the PROPESS and mechanical dilation groups, respectively). The primary outcome was the cesarean section (CS) rate. The secondary outcomes were the prevalence of vaginal delivery within 12 or 24 h after the initial insertion, oxytocin usage rate, chorioamnionitis, additional use of mechanical dilation in the PROPESS group, and neonatal outcomes. **Results:** The CS rate was significantly lower in the PROPESS group than in the mechanical dilation group ($p = 0.02$). A total of 13 patients (31.7%) delivered within 24 h with PROPESS alone, indicating a significantly higher rate of delivery within 24 h in the PROPESS group ($p = 0.02$). Fewer patients required additional oxytocin in the PROPESS group than in the mechanical dilation group ($p = 0.001$). However, 14 (34%) patients in the PROPESS group required additional mechanical cervical dilation, resulting in a longer time to delivery than mechanical dilation. **Conclusions:** PROPESS significantly reduced CS rates and increased delivery rates 24 h after the initial insertion in primiparas with unruptured membranes compared to mechanical dilation. However, failure to respond to PROPESS resulted in an overall longer delivery time than that of the conventional mechanical dilation group; therefore, identifying predictors of response to PROPESS is necessary.

Keywords

PROPESS, Labor Induction, Primiparas, Cervical Ripening, Unruptured Membranes

1. Introduction

During pregnancy, initiating labor before its spontaneous onset is called the induction of labor. To offer better care for both the fetus and mother, it is an increasingly common practice in modern obstetrics [1]. The ARRIVE trial (A Randomized Trial of Induction Versus Expectant Management) reported a significantly lower risk of cesarean section and no significant difference in composite neonatal complications after elective induction at 39 weeks and 0 - 4 days of gestation, compared with expectant management [2]. To achieve the successful induction of labor, cervical ripening is a key step in the initiation, following which adequate and powerful uterine contractions at a regular frequency are required. Drugs are often used to induce cervical ripening and uterine contractions. The two main methods of cervical ripening for labor induction are mechanical dilation using absorbable cervical dilators or balloon catheters and pharmacological methods such as oral and vaginal PGE2 (dinoprostone) and PGE1 (misoprostol). Cervical ripening at the appropriate time is required for women who need induction of labor and have a cervix with a Bishop score of <6; induction of labor with oxytocin has a risk of failure when the Bishop score is <6.

PROPESS is the commercial name of PG2, also known as dinoprostone, a vaginal release drug. In Japan, until the approval of PROPESS in January 2020, only an intravenous formulation of prasterone sulfate sodium hydrate was approved as a pharmacological cervical maturation preparation. Therefore, mechanical cervical ripening methods were more commonly used. Controlled-release dinoprostone vaginal insert (PROPESS Vaginal Delivery System 10 mg) promotes cervical ripening in pregnant women. PROPESS is composed of a thin, flat, hydrogel polymer containing 10 mg of dinoprostone enclosed within a mesh-knitted thread for retrieval [3].

In a previous randomized, double-blind, placebo-controlled study in Japan, a controlled-release dinoprostone vaginal delivery system for PROPESS or placebo was used in 113 women at 41 weeks of gestation with a Bishop score < 4. The time from insertion to vaginal delivery was 26.2 vs. 33.0 h ($p < 0.0001$), which was significantly shorter in the PROPESS group [3]. In a study comparing Foley catheters and PGE2, no significant differences were observed in the rate of vaginal delivery, the incidence of fetal dysfunction, time to delivery, or maternal complications, although oxytocin was more frequently used in the balloon catheter group [4]. Particularly in primiparas, mechanical cervical dilation causes more intense pain. Achieving cervical dilation without causing pain is advanta-

geous in these patients. PROPESS comprises a hydrophilic polymer containing PGE2 and a net with an extraction cord. It is inserted into the posterior vaginal canal, where it remains for up to 12 h to promote painless cervical ripening with a low risk of intrauterine infection. Predicting the success of labor induction is challenging in clinical practice, especially in primiparas with unruptured membranes, necessitating a painless cervical ripening method without the risk of infection. Previous studies have focused on pregnant women with unruptured membranes, but none specifically targeted primiparas. This study aimed to evaluate the effectiveness and safety of PROPESS compared with conventional mechanical cervical ripening methods in primiparas with unruptured membranes.

2. Materials and Methods

We retrospectively analyzed 90 primiparas with intact membranes, including 41 in the PROPESS group (between May 2020 and December 2021) and 49 in the mechanical dilation group (between January 2017 and October 2019).

The mechanical ripening devices used in our department were Dylapan S[®] (TKB Corporation, Japan) and Obatametro[®] (Fuji Latex Co. Ltd., Japan). Dylapan S[®] was used if the cervix was dilated less than 3 cm. Obatametro[®] was used if the cervix was dilated more than 3 cm. For cervical dilation with Obatametro[®], less than 40 mL of sterile water must be injected after insertion. Of the 49 patients in the mechanical dilation group, 24 underwent initial dilation using Dylapan S[®], while 25 received dilation using Obatametro[®]. Cervical dilation was repeated the following day until the Bishop score was ≥ 6 ; oxytocin was administered thereafter. Since May 2020, our first choice for cervical ripening has been PROPESS. PROPESS was inserted into the posterior vaginal canal and remained there for up to 12 h to promote cervical ripening. If labor did not start after using PROPESS, the Bishop score was checked the following day to determine whether mechanical cervical dilation or oxytocin should be used. The adverse effects of PROPESS include uterine hyperstimulation, non-reassuring fetal status (NRFS), fever, elevated blood pressure, and nausea. If adverse effects occur, the cord can be pulled to readily and quickly withdraw the device. Continuous fetal heart rate monitoring should be performed during PROPESS insertion. The criteria for removing PROPESS included 30 min of regular (3-min intervals) and painful contractions, artificial membrane rupture, onset of uterine hyperstimulation (>5 per 10 min), NRFS, and systemic side effects such as vomiting, nausea, and hypotension.

The indications for cervical ripening were defined as follows: singleton pregnancy from 37 weeks 0 days to 41 weeks 6 days gestation, cephalic position, cervical findings with a Bishop score ≤ 6 , no history of CS, and consent for PROPESS or mechanical cervical ripening. Patients were not eligible for labor induction if they met any of the following criteria: already in labor, had undergone surgery involving myomectomy or uterine rupture, fetal dysfunction, pla-

centa previa, placental abruption, cephalopelvic disproportion, breech positioning, or use of another cervical ripening or dilatation agent. The primary outcome was the CS rate in both groups. The secondary outcomes were the rate of delivery within 12 or 24 h after insertion, time required for delivery, CS rate owing to induction failure, prevalence of NRFS and chorioamnionitis, oxytocin use rate, neonatal outcomes, and additional use of mechanical dilation in the PROPESS group. Medical records were reviewed retrospectively; data are presented as the mean and standard deviation (SD) for continuous variables, and the number and percentage for categorical variables. Pearson's chi-square tests were used for categorical variables. All statistical analyses were conducted using JMP Pro 15. P values < 0.05 were considered statistically significant. This study adhered to the relevant ethical considerations. Ethical approval was obtained from the ethics committee of our university (approval no. 1959, registered on 06/17/2022), and informed consent was obtained from all participants.

3. Results

Table 1 shows patient characteristics and reasons for labor induction in the PROPESS and mechanical dilation groups. No significant differences were observed in the maternal age, gestational age at induction, baseline Bishop score, or frequency of maternal complications between the two groups. However, the PROPESS group had a significantly higher incidence of diabetes mellitus (DM) or gestational diabetes mellitus (GDM). **Figure 1** shows the outcomes of the PROPESS and mechanical dilation groups. Of the individuals who received PROPESS alone, 15 (36.6%) individuals delivered transvaginally, of whom three delivered within 12 h and six within 24 h. Conversely, vaginal delivery was successful in two (4.1%) individuals in the mechanical dilatation group, with none occurring within 12 h and two within 24 h. The PROPESS group had significantly fewer patients requiring additional oxytocin compared to the mechanical dilation group (65.9% vs. 91.8%; $p = 0.003$). The addition of oxytocin resulted in 13 vaginal deliveries in the PROPESS group and 15 deliveries in the mechanical dilatation group, with significantly higher rates in the PROPESS group (63.4% and 38.8%, respectively; $p = 0.02$). After using PROPESS, 14 patients (34%) required additional mechanical cervical dilation, 2 with Dylapan[®], and 12 with Obatametro[®]. **Table 2** presents the delivery outcomes of both groups. The CS rate was significantly lower in the PROPESS group (36.6% vs. 61.2%, $p = 0.02$), and the delivery rates within 12 and 24 h after administration were higher in the PROPESS group than in the mechanical dilation group. However, no significant differences were observed in the overall delivery times between the two groups. We compared the delivery time between cases of failed cervical ripening with PROPESS requiring additional mechanical dilation ($n = 14$) and those in the mechanical dilation group ($n = 49$). The PROPESS group had a delivery time of 108 ± 54.7 h, while the mechanical dilatation group had a delivery time of 54 ± 8 h, indicating a shorter delivery time in the mechanical dilatation group ($p = 0.01$). To identify predictors of response to PROPESS, we compared patient

backgrounds between cases in which vaginal delivery was achieved with a Bishop score ≥ 7 at the time of PROPESS removal (effective group; $n = 19$) and cases requiring additional mechanical dilation with PROPESS (ineffective group; $n = 14$) (Table 3). However, we found no significant differences between the two groups in terms of maternal age, history of fertility treatment, pre-pregnancy body mass index, body mass index at delivery, gestational age at induction, or Bishop score at insertion. Additionally, multivariate analysis revealed no significant differences. No significant difference was observed between the two groups in the incidence of NRFS, chorioamnionitis, or neonatal outcomes.

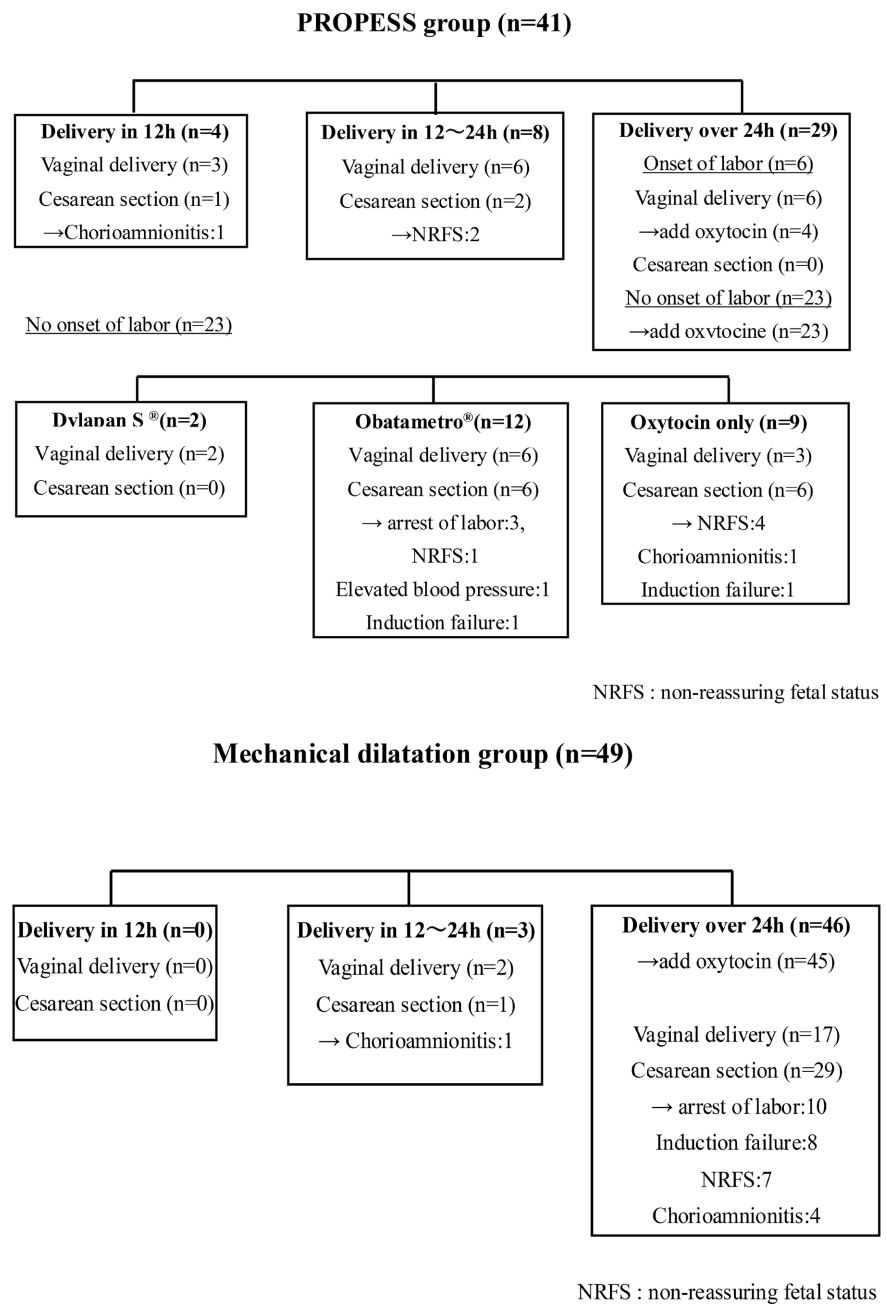


Figure 1. Outcomes of the PROPESS groups and the mechanical dilatation group.

Table 1. Patient characteristics and reason for labor induction in the PROPESS and mechanical dilatation groups.

| | PROPESS group (n = 41) | Mechanical dilatation group (n = 49) | p-value |
|--|--------------------------|--------------------------------------|---------|
| Age (years) | 32.5 ± 0.9 (21 - 45) | 34.3 ± 0.8 (19 - 45) | 0.14 |
| Pre-pregnancy body mass index (kg/m ²) | 25.1 ± 0.8 (18.4 - 49.9) | 24.0 ± 0.7 (17.2 - 37.0) | 0.33 |
| Gestational age at induction (weeks) | 39.2 ± 0.2 (37 - 41) | 39.7 ± 0.2 (37 - 41) | 0.07 |
| Pre-treatment Bishop score | 1.8 ± 0.2 (0 - 5) | 1.2 ± 0.2 (0 - 5) | 0.07 |
| Reason for induction | | | |
| Prevention of post-term delivery | 19 | 29 | 0.22 |
| DM/GDM | 11 (7/4) | 1 | 0.002 |
| HDP | 8 | 15 | 0.13 |
| Oligohydramnios | 2 | 2 | 0.85 |
| FGR | 1 | 1 | 0.90 |

DM, diabetes mellitus; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; FGR, fetal growth restriction.

Table 2. Delivery outcomes in the PROPESS and mechanical dilatation groups.

| | PROPESS group (n = 41) | Mechanical dilatation group (n = 49) | p-value |
|---|------------------------|--------------------------------------|---------|
| Delivery outcomes | | | |
| CS (%) | 15 (36.6) | 30 (61.2) | 0.02 |
| Vaginal delivery within 12 h (n, %) | 3 (7.3) | 0 (0) | 0.09 |
| Vaginal delivery within 24 h (n, %) | 9 (21.9) | 2 (4.1) | 0.02 |
| Delivery time (overall) (h) | 53 ± 7 | 54 ± 8 | 0.92 |
| Additional mechanical dilation * | 14 (34.1) | - | |
| Delivery time (PROPESS + mechanical dilatation vs. mechanical dilatation group). (h) ** | 108 ± 54.7 (n = 14) | 54 ± 8 | 0.01 |
| Oxytocin usage (n, %) | 27 (65.9) | 45 (91.8) | 0.003 |
| CS for induction failure (n, %) | 2 (4.8) | 8 (16.3) | 0.1 |
| CS for arrest of labor (n, %) | 3 (7.3) | 10 (20.4) | 0.13 |
| CS for NRFS (n, %) | 7 (17.0) | 7 (14.3) | 0.72 |
| Chorioamnionitis (n, %) | 2 (4.8) | 5 (10.2) | 0.45 |
| Neonatal outcomes | | | |
| Apgar score 1 min | 7.8 ± 0.1 | 7.8 ± 0.1 | 0.61 |
| Apgar score 5 min | 8.6 ± 0.1 | 8.6 ± 0.1 | 0.61 |
| Neonatal umbilical cord arterial blood pH | 7.28 ± 0.01 | 7.27 ± 0.01 | 0.25 |
| NICU administration (n, %) | 20 (48) | 32 (65) | 0.11 |

CS, cesarean section. * Cases requiring additional mechanical dilation for PROPESS included Dylapan S[®] (n = 2) and Obatametro[®] (n = 12), ** Comparison of delivery times in cases where cervical dilation was unsuccessful with PROPESS requiring additional mechanical dilation versus those in the mechanical dilation group.

Table 3. Comparison of patient backgrounds for effectiveness with PROPESS.

| | Effective group (n = 19) | Non effective group (n = 14) | p-value |
|--|--------------------------|------------------------------|---------|
| Age | 31.7 ± 6.9 | 31.7 ± 4.7 | 0.88 |
| History of fertility treatment | 8 (42.1%) | 5 (35.7%) | 1.0 |
| Pre-pregnancy body mass index (kg/m ²) | 24.5 ± 4.0 | 24.4 ± 4.0 | 0.88 |
| Body mass index at delivery (kg/m ²) | 28.1 ± 4.0 | 28.0 ± 4.0 | 0.88 |
| GA at induction (weeks) | 39.2 ± 1.2 | 39.4 ± 1.3 | 0.4 |
| Bishop score at the insertion | 2.1 ± 1.8 | 1.9 ± 1.7 | 0.58 |

Effective group: patients with a BS > 7 at the time of PROPESS extraction, resulting in vaginal delivery. Non-effective group: patients requiring additional mechanical dilation for PROPESS included Dylapan S® (n = 2) and Obatametro® (n = 12).

4. Discussion

4.1. Comparison of PGE2 Vaginal Administration and Mechanical Cervical Dilation

This study compared the outcomes of PROPESS and mechanical cervical dilation during induced labor in Japanese primiparous women with unruptured membranes. The PROPESS group had a significantly higher incidence of DM and GDM, which was attributed to a change in our management policy from 2020 to induce delivery at 38 weeks of gestation for pregnancies complicated by DM or GDM with poor glycemic control. The PROPESS group had a lower CS rate and higher rates of vaginal delivery within 12 and 24 h. Since labor induction success rates are low, especially for primiparas with unruptured membranes, identifying the most effective method between conventional mechanical ripening and pharmacological methods can improve outcomes.

Table 4 summarizes previous studies comparing cervical dilation using vaginal administration of PGE2 with mechanical cervical dilation via a double-balloon method. CS and vaginal delivery rates were often similar in both groups [5]-[8]. Cromi *et al.*, in a randomized controlled trial (n = 208), found that delivery rates within 24 h were higher with double-balloon dilation than with intravaginal PGE2 administration [5]. However, a subsequent meta-analysis (n = 1866) reported similar 24-h delivery and CS rates in both groups [8]. Another meta-analysis (n = 1453) comparing the efficacy of Foley catheter and PGE2 vaginal administration found similar 24-h delivery and CS rates [6]. This study showed a significantly higher delivery rate within 24 h and a lower CS rate in the PROPESS group. Tseng *et al.* reported on 65 patients, 53 (81.5%) of whom had successful vaginal deliveries, with a vaginal delivery rate of 100% in multiparous women and 74.5% in nulliparous women. Significantly higher rates of vaginal deliveries have been reported in multiparous pregnant women. Additionally, they found that parity is one of the most significant predictors of successful vaginal delivery in women treated with a slow-release dinoprostone vaginal insert for the induction of labor [9]. Previous studies focused on pregnant women with unruptured membranes, but none specifically targeted primiparas.

This study focused on primiparas with unruptured membranes, a group with a low success rate in inducing labor. Variations in the results from previous studies may be attributed to differences in mechanical dilation methods, patient backgrounds, and the retrospective nature of the studies. In the mechanical dilation group, oxytocin was used in 91.8% of cases, and the vaginal delivery rate was as low as 38.8%, reflecting the low success rate of mechanical cervical dilation for primiparas with unruptured membranes. Vaginal administration of PGE2 reportedly decreases the need for oxytocin [6] [7] and reduces delivery time [10]. However, when cervical dilation is not achieved with PROPESS, additional mechanical cervical dilation is required, resulting in a longer delivery time in the PROPESS group than in the mechanical group. Specifically, failure to respond to PROPESS delays delivery. In this study, 34% of patients were unresponsive to PROPESS, which causes hesitation in using PROPESS in nulliparous women with unruptured membranes. Imai *et al.* reported that the efficacy of PROPESS depends on the Bishop score and vaginal bleeding at the time of insertion during cervical ripening in term pregnant women [11]. Although we found no predictors of response to PROPESS, clarifying these predictors is necessary, especially in primiparas with unruptured membranes.

Table 4. Studies comparing mechanical cervical dilation with PGE2 and PGE1 vaginal insertion for cervical dilation.

| Authors (year) | Labor induction indication | Materials and methods | Rate of CS or vaginal delivery | Other outcomes |
|------------------------------------|--|---|---|---|
| Cromi A <i>et al.</i> (2012) [5] | · Over 34 weeks · Singleton pregnancy · Non-ruptured membrane · Bishop score ≤ 6 | RCT (n = 208); Double balloon (50 mL/50mL) (n = 105) vs. PGE2 (sustained-release vaginal insert) (n = 103) | <Rate of CS> PGE2 26.2% vs. double- balloon 23.8% (p = 0.75) <Rate of vaginal delivery within 24 h> PGE2. 49% vs. Double balloon 68% (p = 0.007) | |
| YM Du <i>et al.</i> (2017) [8] | 34 - 36 weeks Bishop score $\leq 4 - 6$ | Meta-analysis (n = 1866); Double balloon vs. vaginal PGE2 | <Rate of CS> <Rate of vaginal delivery within 24 h> No significant difference | The number of excessive uterine contractions and NICU administration are higher in the vaginal PGE2 group |
| Whag H <i>et al.</i> (2016) [6] | | Meta-analysis (n = 1453); Foley catheter (n = 731) vs. vaginal PGE2 (n = 722) | <Rate of CS> <Rate of vaginal delivery within 24 h> No significant difference | In the vaginal PGE2 group Excessive uterine contractions \uparrow (RR 0.07, 95% CI 0.03 - 0.19) |
| Liu <i>et al.</i> (2019) [7] | Singleton pregnancy | Meta-analysis (n = 603); Double balloon (n = 305) vs. vaginal PGE2 (n = 298) | <Rate of CS> <Rate of vaginal delivery within 24 h> No significant difference | In the vaginal PGE2 group Excessive uterine contraction \uparrow (RR 0.17, 95% CI 0.06 - 0.54) |
| Diguisto <i>et al.</i> (2021) [10] | $\geq 41 + 0$ weeks' gestation Intact membranes Bishop score < 6 | RCT (n = 1220); Double balloon (n = 610) vs. slow release of dinoprostone (n = 610) | <Rate of CS for NRFS> PGE2 5.8% vs. double-balloon 5.3% (p = 0.70) | Time from cervical ripening to delivery PGE2 23 h vs. double-balloon 32 h (p < 0.001) |

Continued

| | | | | |
|--|---|--|---|--|
| Yamaguchi M, <i>et al.</i> (2021) [13] | Bishop score < 6 Over 37 weeks | Retrospective study PROPESS (n = 51) vs. Mechanical (n = 49) | <Rate of vaginal delivery (primipara)> PROPESS 76.5% vs. Mechanical r 48.1% (p = 0.01) <Rate of CS> PROPESS 36.6% Mechanical 61.2% (p = 0.02) | Rate of vaginal delivery within 12 h PROPESS 28.6% vs. Mechanical r 5.3% (P < 0.01) |
| Current study (2023) | >37 weeks Singleton pregnancy Primipara with intact membranes Bishop score ≤ 6 | Retrospective PROPESS (n = 41) vs. Mechanical (n = 49) | <Rate of vaginal delivery within 24 h> PROPESS 24% Mechanical 6% (p = 0.01) | Oxytocin usage PROPESS group 70.7% (↓) Mechanical 91.8% (p = 0.001) |

RR, relative risk; CI, confidence interval; NRFS, non-reassuring fetal status; NICU, neonatal intensive care unit; CS, cesarean section.

4.2. Safety of PGE2 Vaginal Insertion

Although the use of labor induction has continued to rise, the American College of Obstetrics and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine, and the American College of Nurse-Midwives have all agreed that the results of the ARRIVE trial should not be widely or uncritically adopted.

Induction of labor has several medical indications recommended by various international guidelines, including gestational age of 41 completed weeks or more, prelabor rupture of amniotic membranes, pregnancy-related hypertension, diabetes, intrauterine growth restriction, premature rupture of membranes after 34 weeks, and other complications. Pharmacological agents such as prostaglandins (dinoprostone and misoprostol), which induce artificial cervical ripening and boost cervical dilatation, are commonly used to reduce the duration of labor and promote vaginal delivery. Dinoprostone is widely used in Europe and the United States; key safety considerations regarding its use include an increased risk of uterine rupture, tachysystole, and hyperstimulation in pregnant women, which could potentially lead to a non-reassuring fetal heart rate and fetal hypoxemia. In July 2021, the Italian Medicines Agency, in agreement with the European Medicines Agency (EMA), updated the restrictions and contraindications for its usage underlining the risk of maternal and fetal complications [12].

Previous studies have suggested that intravaginal administration of PGE2 significantly increases the rate of excessive uterine contraction [6]-[8], the frequency of neonatal umbilical cord arterial blood pH reaching <7.1, and neonatal intensive care unit (NICU) admission [7] [8]. However, the neonatal umbilical cord arterial blood pH and the rate of NICU admission were not significantly different between the two groups in this study. Diguisto *et al.* reported no significant difference in the CS rate for NRFS between the double-balloon and intravaginal PGE2 groups [10]. In this study, the CS rate for NRFS was not significantly different between the two groups. Furthermore, in a systematic review comparing the misoprostol (PGE1) and dinoprostone (PGE2) groups by Cristina *et al.*, the CS rate (odds ratio [OR]: 0.94; 95% CI: 0.84 - 1.05), instrumental delivery rate (OR: 1.04; 95% CI: 0.90 - 1.19), tachycardia (OR: 1.21; 95% CI: 0.91 -

1.60;), chorioamnionitis (OR: 0.94; 95% CI: 0.76 - 1.17), Apgar score < 7 after 5 min (OR: 0.83; 95% CI: 0.61 - 1.12), NICU admission rate (OR: 0.91; 95% CI: 0.77 - 1.09), and infant death (OR: 0.57; 95% CI: 0.22 - 1.44) were not significantly different. Misoprostol and dinoprostone appear to have similar safety profiles. This and other studies suggest that PROPESS can also be used relatively safely. PROPESS can also be used relatively safely if the fetal heart rate is continuously measured while observing the appearance of tachycardia and NRFS during the use of PROPESS. If adverse effects occur, the withdrawal cord should be pulled and the device should be removed promptly [12].

Two key limitations of this study are its small sample size and retrospective design. In the future, a prospective comparative study with a larger number of patients and a more detailed analysis is needed to identify the predictive factors of PROPESS response.

In conclusion, PROPESS use is associated with a significantly lower CS rate, higher delivery rate within 24 h, and a lower rate of oxytocin administration compared to mechanical cervical dilation in primiparas with unruptured membranes. However, failure to respond to PROPESS prolongs the overall delivery time compared to the conventional instrumental dilation group, highlighting the need to identify predictors of response to PROPESS.

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Ethics Approval and Consent to Participate

Ethical approval was obtained from the ethics committee of the University of Ryukyus (Approval no. 1959, registered on 06/17/2022).

Data Accessibility Statement

The datasets created and analyzed in this study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors collaborated in this study. YK and KM contributed substantially to the study concepts and design. YC and TK made substantial contributions to the acquisition of data.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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