

The Efficacy and Safety of Dinoprostone Vaginal Insert for Labor Induction Following Optimization of Standard Operating Procedure: A Retrospective Study in China

Ping Jin, Bao-Min Yin*

Department of Obstetrics, Zhuhai Center for Maternal and Child Health Care, Zhuhai 519000, China

*Corresponding author: Bao-Min Yin, bbyin@163.com

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Abstract: *Background:* The study aimed to assess the efficacy and safety of dinoprostone vaginal insert in labor induction following optimization of standard operating procedure (SOP) and to discover independent predictors of vaginal delivery. *Methods:* This study comprised 551 pregnant women who required cervical ripening with dinoprostone before induction of labor. Using univariate and multivariate analyses, independent predictors of vaginal delivery were identified. *Results:* 443 of the 551 women (80.4%) gave birth vaginally. Vaginal delivery was predicted by maternal age (24–30 vs. < 24, $P < 0.001$; 30–35 vs. < 24, $P = 0.03$), gestational age ($P = 0.005$), birth weight ($P < 0.001$), parity ($P = 0.001$), pre-pregnancy BMI ($P < 0.001$), premature rupture of membranes ($P = 0.001$), meconium-stained amniotic fluid ($P < 0.001$), fundal height ($P < 0.001$) and the Bishop score ($P < 0.001$). None of the women exhibited severe postpartum hemorrhage. *Conclusions:* The maternal age, gestational age, birth weight, parity, body mass index, premature membrane rupture, amniotic fluid contamination, fundal height, and the Bishop score were independent predictors of vaginal delivery. These may guide the clinical use of dinoprostone for induction of labor.

Keywords: Dinoprostone vaginal insert; Induction of labor; Standard operating procedure; Vaginal delivery

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1. Introduction

Since China replaced its one-child policy with a universal two-child policy, Chinese couples have been permitted to have a second child, resulting in a considerable increase in the proportion of multipara and advanced maternal-age women [1]. It is well recognized that the risk of unfavorable pregnancy outcomes, including cesarean section, is increased in women of advanced maternal age compared to women of non-advanced maternal age [2-4]. Nearly half of China's infants were delivered via cesarean section in 2007–2008, which is three times more than the 15 percent threshold suggested by the World Health Organization [5]. Although the cesarean section rate in China decreased to about 36.7% in 2018, it is still high compared to other countries [6]. Studies have revealed that women who receive a cesarean section without a medical indication are at a greater risk for death and other problems [7]. Moreover, babies born via cesarean section are more prone to develop respiratory issues, obesity, and other metabolic illnesses [8]. These data imply that the rate of cesarean sections in China must be regulated.

Induction of labor refers to the initiation of uterine contractions by mechanical methods (e.g., balloon

catheter), or pharmacologic agents (prostaglandins, oxytocin), before the commencement of spontaneous labor^[9-12]. Successful induction of labor aims to reduce pregnancy risk, shorten the time between induction and delivery, lower the rate of cesarean section, and achieve vaginal birth^[13]. By the time of this study, Prostaglandin E2 (PGE2, dinoprostone) was the only prostaglandin approved for cervical ripening in the induction of labor by the Food and Drug Administration (FDA) of the United States^[14]. Previous research has confirmed that dinoprostone is a safe and effective ripening agent for inducing labor, and it has been frequently utilized in clinics^[15-17]. Despite current studies being inconclusive in comparing the efficacy outcomes of dinoprostone with mechanical methods, a potential disadvantage of mechanical methods is that their application may be more difficult or technically challenging than the use of pharmacologic agents^[18]. Besides, a systematic review has shown that induction of labor with a mechanical method has a higher probability of maternal and neonatal infectious morbidity than pharmacologic agents^[19]. Therefore, in Zhuhai Center for Maternal and Child Health Care (a Third-Grade Class-A maternity facility), dinoprostone is preferred over the balloon catheter for cervical ripening before induction of labor. Despite this, the cesarean section rate remained extremely high in 2013, at 53.8%. To ensure the safety of the mother and newborn, our hospital must optimize the current standard operating procedure (SOP) for dinoprostone-induced labor to lower the cesarean section rate. In this study, we sought to retrospectively assess the efficacy and safety of dinoprostone vaginal insert in labor induction after optimizing the SOP, as well as to identify significant parameters for vaginal delivery.

2. Methods

2.1. Patients

This retrospective study was conducted at Zhuhai Center for Maternal and Child Health Care between October 2013 and December 2014. This study included 551 pregnant women who presented for labor induction with a dinoprostone vaginal insert as a cervical ripening agent. Singleton pregnancies with a Bishop score ≤ 6 , gestational age between 37 and 42 weeks, cephalic presentation, and normal fetal heart rate were included. This study excluded pregnant women with dinoprostone contraindications, past uterine or cervical surgery, or contraindications for vaginal delivery (such as cephalopelvic disproportion, reproductive tract infections, and placenta previa). The Institutional Review Board of Zhuhai Center for Maternal and Child Health Care granted ethical approval, and informed consent was acquired from each participant.

2.2. Treatment protocols

To analyze the amniotic fluid index, fetal weight, and obstetric problems, all pregnant women underwent a comprehensive laboratory examination, ultrasound assessment, physical examination, Bishop score, and fetal heart rate monitoring before induction of labor.

The SOP before optimization was mainly as follows:

- (1) A dinoprostone vaginal insert (Propess 10 mg; Ferring Pharmaceuticals Ltd. Co. Switzerland) was administrated into the posterior vaginal fornix transversely for cervical ripening at 8:30–9:30 am.
- (2) Pregnant women remained in bed for at least 30 minutes after dinoprostone insertion.
- (3) Continuous electronic fetal monitoring was performed after regular uterine contractions (every 5 min, each lasting 30–40 s).
- (4) The indication for the removal of the dinoprostone insert included regular uterine contraction and cervical dilation of 1.0 cm, fetal distress, premature rupture of membrane, unbearable pain, and the dinoprostone insert used for 24 hours, regardless of the maturity of the cervix (a Bishop score < 7).
- (5) Administration of oxytocin at least 30 minutes after removal of dinoprostone insert for pregnant women with uterine inertia or inadequate progress.

The modified SOP was summarized as follows:

- (1) At 8:30–9:30 am, a dinoprostone vaginal insert (Propess 10 mg; Ferring Pharmaceuticals Ltd. Co., Switzerland) was administered transversely into the posterior vaginal fornix for cervical ripening.
- (2) After inserting dinoprostone, pregnant women must stay in bed for at least 30 minutes.
- (3) Evaluation following insertion for a Bishop score between 1 and 4 included: fetal heart rate to be monitored every four hours before regular contractions (every five minutes, each lasting 30–40 seconds); fetal heart rate monitoring was to be increased to every two hours once regular contractions began, and gynecological examinations were to be performed every hour; continuous monitoring of the fetal heart rate during active labor and transfer to the labor room as soon as the cervix has dilated to 2.0 cm.
- (4) Evaluation following insertion for a Bishop score between 5 and 6 included: fetal heart rate was to be monitored every two hours before regular contractions (every five minutes, each lasting 30–40 seconds); fetal heart rate monitoring was to be increased to every hour once regular contractions began and gynecological examinations were to be performed every 30 minutes; continuous monitoring of fetal heart rate during active labor, with special care paid to the removal of the dinoprostone vaginal insert.
- (5) Emphasize patient education: alert medical workers promptly in the event of frequent contractions, vaginal bleeding, vaginal fluid leakage, feces, or if the patient felt that the dinoprostone vaginal insert was no longer in the vagina.
- (6) The indications for removing the dinoprostone insert are as follows: unbearable pain; the dinoprostone insert used for more than 24 hours; rupture of membrane; fetal distress; uterine hyperstimulation was defined as more than 5 contractions within 10 minutes, and uterine hypercontractility was defined as continuous contractions for more than 1 minute.
- (7) In the event of uterine hyperstimulation, continuous fetal monitoring was performed, and tocolytics are administered if uterine contractions did not cease within 5 to 10 minutes.

Failure of induction, fetal distress, acute aggravation of any pregnancy complication (such as severe preeclampsia), abnormal fetal position (persistent occiput posterior or transverse position; sincipital presentation), and failure in progress are the indications for cesarean section following induction of labor. Failure to advance is defined as no change in cervical dilatation or fetal head drop within four hours of the active phase. Failure of induction was defined as no change in cervical dilation or lack of regular uterine contractions 36 hours after induction.

2.3. Outcomes assessment

Maternal age, height, body mass index (BMI), gestational age, parity, time to delivery, mode of delivery, Bishop score, fundal height, birth weight, premature membrane rupture, and meconium-stained amniotic fluid were extracted from the medical records of each participant. The vaginal delivery rate served as the primary efficacy endpoint for evaluating the treatment's effectiveness. Maternal and neonatal outcomes were used to assess the safety of labor induction. The maternal outcomes were assessed including postpartum hemorrhage, intrapartum fever, amniotic fluid embolism, and uterine hyperstimulation. Postpartum hemorrhage was defined as a blood loss of 1000 mL after cesarean delivery or 500 mL after vaginal delivery. Meanwhile, fetal distress, Apgar score, and admission to the neonatal intensive care unit (NICU) were chosen to assess neonatal outcomes.

2.4. Statistical analysis

All statistical analyses were conducted using version SPSS 22.0 (SPSS Institute, IL, USA). The mean and standard deviation (mean \pm SD) were used to represent quantitative data. Quantitative and percentage

representations of qualitative data were used. Using a *t*-test for independent samples, differences in continuous variables were analyzed. Using the χ^2 test or Fisher's exact test, differences in categorical variables were assessed. The independent predictors associated with vaginal delivery were then determined using multivariate logistic regression analysis. The significance level was set at $P < 0.05$.

3. Results

3.1. Demographic characteristics

This retrospective study included 551 pregnant women (mean age of 28.0 ± 4.0 years old; range 20.0–40.0 years old) who were administered a dinoprostone vaginal insert for cervical ripening before induction of labor.

Table 1 shows the baseline characteristics of eligible pregnant women. 469 (85.1%) of the 551 women were primiparous, while 82 (14.9%) were multiparous. The mean pre-labor BMI of eligible pregnant women was determined to be 27.8 ± 3.7 kg/m² (range: 19.7–38.5 kg/m²), and their average height was 161.0 ± 3.9 cm (range: 150.0–172.0 cm). In addition, the average gestational age was 40.0 ± 1.6 weeks (range: 34.0–41.7 weeks), and the average fundal height was 33.5 ± 1.6 cm (range: 26.0–38.0 cm).

Table 1. Baselines characteristics of included pregnant women

Characteristics	Mean \pm SD (range)
Maternal age (years)	28.02 ± 3.97 (20.00–40.00)
Pre-labor BMI (kg/m ²)	27.83 ± 3.68 (19.66–38.46)
Height (cm)	161.02 ± 3.91 (150.00–172.00)
Gestational age (weeks)	40.03 ± 1.58 (34.00–41.71)
Parity (nulliparous/multiparous)	469 (85.1%) / 82 (14.9%)
Fundal height (cm)	33.47 ± 1.62 (26.00–38.00)

Note: SD, standard deviations; BMI, body mass index

The most common indications for inducing labor (**Table 2**) were post-term pregnancy (57.5%), premature membrane rupture (30.1%), gestational diabetes mellitus (11.6%), and oligohydramnios (4.7%).

Table 2. Indications for use of dinoprostone vaginal insert

Indications	Number (%)
Post-term pregnancy	317 (57.5)
Premature rupture of membrane	166 (30.1)
Gestational diabetes mellitus	64 (11.6)
Oligohydramnios	26 (4.7)
Scarred uterus	13 (2.4)
Hypofunction of the placenta	12 (2.2)
Fetal malformation	7 (1.3)
Social factors	5 (1.1)

Note: Fetal malformation was defined as a structural or chromosomal abnormality occurring in the uterus; Hypofunction of the placenta was defined as fetal heart monitoring class II after admission.

Only 13 (2.4%) of the 551 pregnant women with dinoprostone-induced labor had cesarean sections due to the failure of induction, while the overall cesarean section rate was 19.6% (108/551) and 443 (80.4%)

had vaginal deliveries. The delivery duration of dinoprostone-induced vaginal births was analyzed. According to **Table 3**, the average time to labor onset was 16.9 ± 11.62 h (0.0–69.0 h) hours. In addition, the average duration of all stages of labor was 26.5 ± 13.1 h, with the first stage lasting 8.9 ± 6.8 h, the second stage lasting 1.2 ± 0.6 h, and the third stage lasting 0.3 ± 0.2 h on average.

Table 3. The delivery time of women with dinoprostone-induced vaginal delivery

Delivery time interval	Mean \pm SD (range)
Time to onset of labor (h)*	16.9 ± 11.6 (0.0–69.0)
Total stage of labor (h)*	26.5 ± 13.1 (5.2–78.7)
The first stage of labor (h)	8.9 ± 6.8 (0.0–43.0)
The second stage of labor (h)	1.2 ± 0.6 (0.2–2.4)
The third stage of labor (h)	0.3 ± 0.2 (0.0–2.4)

Note: SD, standard deviations; h, hours; *The data were not available for all subjects; Time to onset of labor = delivery time-time of the dinoprostone vaginal insert

3.2. Safety analysis

Maternal and newborn outcomes were analyzed (**Table 4**). Among the 551 pregnant women, 56 (10.2%) experienced postpartum hemorrhage (≥ 500 mL of blood loss), but none experienced severe postpartum hemorrhage (≥ 1000 mL of blood loss). In addition, three (0.5% of the study population) cases of uterine hyperstimulation were identified. In this study, no additional adverse events such as intrapartum fever or amniotic fluid embolism were observed.

Concerning neonatal outcomes, this study population included 7 (1.3%) cases of fetal distress and 5 (0.9%) cases with an Apgar score < 7 at 5 minutes. In this study, no additional adverse events, such as admission to the NICU, were observed.

Table 4. The maternal and neonatal outcomes of included pregnant women

Outcomes	Number (%)
Maternal outcomes	
Postpartum hemorrhage	56 (10.2)
Uterine hyperstimulation	3 (0.5)
Intrapartum fever	0 (0.0)
Amniotic fluid embolism	0 (0.0)
Neonatal outcomes	
Fetal distress	7 (1.3)
Apgar score < 7 at 5 min	5 (0.9)
NICU admission	0 (0.0)

Note: NICU, neonatal intensive care unit

3.3. Relevant factors for vaginal delivery

The influence factors for vaginal delivery were further analyzed (**Table 5**). Univariate analysis showed that maternal age (24–30 vs. < 24 , OR = 3.5, 95% CI: 2.0–6.1, $P < 0.001$; 30–35 vs. < 24 , OR = 2.8, 95% CI: 1.5–5.4, $P = 0.001$; ≥ 35 vs. < 24 , OR = 3.5, 95% CI: 1.3–9.4, $P = 0.01$), parity (nulliparous vs. multiparous, OR = 0.04, 95% CI: 0.008–0.2, $P < 0.001$), pre-labor BMI (< 30 vs. ≥ 30 kg/m², OR = 0.5, 95% CI: 0.3–0.8, $P = 0.006$), premature rupture of membrane (OR = 2.6, 95% CI: 1.5–4.3, $P < 0.001$), meconium-stained

amniotic fluid (OR = 4.159, 95% CI: 2.8–6.3, $P < 0.001$), fundal height (OR = 1.3, 95% CI: 1.2–1.5, $P < 0.001$) and the Bishop score (OR = 0.8, 95% CI: 0.6–0.9, $P < 0.001$) were significantly associated with vaginal delivery.

Multivariable regression analysis showed that maternal age (24–30 vs. < 24, OR = 3.6, 95% CI: 1.9–7.0, $P < 0.001$; 30–35 vs. < 24, OR = 2.3, 95% CI: 1.1–4.8, $P = 0.03$), gestational age (OR = 0.4, 95% CI: 0.2–0.7, $P = 0.005$), birth weight (OR = 7.9, 95% CI: 3.0–20.8, $P < 0.001$), parity (OR = 0.02, 95% CI: 0.004–0.1, $P = 0.001$), pre-labor BMI (OR = 0.3, 95% CI: 0.2–0.5, $P < 0.001$), premature rupture of membrane (OR = 0.3, 95% CI: 0.1–0.5, $P = 0.001$), meconium-stained amniotic fluid (OR = 3.4, 95% CI: 2.2–5.5, $P < 0.001$), fundal height (OR = 1.4, 95% CI: 1.2–1.7, $P < 0.001$) and the Bishop score (OR = 0.7, 95% CI: 0.6–0.9, $P = 0.008$) were independent predictors of vaginal delivery.

Table 5. Univariate and multivariate analysis of independent factors for dinoprostone-induced vaginal delivery

Independent factors	Univariate analysis				Multivariate analysis	
	Vaginal delivery [n = 443, (%)]	Cesarean section [n = 108, (%)]	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age (years)						
< 24 years	43 (9.7)	28 (25.9)	--	--	--	--
24-30 years	255 (57.6)	48 (44.4)	3.5 (2.0–6.1)	< 0.001	3.6 (1.9–7.0)	< 0.001
30-35 years	113 (25.5)	26 (24.1)	2.8 (1.5–5.4)	0.001	2.3 (1.1–4.8)	0.03
≥ 35 years	32 (7.2)	6 (5.6)	3.5 (1.3–9.4)	0.01	0.5 (0.1–1.7)	0.2
Gestational age (≤ 40 / > 40 weeks)	130 (29.3) / 313 (70.7)	30 (27.8) / 78 (72.2)	1.1 (0.7–1.6)	0.7	0.4 (0.2–0.7)	0.005
Birth weight (< 4 / ≥ 4 kg)	430 (97.1) / 13 (2.9)	100 (92.6) / 8 (7.4)	2.6 (1.2–5.7)	0.06	7.9 (3.0–20.8)	< 0.001
Parity (nulliparous/multiparous)	362 (81.7) / 81 (18.3)	107 (99.1) / 1 (0.1)	0.04 (0.008–0.2)	< 0.001	0.02 (0.004–0.1)	0.001
BMI (< 30 / ≥ 30 kg/m ²)	302 (68.2) / 141 (31.8)	88 (81.5) / 20 (18.5)	0.5 (0.3–0.8)	0.006	0.3 (0.2–0.5)	< 0.001
Premature rupture of membrane (yes / no)	153 (34.5) / 290 (65.5)	13 (12.0) / 95 (88.0)	2.6 (1.5–4.3)	< 0.001	0.3 (0.1–0.5)	0.001
Meconium-stained amniotic fluid (yes / no)	53 (12.0) / 390 (88.0)	39 (36.1) / 69 (63.9)	4.2 (2.8–6.3)	< 0.001	3.4 (2.3–5.5)	< 0.001
Fundal height (cm)	33.3 ± 1.7	34.0 ± 1.4	1.3 (1.2–1.5)	< 0.001	1.4 (1.2–1.7)	< 0.001
Bishop score	3.9 ± 1.3	3.6 ± 0.8	0.8 (0.7–0.9)	< 0.001	0.7 (0.6–0.9)	0.008

Note: 95% CI, 95% confidence interval; BMI, body mass index; OR, odds ratio

4. Discussion

In China, the cesarean section rate reached approximately 50% in 2007–2008 and decreased to 36.7 percent in 2018; this is dramatically higher than the 15% recommended by the World Health Organization (WHO) [5,6]. In 2013, the cesarean section rate at our hospital reached 53.8% based on the old SOP for dinoprostone-induced labor. Consequently, controlling the rate of cesarean sections in China has received increasing attention. To reduce the rate of cesarean sections, our hospital must optimize the SOP for dinoprostone-induced labor to ensure the safety of the mother and infant. The purpose of the present study was to assess the efficacy and safety of dinoprostone vaginal insert in labor induction after SOP optimization and to identify relevant factors for vaginal delivery.

In addition to regular gynecological examinations, the major discrepancy between the modified SOP

and the old SOP was the frequency of fetal heart rate monitoring. The modified SOP established a strict frequency of fetal heart monitoring and gynecological examinations based on the Bishop score and contraction status. In 2014, after optimizing the SOP for dinoprostone-induced labor, the cesarean section rate was 19.6%, which was dramatically lower than the 53.8% before optimization. These results indicated that a more detailed and standardized SOP of dinoprostone-induced labor plays an important role in reducing the cesarean section rate in the Chinese population. In China, the rate of cesarean section in dinoprostone-induced labor varied from study to study. In dinoprostone-induced labor at the Obstetrics Department of Sun Yat-sen Memorial Hospital, a cesarean section rate of 31.7 percent was observed, which was significantly higher than our reports [20]. Similarly, our result was slightly lower than that of Zhao et al. [21], who reported a cesarean section rate of 23.91 percent in a tertiary Chinese maternity hospital. A comparatively lower cesarean section rate of 18.1% was reported in a multicenter randomized controlled trial [22]. The possible reason was that our hospital was one of the first designated rescue centers for pregnant women in critical condition in Zhuhai, and the proportion of high-risk patients was relatively high. Besides, geographic variations might also contribute to the heterogeneity between this study and previous studies [23].

This study assessed the safety of dinoprostone-induced labor by analyzing maternal and neonatal outcomes. Regarding maternal outcomes, the most common adverse events were uterine hyperstimulation (0.5%) and postpartum hemorrhage (10.2%). This study found no cases of severe postpartum hemorrhage (1000 mL of blood loss). Regarding neonatal outcomes, this study identified a total of 7 (1.3%) cases of fetal distress and 5 (0.9%) cases with an Apgar score of 7 at 5 minutes. This was marginally greater than previous estimates [24-26]. A possible explanation was that our research was conducted in China in a real-world setting. The pregnant women involved in this study were more complex, and our hospital had a relatively high proportion of critical patients. In this study's population, neither maternal nor neonatal complications were serious. Overall, our study demonstrated that dinoprostone-induced labor is safe after SOP optimization.

Several variables may influence the effectiveness of dinoprostone-induced vaginal delivery. Pevzner et al. conducted a secondary analysis of data collected from women who underwent dinoprostone-induced labor in a multicenter, randomized, double-blind trial [27,28]. The analysis revealed that the characteristics of pregnant women, including the Bishop score, gestational age, BMI, age, parity, height, neonatal birth weight, and race, could predict the success of labor induction independently. In this investigation, multivariate regression analysis revealed that maternal age, gestational age, birth weight, parity, BMI, and the Bishop score were all independent predictors of vaginal delivery. The role of premature membrane rupture in cesarean section and delivery vaginally is still controversial. Premature membrane rupture was a complication of pregnancy and one of the reasons for the increase in the rate of cesarean section [29]. Nevertheless, a systematic review and meta-analysis of randomized controlled trials demonstrated that routine early amniotomy after cervical ripening did not increase the risk of cesarean delivery and shortened the time between induction and delivery [30]. The current study revealed that pregnant women with premature membrane rupture were more likely to deliver vaginally. The current study also revealed that the cesarean section rate among pregnant women with meconium-stained amniotic fluid was 3.44 times that of pregnant women without such a stain. Traditionally, fundal height was measured to estimate gestational age and birth weight [31,32]. In this study, we found that fundal height was an independent predictor of vaginal delivery for the first time.

Although the results of the present study were very encouraging, the principal limitation was that this was a retrospective study conducted at a single institute and with a small sample size. Therefore, a prospective study with a larger sample size should be conducted in the future to further optimize the SOP of dinoprostone-induced labor.

5. Conclusion

After optimizing the SOP, the vaginal delivery rate with dinoprostone vaginal insert for labor induction was 80.4% with good safety. Age of the women, gestational age, birth weight, parity, pre-pregnancy BMI, premature membrane rupture, amniotic fluid contamination, fundal height, and the Bishop score were independent predictors of vaginal delivery. These may guide the clinical use of dinoprostone for induction of labor.

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Disclosure statement

The authors declare no conflict of interest.

Author contributions

B.Y. and P.J. conceived and designed the idea of the study. P.J. collected, analyzed, interpreted the data, and drafted the article. B.Y. provided administrative support. All the authors have read and approved the final manuscript.

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