# Comparison of Dinoprostone and Oxytocin for the Induction of Labor in Late-Term Pregnancy and the Rate of Cesarean Section: A Retrospective Study in Ten Centers in South China

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Background: Dinoprostone is the recommended primary option for induction of labor (IOL) in late-term pregnancies (LTPs). However, oxytocin is used in developing and rural areas, and studies have supported similar effectiveness for oxytocin and dinoprostone in reducing the rate of cesarean delivery of LTPs with a Bishop's score of between 4–6. This study aimed to compare dinoprostone and oxytocin for IOL in LTPs and the rate of cesarean section in ten centers in South China.

Material/Methods: A retrospective study included 1,408 women with LTP, with subgroups including a Bishop's score of 0–3 and 4–6. Rates of cesarean delivery were compared between women given vaginal dinoprostone and intravenous oxytocin for IOL. Secondary outcomes included the duration of labor, and maternal and fetal complications.

Results: Comparison between women who received oxytocin (N=365) and dinoprostone (N=1,043) showed significantly lower rates of cesarean delivery with dinoprostone, but no significant difference between the subgroups with Bishop's scores of 0–3 and 4–6. The interval between induction to labor and duration of the active phase of labor were significantly reduced in the dinoprostone group with a Bishop's score of between 4–6.

Conclusions: For LTPs with a Bishop's score of 0–3, dinoprostone was superior to oxytocin for IOL with a lower rate of cesarean delivery, but both agents had a similar outcome for women with a Bishop's score of 4–6. These findings may have implications for the choice of agent used in IOL when dinoprostone is unavailable.

MeSH Keywords: Cervical Ripening • Cesarean Section • Dinoprostone • Labor, Induced • Oxytocin • Pregnancy, Prolonged

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# Background

Post-term pregnancy has an incidence of 5.49% of all pregnancies in the US [1]. Post-term pregnancy is defined as gestation beyond 42 weeks from the first day of the last menstrual period [2]. Previous studies have shown that as the gestational age advances beyond the expected delivery date, the risk of adverse maternal and fetal outcomes increases, including deterioration in coexisting maternal medical conditions, fetal distress, and fetal death [3]. Therefore, clinicians have reached a consensus that pregnant women should be induced for labor at $41^{0/7}$ weeks through to $41^{6/7}$ weeks, a period designated as late-term pregnancy (LTP) [4].

There are several strategies for the induction of labor (IOL), and pharmacologic agents, including oxytocin and prostaglandins, are most commonly used in clinical practice [5]. Compared with oxytocin, the prostaglandin E2 agent, dinoprostone, has been regarded as more effective for the induction of labor of LTPs with a non-dilated cervix [6,7]. The World Health Organisation (WHO) recommends that oxytocin alone is indicated if prostaglandins are not available [8]. Unfortunately, due to the high cost of dinoprostone [9,10], and instability of pharmacy-prepared dinoprostone gel [10], oxytocin remains in use for IOL at medical centers in developing and rural areas [11].

During labor, the readiness of the uterine cervix for IOL can be assessed by several methods, including the use of the Bishop's score. A recently reported cohort study that recruited LTPs with a Bishop's score of between 4–6 showed that when compared with vaginal dinoprostone, intravenous oxytocin resulted in fewer cesarean deliveries and was more effective in IOL [12]. However, this previous study was limited by the small number of cases of LTP studied, which included 90 cases for each group with either dinoprostone or oxytocin [12]. Also, LTPs with a Bishop's score of <3 were not included in this previous study [12].

Because of the remaining controversies associated with the management of LTPs, particularly in developing and rural areas, this study aimed to compare dinoprostone and oxytocin for elective IOL in LTPs and the rate of cesarean section in ten centers in South China. Two subgroups were studied that included LTPs with a Bishop's score of between 0–3 and between 4–6. The secondary outcomes evaluated were the occurrence of maternal and fetal complications.

# Material and Methods

### Patients and subgroups

The patients were recruited between January 2010 to December 2014 from ten medical institutes including Nanfang Hospital, the Third Affiliated Hospital of Guangzhou Medical University, Sun Yat-sen Memorial Hospital, the First People's Hospital of Shunde, the Women and Child Hospital of Zhuhai, the Central Hospital of Panyu, the Xiaolan People's Hospital of Zhongshan, the Central Hospital of Chancheng, Foshan, the Hexian Memorial Hospital of Panyu and the Huadu People's Hospital of Guangzhou. The Ethical Committee of Nanfang Hospital approved the study. All pregnant women enrolled in this study provided informed consent.

Women who underwent induction of labor (IOL) were identified as either group A, who were given intravenous oxytocin, or group B, who were given vaginal dinoprostone. The study inclusion criteria were viable singleton pregnancies, gestational age from 410/7 weeks to 416/7 weeks, confirmed by crown-rump length measurement during the first trimester, a cervical Bishop's score of <6, normal fetal heart electric monitoring, cephalic presentation, and intact membranes without spontaneous uterine contractions. The study exclusion criteria were an estimated birth weight <4,000 g, and the presence of contraindications for prostaglandin treatment.

### Assessment of labor and administration of dinoprostone or oxytocin

Before IOL, all pregnant women received a cervical assessment to determine the Bishop's scores, as previously described [13], following by surveillance of maternal contractions and fetal heart rate. In group A, oxytocin was administrated intravenously, starting at 2 mU/min, and then doubled every 30 min to a maximum of 32 mU/min, or until four contractions occurred within 10 minutes, which was regarded as active labor.

In group B, a 10 mg dinoprostone suppository was placed in the posterior fornix for up to 12 hours, according to the manufacturer's recommendations. Both groups were divided into LTPs with a Bishop's score of between 0–3 (A1 or B1) and between 4–6 (A2 or B2) for the study analysis.

### Primary and secondary outcomes

After being given dinoprostone or oxytocin, LTPs in both groups were identified as having a failure in initiating IOL, defined as a non-contraction pattern in the dinoprostone group or after an 18-hour oxytocin infusion in the oxytocin group. Fetal distress or failure to progress during labor, defined as no cervical dilatation within an interval for four hours at the active phase, or without fetal descent in a three-hour interval at the second stage, resulted in cesarean section. Cesarean delivery rate was considered to be the primary outcome.

Secondary outcomes included postpartum hemorrhage, with blood loss estimated as previously described [14]. Briefly, blood
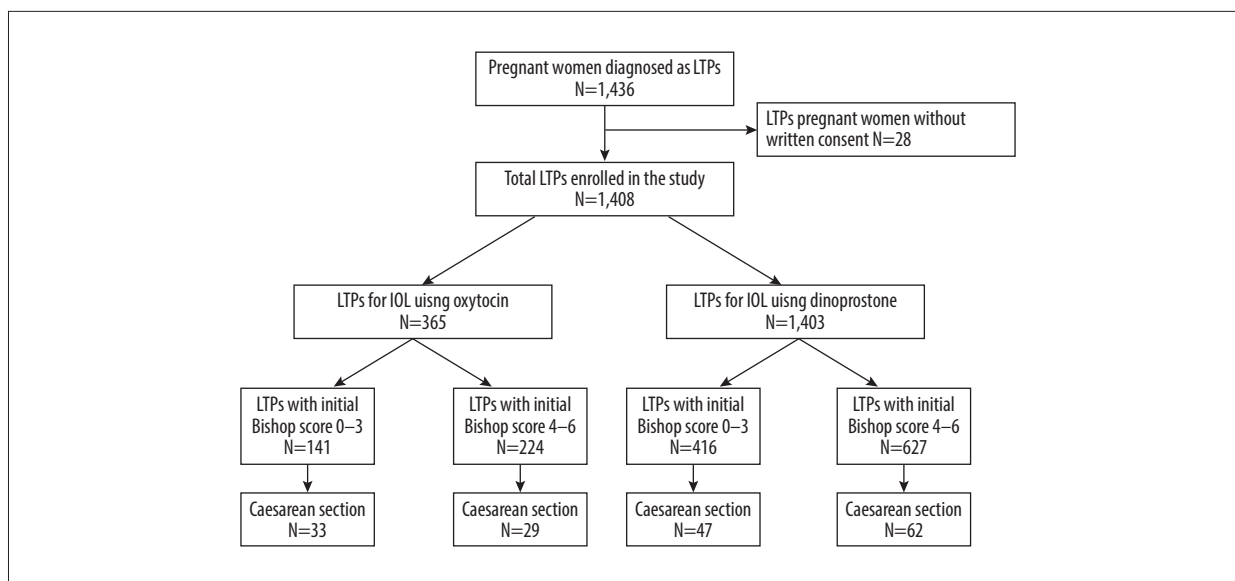
**Figure 1.** Flow diagram of the study design and patient groups of women undergoing induction of labor (IOL) in late-term pregnancy (LTP).

loss volume in ml was measured during 24 h after delivery, the hemoglobin level in g/dL was measured, and any required transfusion blood volume in ml was recorded, with 1,500 ml of blood loss defined as postpartum hemorrhage [14]. Uterine hyperstimulation was defined as more than five contractions in 10 minutes, averaged over 30 minutes [15]. The time interval from induction to vaginal delivery, duration of the stages of labor, neonatal birth weight, and the Apgar scores at 1 minute and 5 minutes were evaluated.

## Statistical analysis

Data were analyzed using SPSS version 22.0 software (SPSS Inc, Chicago, IL, USA) with the chi-squared $\chi^2$ test for categorical data and the unpaired t-test for continuous data. $P < 0.05$ was considered to indicate a statistically significant difference.

## Results

### Clinical and demographic findings and Bishop's scores in women with late-term pregnancies (LTPs) requiring induction of labor (IOP)

There were 1,456 women with late-term pregnancy (LTP) who were recruited into the study (Figure 1). Three hundred sixty-five cases of LTPs received intravenous oxytocin (group A) including 141 cases with a Bishop's score between 0–3 (subgroup A1), and 224 cases with a Bishop's score between 4–6 (subgroup A2). A further 1,043 cases of LTPs underwent vaginal dinoprostone treatment (group B), including 416 cases with a Bishop's score between 0–3 (subgroup B1), and

627 cases with a Bishop's score between 4–6 (subgroup B2). There were no significant differences in maternal age, body mass index (BMI), parity, and gestational weeks between both groups A and B, or subgroups A1 and B1, or A2 and B2 (Table 1).

### Indications for cesarean section

Both groups of women showed similar indications for cesarean section, as fetal distress accounted for most cases, following by failure to progress, and failure to initiate IOL (Figure 2A). The total cesarean delivery rate was significantly lower in group B, especially in women with failure in progress to delivery ($P < 0.05$) (Figure 2B). Comparison of the cesarean delivery rates between the subgroups showed that for LTPs with a Bishop's score between 0–3, subgroup B1 with dinoprostone showed fewer cesarean deliveries than subgroup A1 given oxytocin ($P < 0.05$) (Table 2). However, for women with a Bishop's score between 4–6, there was no significant difference in the rate of cesarean delivery between subgroup B2 and A2 ($P > 0.05$) (Table 2).

### Comparison of the cesarean delivery rates and indications in the groups and subgroups

We considered how the diverse indications contributed to the cesarean delivery rates in each subgroup. As confirmed in the forest plot (Figure 3), when the aim was to reduce the cesarean delivery rate for IOL, the dinoprostone group performed better than the oxytocin group for the subgroups with a Bishop's score of between 0–3. However, there was no difference between group A and B when the Bishop's score was between 4–6. A Bishop's score of between 0–3 in the dinoprostone group

**Table 1.** Patient demographic characteristics.

| | Group A (n=365) | Group B (n=1,043) | P-value |
|---|---|---|---|
| Bishop's score 0–3 | A1 (n=141) | B1 (n=416) | |
| Maternal age (yrs) | 26.68±3.87 | 27.29±3.77 | 0.103 |
| BMI (kg/m$^2$) | 25.77±2.74 | 26.36±2.57 | 0.078 |
| Gestational age (weeks) | 41.13±0.55 | 40.94±0.80 | 0.204 |
| Nulliparity (n) | 110 (78.01%) | 350 (84.13%) | 0.098 |
| Bishop's score 4–6 | A2 (n=224) | B2 (n=627) | |
| Maternal age, y | 27.79±4.81 | 27.33±4.14 | 0.206 |
| BMI (kg/m$^2$) | 26.78±3.37 | 26.70±2.94 | 0.781 |
| Gestational age (weeks) | 41.02±0.59 | 40.99±0.80 | 0.608 |
| Nulliparity (n) | 179 (79.91%) | 520 (82.93%) | 0.310 |

Group A – intravenous oxytocin infusion. Group B – dinoprostone insert placed in the posterior fornix. Data are expressed as the mean±SD. BMI – body mass index.
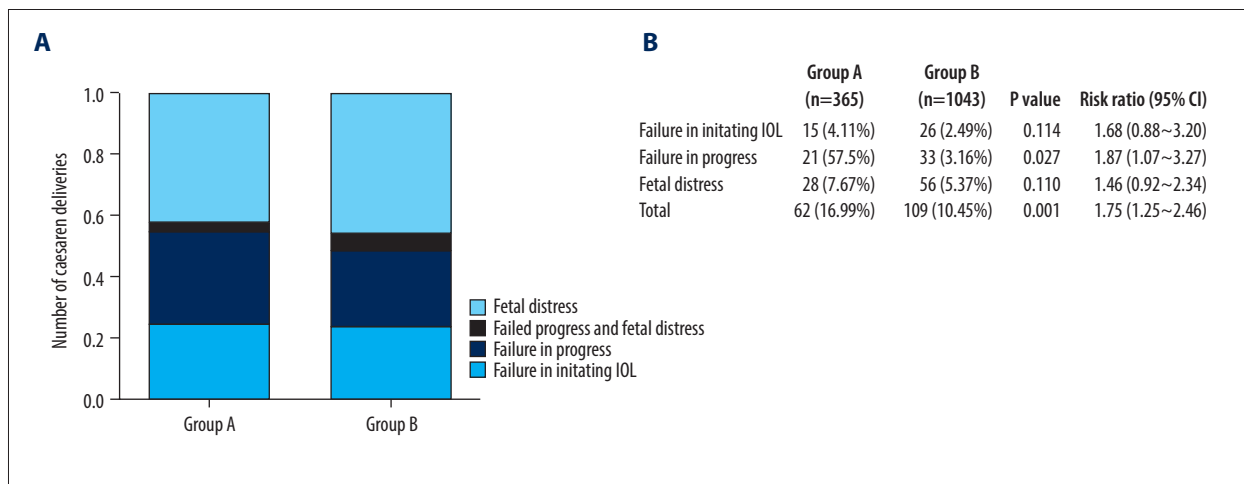


| | Group A (n=365) | Group B (n=1043) | P value | Risk ratio (95% CI) |
|---|---|---|---|---|
| Failure in initating IOL | 15 (4.11%) | 26 (2.49%) | 0.114 | 1.68 (0.88~3.20) |
| Failure in progress | 21 (57.5%) | 33 (3.16%) | 0.027 | 1.87 (1.07~3.27) |
| Fetal distress | 28 (7.67%) | 56 (5.37%) | 0.110 | 1.46 (0.92~2.34) |
| Total | 62 (16.99%) | 109 (10.45%) | 0.001 | 1.75 (1.25~2.46) |

**Figure 2.** Comparison of the rates of cesarean delivery and their indications in the study groups undergoing induction of labor (IOL) in late-term pregnancy (LTP). (**A**) The indications for cesarean delivery rates. (**B**) Comparison of the cesarean delivery rates between the two study groups. Group A – IOL with intravenous oxytocin infusion. Group B – IOL with dinoprostone in the posterior vaginal fornix.

**Table 2.** Late-term pregnancies (LTPs) with cesarean delivery in groups A and B.

| | Group A (n=365) | Group B (n=1,043) | P-value |
|---|---|---|---|
| Bishop's score 0–3 | 33 (9.04%) | 47 (4.51%) | 0.001* |
| Bishop's score 4–6 | 29 (7.95%) | 62 (5.94%) | 0.181 |
| Total | 62 (16.99%) | 109 (10.45%) | 0.001* |

Group A – intravenous oxytocin infusion. Group B – dinoprostone insert placed in the posterior fornix. * P<0.05.
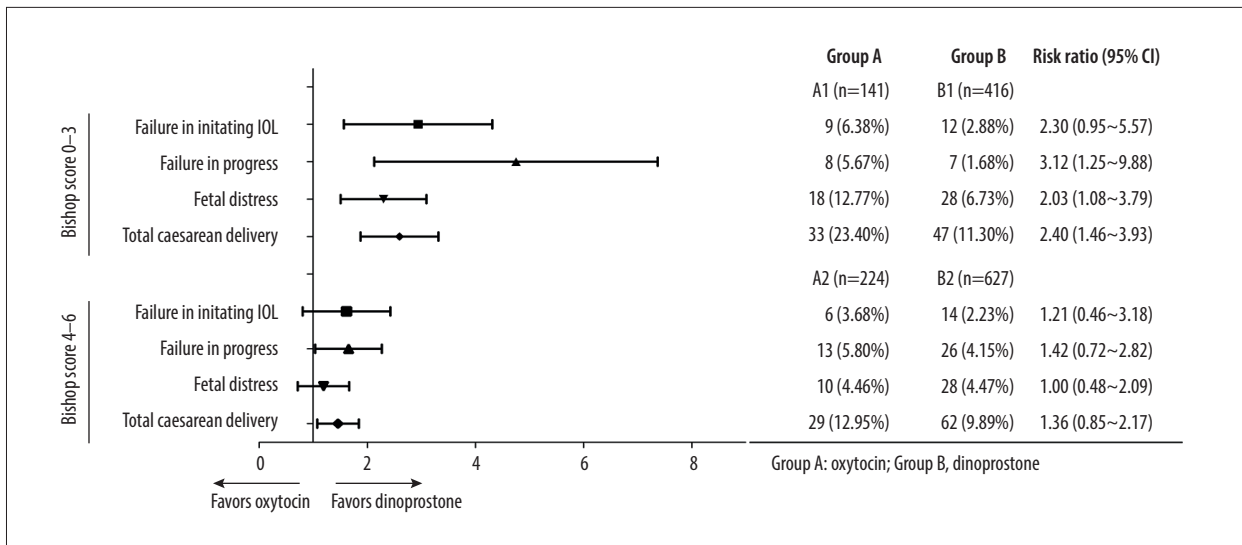
**Figure 3.** Comparison of the rates of cesarean delivery and their indications in the subgroups according to the Bishop's scores (of 0–3 and 4–6) in women undergoing induction of labor (IOL) in late-term pregnancy (LTP). Group A – IOL with intravenous oxytocin infusion. Group B – IOL with dinoprostone in the posterior vaginal fornix.

**Table 3.** Time intervals for labor in each group and subgroup: the interval between induction to labor, the latent stage, the active phase, and the second stage of labor.

| | Group A (n=365) | Group B (n=1,043) | P-value |
|---|---|---|---|
| Bishop's score 0–3 | A1 (n=141) | B1 (n=416) | |
| Induction-labor interval, hrs | 11.73±13.84 | 9.57±7.91 | 0.121 |
| Duration of latent phase, hrs | 3.68±2.37 | 3.75±2.18 | 0.815 |
| Duration of active phase, hrs | 1.82±1.23 | 1.71±1.52 | 0.554 |
| Duration of second stage, hrs | 0.53±0.46 | 0.45±0.34 | 0.090 |
| Bishop's score 4–6 | A2 (n=224) | B2 (n=627) | |
| Induction-labor interval, hrs | 11.46±13.25 | 8.57±7.82 | 0.006* |
| Duration of latent phase, hrs | 3.61±2.42 | 3.60±2.03 | 0.979 |
| Duration of active phase, hrs | 2.16±1.91 | 1.71±1.25 | 0.014* |
| Duration of second stage, hrs | 0.46±0.36 | 0.52±0.38 | 0.075 |

Group A – intravenous oxytocin infusion. Group B – dinoprostone insert placed in the posterior fornix. * $P<0.05$.

was associated with a reduction in the number of cesarean deliveries due to failure in the labor induction process, followed by failure in initiating IOL, and due to fetal distress (Figure 3).

**Time intervals for labor in each group and subgroup: the interval between induction to labor, the latent stage, the active phase, and the second stage of labor**

The findings for the effects of the reagents on the time intervals in each subgroup showed that for LTPs with a Bishop's score 0–3, there were no differences in the time intervals for labor in each subgroup, including the interval between induction to labor, the latent stage, the active phase, and the second stage of labor, between subgroups A1 and B1 ($P>0.05$) (Table 3). However, for LTPs with a Bishop's score between 4–6, both the interval between induction to labor and the duration of the active phase were significantly reduced in subgroup B2 who were given dinoprostone ($P<0.05$) (Table 3).

**Maternal and fetal complications in each group and subgroup**

For LTPs with a Bishop's score between 0–3, subgroup B1 given dinoprostone showed reduced rates of postpartum hemorrhage but an increased hyperstimulation rate ($P<0.05$). However, there was no difference in these incidences between subgroups

**Table 4.** Maternal complications in each group and subgroup.

| | Group A (n=365) | Group B (n=1,043) | P-value |
|---|---|---|---|
| Bishop's score 0–3 | A1 (n=141) | B1 (n=416) | |
| Postpartum hemorrhage, n (%) | 10　(7.09%) | 4　(0.96%) | 0.000* |
| Hyperstimulation of uterine, n (%) | 1　(0.71%) | 8　(1.92%) | 0.047* |
| Bishop's score 4–6 | A2 (n=224) | B2 (n=627) | |
| Postpartum hemorrhage, n (%) | 11　(4.91%) | 32　(5.10%) | 0.910 |
| Hyperstimulation of the uterus, n (%) | 1　(0.45%) | 15　(2.39%) | 0.084 |

Group A – intravenous oxytocin infusion. Group B – dinoprostone insert placed in the posterior fornix. * P<0.05.

**Table 5.** Fetal complications in each group and subgroup.

| | Group A (n=365) | Group B (n=1,043) | P-value |
|---|---|---|---|
| Bishop's score 0–3 | A1 (n=141) | A2 (n=416) | |
| Birth weight, kg | 3.42±0.39 | 3.41±0.33 | 0.903 |
| 1 min Apgar <7, n (%) | 2　(1.42%) | 10　(2.40%) | 0.718 |
| 5 min Apgar <7, n (%) | 0 | 3　(0.72%) | 0.730 |
| Bishop's score 4–6 | A1 (n=224) | A2 (n=627) | |
| Birth weight, kg | 3.45±0.41 | 3.42±0.39 | 0.332 |
| 1 min Apgar <7, n (%) | 2　(0.89%) | 11　(1.75%) | 0.559 |
| 5 min Apgar <7, n (%) | 0 | 1　(0.16%) | 1.000 |

Group A – intravenous oxytocin infusion. Group B – dinoprostone insert placed in the posterior fornix. * P<0.05.

with a Bishop's score between 4–6 (Table 4). No differences in neonatal birth weight and Apgar scores at 1 minute and 5 minutes were observed between the groups (Table 5).

## Discussion

In this retrospective cohort study, women were recruited from ten medical centers in South China with late-term pregnancies (LTPs) who had an unfavorable or non-ripened cervix. Women underwent induction of labor (IOL) with either oxytocin (N=365) or dinoprostone (N=1043). After stratifying the women into two groups using Bishop's scores, we compared cesarean delivery rates as the primary outcome and maternal and neonatal complications as the secondary outcomes.

The findings from the present study showed that 10.45% of LTPs that used dinoprostone for IOL underwent cesarean sections, which is lower than the previously reported range of 10.5–38.6% [16]. This lower total cesarean delivery rate supports the use of dinoprostone for IOL in LTP [16,17]. In a Cochrane review of 58 clinical trials, prostaglandins were shown to be more effective in IOL than oxytocin and resulted in fewer cesarean sections [11]. However, oxytocin also reduced the rate of unsuccessful vaginal delivery when compared with

expectant management [11]. The findings from the present study showed that the subgroup with a Bishop's score of between 4–6 showed no superiority for dinoprostone over oxytocin, which is a finding supported by previous studies [18–20]. Some of the differences in the findings from previous studies may be due to the lack of subgroup stratification according to Bishop's scores. For example, in 2012, Akay et al. reported that both oxytocin and dinoprostone for IOL had similar obstetric outcomes in LTPs, but that oxytocin showed significant superiority for a shorter delivery period [18]. The cohort studied by Koc et al. included only women with a Bishop's score of between 4–6 and showed similar results to those of the present study [12]. Also, this previous study showed no difference in the rates of cesarean delivery between dinoprostone and oxytocin, for either primiparous or multiparous pregnancies [12].

Also, the design of the present study differed from previous studies on LTPs, as a subgroup was analyzed that had Bishop's scores of between 0–3, in which dinoprostone was more effective than oxytocin. The different mechanisms of action might explain these varied effects of dinoprostone and oxytocin in LTPs as determined by the different Bishop's scores. Both oxytocin and dinoprostone can bind to specific receptors in the myometrium to initiate or enhance uterine contraction [21,22]. However, dinoprostone with functional prostaglandin E2 also

modulates fibroblast activity and the extracellular matrix (ECM) to promote cervical ripening [23,24], which might be more important for an unfavorable cervix even before uterine contractions begin [3,25].

When the maternal and neonatal complications were considered, both oxytocin and dinoprostone were safe for IOL of LTPs with a Bishop's score of between 4–6. However, for women with a Bishop's score of between 0–3, dinoprostone reduced postpartum hemorrhage and significantly shortened the time intervals, which was also a finding in the group with a Bishop's score of between 4–6. Therefore, despite insufficient positive cases to confirm the effect of overstimulation of dinoprostone, caution should still be recommended for the use of this vaginal prostaglandin reagent with control of the dose.

This study was conducted in ten centers in South China and included developing and rural population areas. In these areas, dinoprostone may be unavailable, or its use may be too costly. The findings from this study provide support for the rationale of using oxytocin to induce labor in LTPs with a Bishop's score of between 4–6. In addition to pharmacological IOL with oxytocin and dinoprostone, non-pharmacological methods, especially those that are less costly should not be ignored [26]. Among the low-cost mechanical methods for IOL, amniotomy is not currently recommended because of its undetermined effectiveness, and it is also an invasive procedure that is associated with the risk of possible infection with group B Streptococcus or vertical transmission of the human immunodeficiency virus (HIV) [27]. Alternatively, the use of a Foley catheter is a cheap and effective choice, although the current guidelines from the National Institute for Health and Care Excellence (NICE) in the UK do not recommend its use [28]. However, future studies to compare the effectiveness of low-cost IOL methods, such as intravenous oxytocin with mechanical methods, would be clinically meaningful.

This study had several limitations. This study was retrospective, was not controlled, and was dependent on the quality and availability of data present in the medical records. There are current clinical recommendations on the use of dinoprostone and oxytocin in pregnant women, which on ethical grounds would limit their use in randomized controlled studies. For this reason, data were evaluated from a retrospective clinical study, which may provide support for future prospective clinical studies. Also, despite the long-term and worldwide use of the Bishop's scoring system, the use of the method alone remains controversial, and it has some limitations [29]. For example, experienced obstetricians may be able to distinguish between a cervix with a Bishop's score of 3 and 6, but possibly not between a Bishop's score of 3 and 4. Therefore, more reliable indices of IOL in future studies might include the use of serum biomarkers, and the assessment of the internal os or cervical length using ultrasound or magnetic resonance imaging (MRI).

## Conclusions

This study aimed to compare dinoprostone and oxytocin for elective induction of labor (IOL) in late-term pregnancies (LTPs) and the rate of cesarean section in ten centers in South China. For LTPs with a Bishop's score of 0–3, dinoprostone was superior to oxytocin for IOL with a lower rate of cesarean delivery, but both agents had a similar outcome for women with a Bishop's score of 4–6. Clinicians in developing areas where dinoprostone is unavailable may consider the use of low-cost oxytocin, rather than a cesarean section, for women with a Bishop's score of 4–6.

### Acknowledgments

### Conflict of interest

None.

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