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Original Research

# The role of dinoprostone for labor induction in postterm and high-risk term pregnancies

**I.F. Urunsak[1], U.K. Gulec[1,*], E. Eser[2], M. Sucu[1], C. Akcabay[1], S. Buyukkurt[1]**

[1] *Cukurova University, Faculty of Medicine, Department of Obstetrics and Gynecology (Turkey)*

[2] *Niğde Ömer Halisdemir University, Faculty of Medicine, Department of Obstetrics and Gynecology (Turkey)*

**Summary**

*Purpose:* To determine the effect of controlled release vaginal dinoprostone (CRVD) in post-term and high-risk term pregnancies on successful ripening, the length of active labour, the total time for delivery, route of delivery, and maternal-neonatal outcomes. *Methods:* We performed a retrospective study on women undergoing cervical ripening with CRVD. A total of 94 post-term pregnancies (group 1) were compared with 138 high-risk pregnancies requiring labour induction due to maternal and/or fetal indications at term (group 2). The primary outcome of the study was vaginal delivery within 24 hours. Length of active labour, the total time for delivery, route of delivery and maternal and neonatal outcomes were evaluated as secondary outcomes. *Results:* Vaginal delivery rates were 73.4% (69/94) and 81.9% (113/138) in groups 1 and 2, respectively ($p = 0.123$). The mean delivery lengths were $16.6 \pm 9.5$ and $16 \pm 8.9$ hours in groups 1 and 2, respectively ($p = 0.259$). Both groups were also similar regarding the length of active labour ($9.3 \pm 6.7$ and $9.6 \pm 6.8$ hours; $p = 0.717$). Cesarean section rates were 23.4% and 13% in groups 1 and 2, respectively ($p = 0.04$). There were no differences in maternal and neonatal outcomes between the groups. *Conclusion:* Our study showed that dinoprostone is effective for labour induction, particularly in high-risk term pregnancies.

*Key words*: Dinoprostone; High-risk pregnancy; Induction of labour; Oxytocin; Post-term pregnancy.

## Introduction

While labour induction is one of the most frequently used techniques in obstetric practice, doses, drugs, and modes of application for labour induction and cervical ripening are still a matter of debate. Cervical ripeness is a major factor in estimating successful labour induction. Prostaglandins, specifically PGE, are known as the most effective drugs to provide adequate cervical ripening [1]. Prostaglandin E2, placed locally in the cervix or the vagina, has been investigated widely and determined to be a safe and successful induction agent [1]. There are many prospective or retrospective trials with reviews evaluating different prostaglandin derivates, doses, modes of application, and the use of oxytocin. However, the question of how to prepare the unfavorable cervix is still not resolved. Most studies evaluated the effectiveness, modes of application, and safety profile of the PGE1 and PGE2 analogs [1, 2]. Dinoprostone, the analogue of PGE2 which is an effective drug for cervical ripening and labour induction, is available as a gel, tablet, pessary or suppository [3]. However, it is relatively expensive, requires cold storage conditions and frequent use of oxytocin augmentation [4]. There is a lack of data in order to compare the use of dinoprostone for labour induction between high-risk term and post-term pregnancy.

This study aims to compare the effectiveness and safety of dinoprostone in post-term and high-risk term pregnancies in both multiparous and nulliparous women.

## Materials and Methods

Data over six years on women without contraindication for vaginal delivery were reviewed. Singleton pregnancies with gestational age between 37 and 42 weeks and a cephalic presentation were included in this study. Gestational age was determined according to the date of the last menstrual period and/or sonographic data obtained during the first trimester. The Bishop scoring system was used for cervical evaluation. Patients with a Bishop score of $\leq$ 5 and a uterine contraction frequency of $\leq$ 4/hour were included in this study. Exclusion criteria were nonstress tests indicating fetal compromise before induction or an allergy to prostaglandins. After obtaining the approval of the local ethics committee (Faculty of Medicine, University of Cukurova, Ethics Committee, Date: July/ 7 th/2012, Number 9/2), signed written informed consent was received from all patients. Group 1 consisted of post-term pregnancies (n = 94). Pregnant women between 37 and 41 weeks with an indication for labour induction formed group 2 (n = 138). Post-term pregnancy was described as a gestational age of 41 weeks. Verification was confirmed by early-term ultrasonographic evaluation.

We administered a 10 mg dinoprostone vaginal insert (Propess®; Vitalis, Ankara, Turkey) in transverse position to the posterior fornix during 24 h or in case of regular painful uterine contractions, dinoprostone withdrawal was performed. Dinoprostone vaginal insert produces PGE2 from a hydrogel polymer matrix by the intravaginal release

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Table 1. — *General and obstetric characteristics of the population.*

| | Groups<br>Mean ± SD<br>Median (min-max) | | Subgroups of group 2<br>Mean ± SD<br>Median (min-max) | | | Total<br>Mean ± SD<br>Med (min-max) | *p** | *p*** |
|---|---|---|---|---|---|---|---|---|
| | Group 1<br>Post term<br>(n = 94) | Group 2<br>Term<br>(n = 138) | PROM<br>(n = 59) | PIH<br>(n = 48) | HOUP<br>(n = 31) | (n = 232) | | |
| Age (years) | 27.3 ± 5.9<br>27.0 (17.0-44.0) | 28.4 ± 6.4<br>27.0 (17.0-46.0) | 28.3 ± 6.3<br>27.0 (17.0-40.0) | 29.5 ± 7.4<br>29.5 (17.0-46.0) | 26.9 ± 4.7<br>26.0 (19.0-9.0) | 28.0 ± 6.2<br>27.0 (17.0-46.0) | 0.189 | 0.169 |
| Gravidty | 2.1 ± 1.5<br>2 (1-11) | 2.7 ± 2.5<br>2 (1-15) | 2.4 ± 2.2<br>1 (1-11) | 3.3 ± 3.3<br>2 (1-15) | 2.4 ± 1.6<br>2 (1-7) | 2.5 ± 2.2<br>2 (1-15) | 0.055 | 0.025 |
| Parity | 0.8 ± 1.3<br>0 (0-10) | 1.3 ± 2.2<br>0 (0-11) | 1.1 ± 1.9<br>0 (0-7) | 1.8 ± 2.9<br>0.5 (0-11) | 0.8 ± 1.2<br>0 (0-5) | 1.1 ± 1.9<br>0 (0-11) | 0.089 | 0.026 |
| Abortus | 0.3 ± 0.7<br>0.0 (0.0-3.0) | 0.4 ± 0.8<br>0.0 (0.0-4.0) | 0.3 ± 0.7<br>0.0 (0.0-4.0) | 0.5 ± 0.8<br>0.0 (0.0-4.0) | 0.7 ± 1.0<br>0.0 (0.0-3.0) | 0.4 ± 0.8<br>0.0 (0.0-4.0) | 0.297 | 0.089 |
| Gestational age (week) | 41.1 ± 0.4<br>41 (39-43) | 38.5 ± 1.4<br>38.4 (36-40) | 38.8 ± 1.4<br>39 (36-40) | 38.2 ± 1.4<br>38.2 (36-40) | 38.6 ± 1.2<br>38.5 (36-40) | 39.5 ± 1.7<br>40.2 (36-43) | 0.001 | 0.21 |
| Birth Weight (g) | 3500 ± 430<br>3460<br>(2720-5000) | 3050 ± 500<br>3000<br>(1750-4300) | 3170 ± 450<br>3200<br>(2400-4300) | 3020 ± 560<br>2950<br>(1750-4110) | 2870 ± 450<br>2800<br>(2000-3750) | 3230 ± 520<br>3240<br>(1750-5000) | 0.001 | 0.001 |

*p** comparisons between group 1 and group 2, *p*** comparisons between subgroups of group 2. PROM: Prematur rupture of membrans, PIH: Preganancy induced hypertension, HOUP: History of unsuccessful pregnancy.

of dinoprostone 10 mg with a 0.3 mg/h dose rate during 12 h. After prostaglandin administration, patients were monitored for uterine contractions and fetal heart rate (FHR) over 1 h. As soon as active labour was documented by regular painful contractions at a rate of at least 2 per 10 minutes, patients were then monitored on labour and delivery. We started intravenous oxytocin augmentation at a rate of 2 mU/min and raised as required by 1 mU/min every 20 minutes to a maximum of 30 mU/min in cases with irregular uterine contractions (< 3/10 min) or lack of labor progression for 2 hours. We did not administer oxytocin infusion until at least 30 min after the withdrawal of the prostaglandin insert. If labour did not commence after 24 h, CRVD was removed, and we initiated induction by oxytocin infusion and amniotomy if possible. We monitored labour according to our delivery protocol by continuous cardiotocography recording and external manometry. The cervical assessment was documented per hour by partogram. Apgar score was recorded at 1 and 5 min. We assessed the uterine activity to determine the presence of tachysystole (at least 6 uterine contractions for each 10 min). We recorded hyperstimulation occurrence only if it was related to abnormal FHR. Active labour was described as a recording of at least three uterine contractions lasting 40–50 s duration within 10 min. If active labour was achieved, labour induction was considered successful. Fetal distress was described as an abnormal FHR requiring emergency cesarean delivery. Evaluation of the neonate was performed by the obstetrician who managed the delivery or the pediatrician in case of neonatal distress requiring resuscitation.

Age, gestational age, parity, indication of labour induction, route of delivery, interval of active labour (the time between the insertion of CRVD and active labour), interval of vaginal delivery (the time between the insertion of CRVD and delivery of fetus), the rate of vaginal delivery within 24 h, cesarean section rates for fetal compromise and failed labour induction, intrapartum complications such as uterine hyperstimulation, tachysystole, and meconium-stained amniotic fluid, and adverse effects of dinoprostone including vomiting, nausea, fever, and diarrhea were recorded. Neonatal outcome measures such as umbilical arterial pH recordings below 7.10 (fetal acidosis), APGAR score < 7 at the 5th minute, admittance to neonatal intensive care unit (NICU) and fetal birth weight were also recorded. We compared the groups using those variables to evaluate the effectiveness and safety of dinoprostone on labour induction. Vaginal delivery within 24 h was defined as the primary outcome of the study. The length of active labour, the timing of delivery, the route of delivery, maternal (uterine hyperstimulation and tachysystole, meconium, cesarean section rates, postpartum haemorrhage) and neonatal outcomes were evaluated as secondary outcomes.

Comparisons between groups were performed using the student *t*-test or one-way ANOVA. The Mann-Whitney U test or Kruskal-Wallis test was used if the data was not normally distributed. A Chi-Square test was used for categorical data analysis. Results were demonstrated as mean ± SD and median (min-max), and n (%). All recorded *p*-values are two-tailed. Statistical analysis was applied by the SPSS program (Chicago IL 11).

Table 2. — *Primary and secondary outcomes of the study.*

| | Groups Mean ± SD Median (min-max) | | Subgroups of group 2 Mean ± SD Median (min-max) | | | Total | *p** | *p*** |
|---|---|---|---|---|---|---|---|---|
| | Group 1 Postterm (n = 94) | Group 2 Term (n = 138) | PROM (n = 59) | PIH (n = 48) | HOUP (n = 31) | (n = 232) | | |
| Interval of delivery (hour) | 16.6 ± 9.5 | 16.0 ± 8.9 | 13.5 ± 7.0 | 18.7 ± 10.3 | 16.5 ± 8.9 | 16.3 ± 9.1 | 0.259 | 0.023 |
| | 13.3 (4.5-40) | 14 (3-47) | 12.5 (4-30) | 16.5 (3.5-47) | 13.5 (3-36) | 13.8 (3-47) | | |
| Interval of active phase(hour) | 9.3 ± 6.7 | 9.6 ± 6.8 | 8.8 ± 6.7 | 11.0 ± 7.3 | 9.0 ± 6.5 | 9.5 ± 6.8 | 0.717 | 0.525 |
| | 7.5 (1-26) | 7 (1-28.5) | 6 (2-28.5) | 10 (1-24) | 6.8 (2-25) | 7.5 (1-28.5) | | |
| Success of induction n (%) | 69 (73.4) | 113 (81.9) | 49 (83.1) | 37 (77.1) | 27 (87.1) | 182 (78.4) | 0.123 | 0.346 |

*p** comparisons between group 1 and group 2 , *p*** comparisons between subgroups of group 2. PROM: Prematur rupture of membrans, PIH: Preganancy induced hypertension, HOUP: History of unsuccessful pregnancy.

## Results

Two hundred thirty-two women were eligible for the study, 94 in group 1 and 138 in group 2. Preterm rupture of membranes (PROM), hypertensive disorders of pregnancy and history of unsuccessful pregnancies (HOUP) were present in 59, 48, and 31 of the women of group 2. The demographic data of the women and fetuses are displayed in Table 1. This table also shows factors that could affect the success of labour induction. We did not find a statistically significant difference between the groups regarding the factors influencing success. The unique difference was seen in birth weights. The mean birth weight was 3500 ± 430 g in group 1, and 3050 ± 500 g in group 2 ($p = 0.001$). Delivery within 24 h was similar between the groups (Table 2). Delivery rate within 24 h was 73.4% (69/94) in group 1, and 81.9% (113/138) in group 2 ($p = 0.123$). Time interval to delivery was not statistically significant ($p = 0.259$). Furthermore, the time interval of active labour was also similar ($p = 0.717$). A subgroup analysis in group 2 showed a significant difference between women who had PROM as related to the time interval of delivery ($p = 0.023$).

Secondary outcomes are presented in Table 3. Caesarean section rates were higher in group 1 compared with group 2 (23.4% versus 13%) ($p = 0.04$). There was no difference between the groups in terms of maternal and neonatal outcomes. The presence of meconium was found 8 and 2 in groups 1 and 2, respectively. Fetal acidosis was proven via arterial gas analysis on the umbilical cord in 1 infant in group 2. In our study, three fetuses had an APGAR score below 7 at the 5 minutes, all being in group 1. Both groups were similar in terms of secondary outcomes. Tachysystole and hyperstimulation were present in 3 and 1 fetuses, respectively. All four fetuses experienced PROM. There was no significant difference in any neonatal outcomes. There were four NICU admittances. Postpartum haemorrhage was observed in 2 women in each group. All responded to medical and conservative approaches and none required transfusion. We did not observe any side effects or uterine rupture requiring the need to stop treatment.

## Discussion

Labour induction is one of the most complicated clinical options for obstetricians. Ineffective induction procedures play a considerable role in elevated caesarean rates. This is particularly the case in nulliparous women with an unfavorable cervix [5]. The Bishop scoring system is commonly utilized to predict induction success [6]. In our study, we decided to use the Bishop scoring system. Pevzner *et al.* [7] published a meta-analysis of labour induction with misoprostol and dinoprostone which found that maternal age, ethnicity, BMI, parity, and birth weight are independent factors that influence induction success.

In post-term pregnancies beyond 41 weeks gestation, it has been proven that perinatal mortality and stillbirth rate is decreased with induction [8]. Middleton *et al.* [9] created subgroups in term pregnancies which consisted of women between 37-40 weeks, 41 weeks, and 42 weeks. They demonstrated that labour induction at 41 and 42 weeks did not increase cesarean rates, but diminished the stillbirth rate. Our protocol is that induction is required at 41 weeks of gestation. The results of our study show that dinoprostone is an effective and safe treatment option for labour induction in post-term pregnancies. Torralba *et al.* found that a low dose of vaginal misoprostol and vaginal dinoprostone insert have similar efficacy and safety for labour induction in gestational age beyond 41 weeks [10]. Dinoprostone insert allowed a higher probability of vaginal delivery within 12 h if the Bishop score was $< 4$ [10]. Few studies investigated oxytocin infusion in combination with prostaglandin in terms of cervical ripening and labour induction. Saccone *et al.* [11] studied the risk of cesarean delivery and the maternal and perinatal effects of the approach of labor induction for full-term uncomplicated singleton gestations. They demonstrated that there is no association between labour induction at about 39 weeks and an increased risk of cesarean delivery. In a Cochrane review published in 2009 by Alfirevic [12], the author aimed to compare intravenous oxytocin, prostaglandins and placebo in cervical ripening, and labour induction. As a result of this review, it was concluded that the use of PG provided more vaginal delivery

Table 3. — *Maternal and neonatal outcomes.*

| | Groups n (%) | | Subgroups of group 2 n (%) | | | *p** | *p*** |
|---|---|---|---|---|---|---|---|
| | Group 1 Postterm (n = 94) | Group 2 Term (n = 138) | PROM (n = 59) | PIH (n = 48) | HOUP (n = 31) | | |
| Asidosis | 0 (0.0) | 1 (0.7) | 0 (0.0) | 1 (2.1) | 0 (0.0) | 0.408 | 0.427 |
| Meconium | 8 (8.5) | 2 (1.4) | 0 (0) | 1 (2.1) | 1 (3.2) | 0.09 | 0.119 |
| Cesarean Section | 22 (23.4) | 18 (13.0) | 8 (14.8) | 6 (12.5) | 4 (12.9) | 0.04 | 0.294 |
| Tachysystole | 0 (0.0) | 3 (2.2) | 3 (5.6) | 0 (0.0) | 0 (0.0) | 0.15 | 0.04 |
| Hyperstimulation | 0 (0.0) | 1 (0.7) | 1 (1.9) | 0 (0.0) | 0 (0.0) | 0.408 | 0.507 |
| Apgar score < 7 (At the $5^{th}$ min) | 3 (3.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.035 | 0.347 |
| Postpartum hemorrhage | 4 (4.3) | 2 (1.4) | 2 (3.7) | 0 (0.0) | 0 (0.0) | 0.186 | 0.427 |

*p** comparisons between group 1 and group 2, *p*** comparisons between subgroups of group 2. PROM: Prematur rupture of membrans, PIH: Preganancy induced hypertension, HOUP: History of unsuccessful pregnancy.

within 24 hours than oxytocin. In a review article, the effectiveness of PGE2 and misoprostol were superior to oxytocin to achieve vaginal delivery within 24 h; however there was an association with a higher uterine hyperstimulation rate [13]. Other studies have demonstrated the effectiveness of mechanical methods for labor induction [14, 15].

Our results proposed that CRVD is effective and safe for induction not only in post-term pregnancies but also in high-risk term pregnancies. The role of prostaglandins with or without oxytocin in PROM is subject to debate. We found the success rate of dinoprostone induction in our PROM cohort was 83.1%. A trial by Tan *et al.* [16] evaluated prospectively in a randomized study the concurrent dinoprostone and oxytocin for labour induction in term PROM. They found that the simultaneous administration of vaginal dinoprostone and intravenous oxytocin for the induction of labour of term PROM did not expedit delivery. A randomized study showed that 6 h after CRVD, oxytocin infusion in PROM at term was associated with an increased vaginal delivery rate within 24 h. [17]. Therefore, as we did not use concurrent oxytocin with CRVD, we could not evaluate the additive effect of oxytocin for labour induction. Muzorkevich *et al.* [18] reviewed the role of oxytocin and prostaglandin derivatives in PROM and concluded that immediate labour induction by oxytocin provides an improved outcome status for patients with PROM at term.In a retrospective study evaluating the effect of dinoprostone and oxytocin in nulliparous women with term or preterm PROM on the delivery mode and delivery interval, the authors showed that the labour induction for PROM at term in nulliparous women with an unfavorable cervix resulted in a longer duration in the second stage, and an increased risk of cesarean delivery due to failure to progress, compared to those with intact membranes [19]. Oxytocin was found to be more successful in a study comparing the efficacy of oxytocin and dinoprostone in labor induction in the term, nulliparous, PROM pregnant women [20]. The inclusion of only nulliparous patients in this study may be associated with lower success rates.

We found that induction of labor with dinoprostone was successful (77.1%) and safe in those with hypertensive diseases of pregnancy. Another study reported that preeclamptic patients have lower acceptable ripening and vaginal delivery rates than those without -preeclampsia or non-hypertensive patients [21]. In a comparative study, the efficacy of misoprostol and dinoprostone vaginal inserts in patients with PIH demonstrated similar efficacy [22]. In our study, we observed a high success rate in induction with dinoprostone in the HOUP group. In our study, patients with preeclampsia had a longer time interval for active labour and delivery than post-term pregnancies, however, differences were not significant. Subgroup analysis demonstrated that PROM group had significantly shorter induction labour duration than others. This is an expected result due to the pathophysiology of PROM. These patients had higher vaginal delivery rates than post-term pregnancies. On the other hand, the highest success rate in the HOUP group is an interesting and controversial result.

Although a repeat of the CRVD dose is not recommended, optimal prostaglandin E2 doses also differ among individuals, and the frequency and amount of repeated PGE2 administrations remain uncertain.Furthermore, it was also clear that CRVD left intact beyond 12 hours did not increase the risk of intrapartum complications, cesarean delivery, or adverse neonatal outcomes [23, 24]. We used a vaginal insert through 24 hour period. Oxytocin infusion was started as per the Bishop score at the end of this period and the prostaglandin dose was not repeated. More evidence is needed as related to administration time, repeated doses or oxytocin use for different groups of patients.

The major limitation of our study is that it is retrospective. However, evaluation of the effectiveness of dinoprostone in different patient groups and comparisons between the groups is the major strength of our study.

In conclusion, our study demonstrates that CRVD is effective both in post-term pregnancies and high-risk pregnancies in providing cervical ripening and successful vaginal delivery.

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## Conflict of Interest

The authors declare no conflict of interest.

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Corresponding Author:
ÜMRAN KÜÇÜKGÖZ GÜLEÇ, M.D.
Cukurova University, Faculty of Medicine
Department of Obstetrics and Gynecology
01330 Adana (Turkey)
e-mail: ukucukgoz@yahoo.com