The Effect of Parity on Labor Induction with Prostaglandin E2 Analogue (Dinoprostone): An Evaluation of 2090 Cases

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Abstract

Objective: The aim of this study was to investigate the effect of parity on cervical ripening and labor induction with intravaginal slow-release dinoprostone and to determine the safety and efficacy of this medication in a tertiary referral center.

Methods: The medical records of 2090 pregnant women who underwent cervical ripening and induction of labor with Dinoprostone between January 2007 and December 2010 were retrospectively reviewed. All women included in the study had singleton pregnancies greater than 37 gestational weeks and the Bishop score was less than 4. Our induction of labor policy was to use dinoprostone for patients <35 years old and low parity (≤ 2). Ten milligram of intravaginal slow-release dinoprostone was applied vaginally for 24 hours. Nulliparous and multiparous patient results were compared.

Results: One thousand one hundred seventy two nulliparous and 918 multiparous patients were included in the study. Indications for induction of labor were; post-term pregnancy in 67.2%, oligohydramnios in 11.8%, severe intrauterine fetal growth restriction in 9.7%, severe gestational hypertension or chronic hypertension or preclampsia necessitating delivery in 6.8%, and premature rupture of membranes in 4.4%. The mean patient age, gestational age, parity and Bishop Score before induction were 25.22 ± 4.9, 40.21 ± 1.2, 1.6 ± 0.4 and 2.47 ± 0.2, respectively. The induction to active phase, active phase to vaginal delivery and induction to vaginal delivery durations for nulliparous and multiparous groups were (7.5 ± 6.3 vs. 6.8 ± 6.0, p=0.012) and (7.7 ± 5.6 vs. 5.8 ± 5.0, p=0.001) and (15.6 ± 7.7 vs. 13.5 ± 5.4, p=0.023), respectively. The delivery rates during the first 24 hours after application of dinoprostone were 65.7% and 71.5% for nulliparous and multiparous patients, respectively (p=0.001). In the nulliparous group, the change in Bishop Score was significantly higher than the multiparous patient group (p=0.034). During labor, 31.1% of the patients needed oxytocin augmentation and this was 34.9% in the nulliparous and 26.4% in the multiparous groups (p=0.001). The cesarean delivery rate was higher in the nulliparous group (34.3% vs. 24.9%, p=0.002). The percentage of newborns with 5-minute Apgar scores less than 7 and the percentage of newborns requiring neonatal intensive care unit (NICU) were similar between nulliparous and multiparous groups.

Conclusion: Dinoprostone seems to be an effective agent for induction of labor in patients with an unfavorable cervix for patients <35 years old and with low parity (≤ 2). The induction to vaginal delivery duration is shorter and delivery rate in the first 24 hours is higher in multiparous group. The perinatal outcomes are comparable between groups.

Keywords: Induction of labor; Dinoprostone; Cervical ripening

Introduction

At term, up to 15-30% of pregnancies in obstetric practice are induced for labor due to various fetal-maternal indications [1,2]. One of the main reasons for labor induction is the low Bishop score, as these patients carry high risk for prolonged labor and operative and cesarean delivery [1,3]. Prostaglandins (PG) are widely used for cervical ripening in order to shorten labor, decrease the use of oxytocin and increase the likelihood of vaginal delivery within 24 hours [4]. Particularly Prostaglandin E has been shown to be the most effective agent in achieving cervical ripening [5,6]. Dinoprostone (prostaglandin E2) has been widely used since the 1970’s and is known to be an agent resulting in cervical ripening and activated myometrial contractility [7]. Food and Drug Administration approved dinoprostone (PGE2) vaginal (Propess®) Dinoprostone vaginal delivery system, Ferringllc Sanayi, Istanbul, Turkey in 1995 for cervical ripening, which releases 10 mg of dinoprostone over 12 hours. The effects and properties of PGE2 (dinoprostone) have been investigated and there are many studies in the literature comparing the efficacy of the different formulations available in the market [8-18]. Unfortunately, many of these studies were conducted without regard to parity [9,10,12].

The aim of this study was to investigate the safety and efficacy of intravaginal slow-release dinoprostone insert for cervical ripening and induction of labor in the presence of unfavorable cervix in nulliparous and multiparous patients, and to determine the effect of the drug on perinatal outcomes in a tertiary referral center.

Materials and Methods

A total of 2090 consecutive pregnant women who underwent labor induction for fetal or maternal indications between January 2007 and December 2010 were included in the study. Institutional Review Board approved the study and written informed consents were obtained from all patients. Our maternity hospital is a tertiary teaching and reference center and has more than 16,000 deliveries annually.
The inclusion criteria for the study were singleton pregnancy, cephalic presentation, Bishop Score of ≤ 4, no previous uterine surgery, and gestational age between 37-42 weeks, maternal age less than 35, and parity of 2 or less. In our hospital, our induction of labor policy is to use dinoprostone for patients < 35 years old and low parity (≤2) due to possible relationship of maternal age (≥ 35 years old) and parity (≥ 3 deliveries) with maternal mortality that we have previously experienced and reported [19]. Gestational age was calculated from the LMP and confirmed by ultrasound. Baseline was done in the first or early second trimester. Exclusion criteria were previous uterine surgery, presence of uterine activity (>4 contractions in 20 minutes), any fetal presentation other than cephalic–vertex, active vaginal bleeding, placenta previa, known hypersensitivity or contraindication to prostaglandins and any condition contraindicating vaginal delivery.

Patients received a single dose of 10 mg slow-release dinoprostone vaginal insert (Propess® Dinoprostone vaginal delivery system, Ferrinllac Sanayi, Istanbul, Turkey) placed transversely in the posterior fornix of the vagina. The insert was removed after 24 hours. Induction failure was considered when the Bishop score was still less than 6 and in case regular uterine contractions did not start after 24 hours of dinoprostone use. (Propess is approved in Europe for use up to 24h). Also the insert was removed earlier, if regular painful uterine contractions (occurring every 2-3 minutes) started or if a non-reassuring FHR pattern persisted. A slow-release dinoprostone vaginal insert was inserted only once for each patient.

Following the prostaglandin administration fetal heart rate and uterine activity were recorded for at least a 20 minute period. Every 2 hours, a pelvic examination was performed to assess Bishop Score changes along with electronic fetal monitoring to assess both uterine activity and fetal heart rate. Amniotomy was performed only when labor was established and the cervix was favorable (Bishop Score≥7). Oxytocin augmentation was performed if the progress of labor was considered insufficient. Failure to progress during labor was considered if the patient was not in labor after at least 6 hours of oxytocin administration. Oxytocin administration was initiated with a dose of 0.1 mU/min. and doubled every 15 minutes up to 16 mU/min not exceeding the maximum dose of 32 mU/min or until 4 contractions in 10 minutes were achieved.

Uterine hyperstimulation syndrome was defined as tachysystole (6 or more contractions in any 10-minutes period) or hypertonus (the tone of uterine activity not returning to baseline for >90 second) associated with fetal tachycardia, late decelerations, fetal bradycardia and/or the loss of beat-to-beat variability [20]. This syndrome was managed by changing/turning to left lateral position, infusion of a 500-ml bolus of a crystalloid solution, and administering oxygen via a facial mask. If the non-reassuring FHR pattern persisted, the dinoprostone insert was removed.

The primary outcome was time to vaginal delivery (latency period). Treatment success was considered as a vaginal delivery within 24 hours of induction with dinoprostone. Secondary outcomes were cesarean delivery rate, the need for oxytocin augmentation, rate of induction failure, uterine hyperstimulation/tachysystole, an increase in Bishop Score of 3 or more, the rate of maternal and fetal complications, fetal distress requiring admission to the neonatal intensive care unit (NICU) and Apgar scores. Each outcome was evaluated separately for nulliparous and multiparous patients.

Statistics
Continuous variables were compared by the Student's t test. Categorical variables were analyzed by χ² analysis. A p value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS 11.0 for Windows (SPSS, Chicago, Illinois; Microsoft Corp., Redmond, Washington).

Results
A total of 2090 consecutive women were included in the study. Dinoprostone vaginal insert was applied to 3.9 % of total obstetric population of our hospital who were admitted for delivery. During the study period, 66.233 infants were delivered in our institution, of whom 21.592 (32.6 %) were delivered by cesarean delivery. This rate included both primary and recurrent cesarean delivery patients. Our primary cesarean delivery rate was 17.6 %. The mean patient age, gestational age, parity and Bishop Score before induction were 25.22 ± 4.9, 40.21 ± 1.2, 1.6 ± 0.4 and 2.47 ± 0.2, respectively. The indications for induction of labor were: post-term pregnancy in 64.5%, gestational hypertension and preeclampsia in 3.7%, oligohydramnios (amniotic fluid index ≤ 5 cm measured in four quadrants) in 11.5%, premature rupture of membranes in 3.3%, intrauterine fetal growth restriction (IUGR) (Diagnosed when fetal abdominal circumference was below 10th percentile) in 5.7%, low biophysical profile score and non-reactive non-stress test in 8.7%, gestational diabetes mellitus in 1.3% and miscellaneous in 1.4%.

The main outcomes and demographic data of patients are presented in Table 1. The birth rate during the first 24 hours after application of dinoprostone vaginal insert were 65.7 % for nulliparous and 71.5 % for multiparous patients, and this was statistically significant (p=0.001).

<table>
<thead>
<tr>
<th>Nulliparous (n=1172)</th>
<th>Multiparous (n=918)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age (years)</td>
<td>23.1 ± 3.68</td>
<td>27.8 ± 4.78</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>40.2 ± 1.20</td>
<td>40.2 ± 1.24</td>
</tr>
<tr>
<td>Initial Bishop Score</td>
<td>2.9±1.2</td>
<td>3.1±1.1</td>
</tr>
<tr>
<td>Induction to Active phase duration (hours)</td>
<td>7.51 ± 6.3</td>
<td>6.81 ± 6.0</td>
</tr>
<tr>
<td>Active phase to Vaginal Delivery duration (hours)</td>
<td>7.73 ± 5.56</td>
<td>5.77 ± 5.03</td>
</tr>
<tr>
<td>Induction to Vaginal Delivery duration (hours)</td>
<td>15.61 ± 7.74</td>
<td>13.46 ± 5.39</td>
</tr>
<tr>
<td>Vaginal Delivery within 24 h</td>
<td>770 (65.7)</td>
<td>689 (75.1)</td>
</tr>
<tr>
<td>Vaginal Delivery within 12 h</td>
<td>292 (24.9)</td>
<td>456 (40.7)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>402 (34.3)</td>
<td>229 (24.9)</td>
</tr>
<tr>
<td>Requiring Oxytocin Augmentation</td>
<td>409 (34.9)</td>
<td>242 (26.4)</td>
</tr>
<tr>
<td>Apgar score &lt; 7 at 5 minutes</td>
<td>17 (1.45)</td>
<td>12 (1.31)</td>
</tr>
<tr>
<td>Requiring NICU</td>
<td>26 (2.22)</td>
<td>19 (2.07)</td>
</tr>
</tbody>
</table>

Table 1: Demographic data and patient characteristics of the study population.
Between the two groups, there was a significant difference regarding the beginning of labor and the duration of active labor. In multiparous patients both periods and as a result, total labor time was shorter than nulliparous patients (p=0.023).

The changes in Bishop Scores of the whole study group were reviewed. Bishop score was improved by 3-4 scores in 90.6% and by 5+ in 8.9% of patients. In 0.4% cases no change was observed. In the nulliparous patient group, the change in Bishop Scores was significantly higher than the multiparous patient group (p=0.034). Table 2 presents the changes in Bishop Scores according to the groups.

During labor, 31.1% of the patients needed oxytocin augmentation and this was 34.9% in the nulliparous and 26.4% in the multiparous groups (p=0.001). The cesarean delivery rate was higher in the nulliparous group (34.3% vs. 24.9%, p=0.002). Induction failure was observed in 2 (0.17%) of nulliparous and in 7 (7.62%) of multiparous patients and these patients were delivered by cesarean delivery. The nulliparous and multiparous patients cesarean delivery indications are shown in Table 3. There was significant difference between the cesarean delivery indications for the nulliparous and multiparous groups (p=0.003). The main indication was fetal distress in both groups. Uterine hyperstimulation and tachysystole were observed in 8.5% of the study population (n=178). The rate of uterine hyperstimulation and tachysystole was not significantly different between the nulliparous and multiparous groups (p=0.78). All these patients’ contractions returned to normal after the insert was pulled out. Five of the inserts were spontaneously displaced from the vagina after 150 to 345 minutes. They were reinserted before active labor started.

Postpartum hemorrhage was observed in 3 (0.26%) and 4 (0.44%) patients in nulliparous and multiparous groups, respectively and were treated medically. There was one patient in each group who needed hysterectomy as they were unresponsive to conservative management and arterial ligation surgery. There were no maternal deaths. Additionally, no maternal side effects (nausea, vomiting, fever and diarrhea) were reported in any patient. One-minute Apgar scores were below 7, in 17 (1.45%) nulliparous and in 12 (1.31%) multiparous patients and these patients were delivered by cesarean delivery. The nulliparous and multiparous patients cesarean delivery indications are shown in Table 3. There was significant difference between the cesarean delivery indications for the nulliparous and multiparous groups (p=0.003). The main indication was fetal distress in both groups. Uterine hyperstimulation and tachysystole were observed in 8.5% of the study population (n=178). The rate of uterine hyperstimulation and tachysystole was not significantly different between the nulliparous and multiparous groups (p=0.78). All these patients’ contractions returned to normal after the insert was pulled out. Five of the inserts were spontaneously displaced from the vagina after 150 to 345 minutes. They were reinserted before active labor started.

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**Table 2:** Parity and Bishop score changes.

<table>
<thead>
<tr>
<th></th>
<th>Bishop Score</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-4</td>
<td>5+</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>N</td>
<td>1097</td>
</tr>
<tr>
<td>%</td>
<td>93.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Multiparous</td>
<td>N</td>
<td>797</td>
</tr>
<tr>
<td>%</td>
<td>86.8</td>
<td>12.4</td>
</tr>
<tr>
<td>Total</td>
<td>N</td>
<td>1894</td>
</tr>
<tr>
<td>%</td>
<td>90.6</td>
<td>8.9</td>
</tr>
</tbody>
</table>

**Table 3:** Cesarean delivery indications.

<table>
<thead>
<tr>
<th></th>
<th>Fetal Distress</th>
<th>Cephalopelvic Disproportion</th>
<th>Failure to progress during labor</th>
<th>Failure of Induction</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td>N</td>
<td>252</td>
<td>81</td>
<td>63</td>
<td>2</td>
</tr>
<tr>
<td>%</td>
<td>63.3</td>
<td>20.4</td>
<td>15.8</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Multiparous</td>
<td>N</td>
<td>163</td>
<td>23</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>%</td>
<td>71.2</td>
<td>10</td>
<td>15.7</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>N</td>
<td>415</td>
<td>104</td>
<td>99</td>
<td>9</td>
</tr>
<tr>
<td>%</td>
<td>66.2</td>
<td>16.6</td>
<td>15.8</td>
<td>1.4</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

The results of this study showed that multiparous patients delivered earlier than nulliparous patients after dinoprostone insertion. Also, multiparous patients required less oxytocin augmentation and cesarean delivery rates were lower when compared with the nulliparous group. However, as expected, the change in Bishop Scores was higher in nulliparous group.

There are many studies in the literature addressing the effect of dinoprostone as a cervical ripening and labor induction agent and the findings demonstrated that cervical ripening with dinoprostone slow-release vaginal insert was associated with a high rate of women entering active labor [9,11-13,21-23]. But most of these studies did not evaluate the effect of parity on the success of labor induction with dinoprostone. In this sense, our study is the largest study up to date that analyzed the efficacy of dinoprostone insert use for cervical ripening and labor success in nulliparous and multiparous patient groups separately.

Two studies reported similar results. Witter and colleagues [24] found out that, labor time was shorter in multiparous than nulliparous, cesarean delivery rate was lower in multiparous and changes in Bishop scores were better in nulliparous. Marconi and colleagues [25] compared nulliparous and multiparous patients according to the vaginal delivery rates within 24 hours and they found no statistically significant difference. But the number of patients in this study, as they stated out, was inadequate to reach a definitive conclusion.

Effects of dinoprostone and derivatives on cesarean delivery rates are controversial. In literature there are different points of views. The results of a meta-analysis [6,9,10,16-18,25,26] found that dinoprostone vaginal insert didn’t affect cesarean delivery rates when compared with other prostaglandins. Sanches-Ramos, Hannah and Marconi [1,2,27,28] reported that cesarean delivery rates were lower in patients where a dinoprostone vaginal insert had been used for labor induction. However Cammu and Yeast [29,30] founded just the opposite. We believe this confusion resulted from the differences in the parity, gestational age and indications of labor induction for the patients included in the study groups. All of our patients were high-risk pregnancies who underwent labor induction. We therefore need to compare the cesarean delivery rates of our study (30.1%) with the general cesarean delivery rates of our high-risk pregnancy clinic during the same time period. The comparison indicates that induction with dinoprostone vaginal insert in high-risk patients does not cause a significant increase in cesarean delivery rates. In our study, we also found out that cesarean delivery rates in nulliparous patients were higher than multiparous patients. Similar to our result, Cammu and colleagues, in their study in 2002 [29] found increased cesarean delivery rates in elective labor induction used for postdate and nulliparous patients with unfavorable cervix. Considering the good performance of dinoprostone slow-release vaginal insert, the choice toward elective induction of labor in high risk pregnancies seems to be certainly facilitated, in both nulliparous and multiparous patients with an unfavorable cervix.

Uterine hyperstimulation and tachysystole occurred in 6.7% patients in our study. This result is similar to the rate of 5-15% mentioned the previous studies in literature [18,24,31,32]. Nulliparous and multiparous patients were no different with regard to hyperstimulation and tachysystole rates. Smith and colleagues [33] found a higher incidence of uterine hyperstimulation in nulliparous patients. The normalization of uterine contractions mostly without any FHR abnormality, shortly after removal of dinoprostone vaginal insert as seen in our study was reported in all these studies [9,10,16,17].
There was no statistically significant difference between nulliparous and multiparous patients regarding maternal and fetal morbidity and mortality. Previously in 2006, we reported 3 maternal deaths [19] after labor induction with dinoprostone vaginal insert. In this report, we have discussed the increased probability of disseminated intravascular coagulation and amniotic fluid emboli in dinoprostone vaginal insert used patients for labor induction. Also we have mentioned that, maternal age (≥ 35 years old) and parity (≥ 3 deliveries) were important factors affecting maternal morbidity; so one should be cautious when considering dinoprostone for these patients. Of note, after these maternal mortalities, we have changed our induction of labor policy and restricted the use of dinoprostone for patients < 35 years old and low parity (≤ 2) and after that change we did not have any maternal mortality among 918 multiparous patients. Although low dose PGE2 was found to be a safe and efficient method of induction of labor in grand multiparous and great-grand multiparous women [34] and also in grand multiparous women with previous cesarean delivery [35], the low dose vaginal tablet form of PGE2 is different than vaginal insert form. These two forms of PGE2 are comparable for uterine hyperstimulation side effect, though, they may have different pharmacokinetics hence vaginal insert form achieves cervical ripening and subsequently delivery over a shorter time period than PGE2 tablets [36].

In conclusion, the dinoprostone slow-release vaginal insert seems to be easy to use, effective and safe for the mother's and fetus' health, in both nulliparous and multiparous patients < 35 years old and with low parity (≤ 2). Vaginal delivery occurs in a shorter duration in selected multiparous patients than nulliparous patients together with less need for oxytocin augmentation as well as lower cesarean delivery rates.

References

