

Labor induction in term nulliparous women with premature rupture of membranes: oxytocin versus dinoprostone

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Abstract

Introduction: Premature rupture of the membranes (PROM) refers to rupture of the fetal membranes prior to the onset of regular uterine contractions. Premature rupture of the membranes continues to be one of the most vexing issues of obstetrics due to increased maternal and fetal morbidity and mortality. Many studies have focused on how management should be in these cases. The purpose of this study was to investigate whether dinoprostone (PGE₂ analogue) administration is necessary for cervical ripening and labor induction in term women with premature rupture of membranes (PROM) and to compare maternal and neonatal outcomes between oxytocin usage and dinoprostone usage in PROM.

Material and methods: A total of 224 nulliparous singleton pregnant women at term, with PROM \geq 12 h, vertex presentations, no prior uterine surgery, reactive non-stress test and Bishop scores \leq 6 (unfavorable cervixes) were reviewed. Participants were divided into two groups as oxytocin and dinoprostone groups. The primary outcome was vaginal delivery within 24 h.

Results: The women in the oxytocin group were significantly younger than in the dinoprostone group (22.85 \pm 4.10 years vs. 25.99 \pm 4.94 years; $p = 0.001$). There were significant differences in vaginal delivery rates within 24 h. It was 72 of 112 (64.3%) vs. 53 of 112 (47.3%), $p = 0.023$ for oxytocin and dinoprostone groups, respectively.

Conclusions: Vaginal dinoprostone appears to be a relatively inefficient method of inducing labor compared with oxytocin in term pregnancies with PROM and unfavorable cervixes. However, dinoprostone may maintain uterine contractions as effectively as oxytocin once uterine contractions are established.

Key words: dinoprostone, induction of labor, oxytocin, prostaglandin E₂, premature rupture of the membranes.

Introduction

Premature rupture of the membranes (PROM) refers to rupture of the fetal membranes prior to the onset of regular uterine contractions [1]. Premature rupture of the membranes continues to be one of the most vexing issues of obstetrics due to increased maternal and fetal morbidity and mortality. Many studies have focused on how management should be in these cases. The major question regarding the management of patients with PROM is whether to allow them to enter labor spontaneously or to induce labor. A 2017 systematic review of 23 randomized trials

of women with PROM at ≥ 37 weeks of gestation that compared pregnancy outcome of planned early intervention versus expectant management found that patients benefitted from induction of labor compared with expectant management [2]. For women who are not contraindicated for labor and vaginal delivery, there is no consensus on the method of labor induction. Meta-analyses of randomized trials have not demonstrated a clear benefit from initial use of any prostaglandin other than oxytocin in women with PROM, including those with unfavorable cervixes [3, 4]; however, data for the latter subgroup are limited. Recent guidance support the use of oxytocin as the first-line labor induction method in PROM [5]. Prostaglandin E₂ (PGE₂) vaginal inserts have been shown to be safe and efficacious in promoting cervical ripening in women with post-term pregnancies and low Bishop scores. However, there are insufficient data related to the efficacy and safety of PGE₂ in term pregnancies complicated with PROM. Only a few small trials have evaluated pre-induction cervical ripening in women with PROM and an unfavorable cervix [6, 7]. Nulliparous and unfavorable cervixes needing labor induction remain a clinical challenge.

The objective of this study was to investigate whether dinoprostone (PGE₂ analogue) administration is necessary for cervical ripening and labor induction in women with PROM and to compare maternal and neonatal outcomes between those women who were induced with oxytocin and dinoprostone.

Material and methods

The study started after approval of the ethics committee of our hospital. A total of 224 nulliparous singleton pregnant women at term, with PROM ≥ 12 h, vertex presentations, and Bishop scores ≤ 6 (unfavorable cervixes) were reviewed. All subjects gave written informed consent. Patients with regular uterine contraction, ultrasonographically calculated fetal weight over 4500 g, placenta/vasa previa or unexplained vaginal bleeding, past uterine surgeon, prolapsed umbilical cord, signs of chorioamnionitis, and contraindications for prostaglandin or oxytocin administration (i.e. heart disease, glaucoma, bronchial asthma, severe renal insufficiency) were exclusion criteria.

Subjects were divided into two groups: group 1, labor induction with oxytocin ($n = 112$); group 2, labor induction with the dinoprostone vaginal slow release system ($n = 112$). The cases in both protocol groups were compared in terms of the following parameters: age, maternal weight, maternal body mass index (BMI), anemia and other antenatal risk factors, initial Bishop score, time between onset of treatment and active phase, time

between onset of treatment and delivery, change in Bishop score in the first 12 h, mean blood loss in labor, intrapartum fever, fetal tachycardia, uterine hypertonicity, uterine tachysystole, uterine hyperstimulation, birth weight, meconium-stained amnion in labor, fetal sex, first minute Apgar score, fifth minute Apgar score, newborn intensive care need, indication for cesarean delivery.

In group 1, oxytocin (Synpitan forte 5 U, Deva, Turkey) was prepared as 10 U of oxytocin/500 ml 5% dextrose. Induction was started at 4 mU/min and increased by 4 mU/min every 15 min to a maximum of 32 mU/min [8]. In group 2 a 10 mg dinoprostone containing vaginal pessary slow-release system (Propess, Vitalis) was placed digitally in the posterior fornix of the vagina according to the manufacturer's guidelines. The Propess insert was left in situ for 12 h; active labor was determined when cervical dilatation was 4 cm. The Bishop score was assessed and documented every hour by the same clinician. Not achieving active labor despite 12 h of continuous treatment with the Propess insert was considered as induction failure. To avoid bias and confusion during the interpretation of data, no other labor induction methods were used, and for these cases, "failed induction" was reported as the indication for cesarean delivery. The usual prophylactic regimen was an initial dose of 2 g of ampicillin intravenously followed by 1 g of ampicillin intravenously every 4 h until delivery.

The primary outcome was percentage of vaginal deliveries within 24 h. Secondary outcomes were induction-to-delivery interval, mode of delivery, time to complete dilatation, uterine hyperstimulation, change in Bishop score at 12 h, meconium-stained amniotic fluid, estimated intrapartum blood loss, maternal fever, and neonatal outcomes such as neonatal admission for special care and Apgar score.

Statistical analysis

SPSS 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) was used to analyze the data. $P < 0.05$ and $p < 0.01$ were taken as significance levels. For discrete and continuous variables, descriptive statistics (mean, standard deviation, number and percentile) were used. In addition, the homogeneity of the variances, which is one of the prerequisites of parametric tests, was checked by Levene's test. The assumption of normality was tested via the Shapiro-Wilk test. To compare the differences between the groups, Student's t test was used when the parametric test prerequisites were fulfilled, and the Mann-Whitney U test was used when such prerequisites were not fulfilled. Categorical data were analyzed using Fisher's exact test and

the χ^2 test. In cases in which the expected counts for inclusion were not met in less than 20% of the cells, the Monte Carlo simulation method was used and the values were determined.

Results

Demographic characteristics such as age, gestational week, BMI, parity and antenatal risk factors are presented in Table I. The women in the oxytocin group were younger than the women in the dinoprostone group. (22.85 \pm 4.10 vs. 25.99 \pm 4.94 years; $p = 0.001$). There were no significant differences between the two groups in gestational week, maternal weight and antenatal risk factors except anemia, while there was a significant difference in maternal age and BMI. Pre-induction Bishop scores were similar in both groups. There were significant differences in the predefined primary outcomes including vaginal delivery rates within 24 h; they were 72 of 112 (64.3%) vs. 53 of 112 (47.3%), $p = 0.023$ for oxytocin and dinoprostone respectively. There were also significant difference in secondary outcomes. Labor induction to delivery interval was longer in the dinoprostone group, but this difference was not statistically significant ($p = 0.519$). The time from rupture of membranes to initiation of oxytocin and dinoprostone was not significantly different between the groups (12.5 \pm 1.15 h vs. 12.83 \pm 2.30 h, $p = 0.078$). There was no significant difference in the incidence of fetal heart rate abnormalities, tachysystole, or intrapartum fever between two groups, but estimated blood loss was significantly higher in the dinoprostone group than the oxytocin group (533.39 \pm 183.71 ml vs. 454.64 \pm 189.63 ml, $p = 0.002$). Cesarean delivery rates were significantly higher in the dinoprostone group than the oxytocin group (52.7% vs. 35.7%, $p = 0.015$). Labor

contractility was established slightly earlier in the oxytocin group than in the dinoprostone group of patients. For those treated with dinoprostone, mean uterine activity reached a peak within 6–8 h after the medication. In the oxytocin group, the mean uterine activity rose steadily and reached a peak at 2–3 h after treatment. Continuous infusion of oxytocin was required until delivery. One hour after the start of treatment the mean frequency of contractions per 10 min was slightly lower in the dinoprostone treated group of patients (oxytocin 3.2, PGE2 2.2 contractions per 10 min). After approximately 4 h a steady state had been reached, with a mean frequency of contractions per 10 min in the oxytocin group of 4.5 and in the dinoprostone group of 5.2. Also the intensity of contractions increased more rapidly in the group of patients induced by oxytocin. Atypical contractility patterns were significantly more common in dinoprostone induced labor than in labor induced by oxytocin. Uterine hyperstimulation was observed more often in patients treated with dinoprostone (22.3% vs. 7.14%, $p = 0.001$). Uterine hyperactivity was similar between two groups. Clinical and neonatal outcomes of both groups are summarized in Table II.

Discussion

Premature rupture of the membranes continues to be one of the most vexing issues of obstetrics due to increased maternal and fetal morbidity and mortality. Many studies have been conducted on how management should be in these cases, and immediate delivery of the fetus, especially over the 36th gestational week, is the recommended approach. It can be expected for a while in other cases, but this waiting period is also limited to 12 h in many centers [1]. In the case of prolonged

Table I. Demographic characteristics of study population

Parameter	Oxytocin (n = 112)	Dinoprostone (n = 112)	P-value
Age [years]	22.85 \pm 4.10	25.99 \pm 4.94	0.001**
Maternal weight [kg]	69.5 \pm 11.15	70.15 \pm 6.12	0.588
Maternal BMI [kg/m ²]	28.57 \pm 2.83	27.04 \pm 1.96	0.001**
Gestational age [week]	38.85 \pm 1.19	39.10 \pm 1.33	0.140
Parity	1 (0)	1 (0)	–
Antenatal risk factors:			
None	84 (47.2%)	94 (52.8%)	
Gestational diabetes	0	0	0.003**
Anemia	28 (68.3%)	13 (31.7%)	
Hypertension	0	5 (100%)	

* $p < 0.05$, ** $p < 0.01$.

Table II. Clinical and neonatal outcomes of the study population

Parameter	Oxytocin (n = 112)	Dinoprostone (n = 112)	P-value
Pre-induction Bishop score	1.64 ±1.45	1.76 ±1.40	0.098
Bishop score change in 12 h	5.21 ±2.1	5.66 ±3.53	0.244
PROM to induction interval [h]	12.5 ±1.15	12.83 ±2.30	0.078
Induction to active labor onset [h]	5.69 ±5.39	9.45 ±4.25	0.001**
Induction to delivery [h]	12.5 ±7.15	13.03 ±5.07	0.519
Vaginal delivery	72 (64.3%)	53 (47.3%)	0.023*
Cesarean delivery	40 (35.7%)	59 (52.7%)	0.015*
Indication for cesarean delivery:			
Fetal distress	12 (10.7%)	17 (15.2%)	
Cephalopelvic disproportion	20 (17.9%)	10 (8.9%)	0.001**
Failed induction	8 (7.1%)	32 (28.6%)	
Mean Apgar score at 1 min	7.92 ±0.45	7.87 ±0.42	0.367
Mean Apgar score at 5 min	8.92 ±0.45	8.91 ±0.38	0.875
Mean birth weight [g]	3140 ±383.50	3003.97 ±487.15	0.021*
Fetal sex:			
Male	68 (60.7%)	61 (54.5%)	0.417
Female	44 (39.3%)	51 (45.5%)	
Meconium-stained liquor in labor	1.10 ±0.31	1.22 ±0.41	0.019*
Neonatal admission for special care	16 (14.3%)	8 (7.14%)	0.129
Maternal fever	32 (28.6%)	42 (37.5%)	0.155
Delivery blood loss [ml]	454.64 ±189.63	533.39 ±183.71	0.002*
Uterine hypertonicity	8 (7.14%)	9 (8%)	0.801
Uterine tachysystole	12 (10.7%)	17 (15.2%)	0.320
Uterine hyperstimulation	8 (7.14%)	25 (22.3%)	0.001**

* $p < 0.05$, ** $p < 0.01$.

PROM, the obstetric balance has been proven to be impaired in the negative direction [9]. It is suggested that labor should be induced when there are no spontaneous uterine contractions. The purpose of induction is to reduce the risk of operative delivery and fetal complications. The most preferred approach for induction is oxytocin infusion, but several studies have reported that using oxytocin without cervical ripening increases cesarean rates in such cases with an unfavorable cervix [10]. Unfortunately, the cases of PROM are often accompanied by a low cervical score (≤ 4 according to Bishop score) [11]. It has been proposed that PGE₁ and PGE₂ can be administered vaginally to stimulate cervical ripening in term pregnancies with low Bishop scores or complicated with PROM [1, 3].

Prostaglandin E₂ is an efficacious agent that shortens the time from induction to delivery, im-

proves success rates and reduces morbidity associated with labor induction [12]. Prostaglandin E₂ was first used by Calder and Embray in 1973 for induction of labor [13]. Initially, the controlled release dinoprostone ovule (Propress) was reported to be contraindicated in patients with PROM, but it has been recommended for use in patients with PROM since 2006. The number of studies that have investigated the efficacy and safety of dinoprostone ovules in PROM is limited. In our study, it was found that the use of dinoprostone ovule (Propress) vaginally was effective in providing cervical ripening as well as in maintaining uterine contractions required for vaginal birth and without the need for oxytocin. There are some reports showing that this agent significantly shortens the latent phase of delivery. In the present study, labor induction to active labor interval and time from

induction to delivery were found to be longer in the dinoprostone compared to the oxytocin group ($p = 0.001$, $p = 0.519$, respectively). In one study, in term women with PROM oxytocin use shortened the induction to active labor onset compared to dinoprostone. On the other hand, another study comparing dinoprostone with expectant management in the treatment of PROM at term found that the time of dilatation was shorter in the dinoprostone group [14, 15].

We also found that dinoprostone affects the rate of cesarean delivery or indications. In this context, the rates of cesarean delivery for the dinoprostone and oxytocin groups were 52.7% and 35.7%, respectively. In a study conducted by Larrañaga-Azcárate *et al.*, the rate of cesarean section was found to be significantly lower in patients treated with controlled-release dinoprostone ovules compared to the spontaneously monitored group (9.3% vs. 17.6%, $p = 0.04$) [14]. However, we observed higher cesarean rates in patients treated with dinoprostone than those treated with oxytocin ($p = 0.015$). This may be related to a greater number of active phase labor abnormalities in the dinoprostone group. In the dinoprostone group, cesarean deliveries were performed for failed induction, fetal distress and cephalopelvic disproportion with the rate of 28.6%, 15.2%, 8.9% respectively. One of the factors that might affect the cesarean birth rate is fetal birth weight; however, it was found to be 3140 ± 383.50 g in the oxytocin group and 3003.97 ± 487.15 g in the dinoprostone group ($p = 0.021$).

In a study by Ramsey *et al.*, it was found that the fetal cardiotocographic abnormalities associated with PGE2 were less frequent and less severe than those associated with PGE1 [16]. However, the present study demonstrated that the changes in cardiotocographic measurements were similar in the PGE 2 and oxytocin groups, while uterine hyperstimulation was observed more often in patients treated with dinoprostone (22.3% vs. 7.14%, $p = 0.001$).

We used meconium-stained amniotic fluid and 1st and 5th min Apgar score data to evaluate fetal asphyxia. While there was no difference in 1st and 5th min Apgar scores between groups, meconium-stained amniotic fluid was observed more frequently in the dinoprostone group compared to the oxytocin group (22.3% vs. 10.7%, $p = 0.019$). Abdelazim *et al.* compared patients who received antenatal oxytocin and those who underwent elective cesarean section without oxytocin; they reported that the fetal outcomes of patients who underwent spontaneous labor or those who received oxytocin before cesarean section were better than those of patients who did not receive oxytocin before cesarean section [17].

The major limitation of this study is its retrospective design. Patients were allocated to a par-

ticular treatment (dinoprostone or oxytocin) by their attending obstetrician, rather than being randomly assigned. Because an individual clinician's management style affects their choice of induction agent as well as the decision to proceed to cesarean delivery, this may have introduced selection bias and influenced our results. However, at our institution most obstetricians practice in large groups that share labor and delivery coverage. This more closely resembles a hospitalist model and reduces the impact of any one obstetrician's management style on our results.

In conclusion, vaginal dinoprostone appears to be a relatively inefficient method of inducing labor compared with oxytocin in term pregnancies with PROM and unfavorable cervixes. However, PGE₂ may maintain uterine contractions as effectively as oxytocin once uterine contractions are established.

Conflict of interest

The authors declare no conflict of interest.

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