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A Study to Compare the Fetomaternal Outcomes of Dinoprostone Gel Administration for Induction of Labor Across Posterior Fornix versus Intracervical Routes

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ABSTRACT

Objectives: Although Dinoprostone (synthetic prostaglandin) gel as a cervical ripening agent for induction of labour has been extensively studied but there has been a paucity in the current literature, employing its use through the intracervical and posterior routes, especially in the Indian setting. The authors aimed to study and compare the fetomaternal outcomes with the use of 0.5 mg dinoprostone gel for induction of labour across intracervical and posterior fornix routes.

Materials and Methods: An observational study was conducted at a tertiary care hospital in Western India. Pregnant women presenting in the Obstetrics and Gynecology department of the institute were recruited in the study (n = 120). They were allowed to choose between the two groups, posterior fornix (PF; n = 60) and intracervical (IC; n = 60) after taking a valid written and inform consent. Primary outcomes were to measure the rates of normal vaginal delivery. Secondary outcomes that were studied included induction-to-delivery interval, rates of operative vaginal deliveries/ need for emergency caesarean section and incidence of maternal complications and adverse fetal outcomes were compared along the two routes of dinoprostone administration.

Results: Both the groups were homogenous in terms of maternal age, gestational age, or other maternal characteristics. Induction of labor was successful to result in a normal vaginal delivery in 45 and 42 women respectively in IC and PF groups. Participants undergoing emergency cesarean deliveries were 15 in IC and 18 in PF groups, respectively (differences not statistically significant).

Conclusion: Our study revealed that either of the routes can be successfully utilized for induction of labour with equal probability of successful vaginal delivery. Dinoprostone gel being relatively cheaper and more widely available can still serve as a potential cervical ripening agent.

Keywords: cervical ripening, dinoprostone, labor, induced, pregnancy, tertiary care centers.

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Introduction

Induction of labor (IOL) is the process whereby the uterus is stimulated by artificial means to initiate labor[1]. Dinoprostone (PGE2) used as a cervical ripening agent is commercially available in various formulations[2,3]. In recent practice, dinoprostone pessaries are the preferred mode of dinoprostone delivery for IOL[4]. However, the availability of dinoprostone gel maintains its status of a lucrative cervical ripening agent[5,6]. Additionally, there is a paucity in recent literature exploring the gel formulation. Fetomaternal outcomes, success of IOL, rate of uncomplicated vaginal deliveries with least number of adverse effects shall govern the route of dinoprostone gel administration[3,7,8]. Previous studies have compared the two routes for the mentioned outcomes; but there is no consensus of evidence on the preferred route of administration[9-14]. The aim of our study was to compare the effects of the two routes of dinoprostone gel instillation on fetomaternal outcomes.

Materials and Methods

Study design: A quasi-experimental study was conducted over a period of 10 months from February 2016 to November 2016 at a tertiary care hospital in India. Participants were recruited from the out patient department (OPD) and emergency room fulfilling the following inclusion criteria.

Inclusion criteria: Gestational age: ≥ 37 weeks and ≤ 40 weeks and six days, intact membranes, singleton pregnancy with vertex presentation, reassuring admission NST, modified Bishop's score ≤ 4.

Exclusion criteria: Gestational age beyond 41 weeks, history of prior uterine surgery, prelabor rupture of membranes, multiple gestations, maternal high-risk factors such as contracted pelvis, gestational diabetes mellitus (DM), hepatic or cardiac conditions, asthma and moderate or severe anaemia, known fetal anomaly and allergy to prostaglandins.

Sample size calculation:

The number of labour inductions done in the institute were determined for a month (prevalence) and the outcome in terms of normal vaginal deliveries (primary outcome) was calculated. Thirty patients were included, where 14 patients were in the (p1) group and 16 patients in the PF (p2) group. Out of the 14 patients in the p1 group, nine delivered vaginally and of the 16 patients in the p2 group, 11 patients delivered vaginally. Hence, the sample size of the index study performed was then calculated as follows:

$$N = \frac{\sqrt{[Z\alpha\sqrt{2p'q'} + Z_\beta \sqrt{p1q1+p2q2)}]}}{(p1-p2)}$$

Where p' = (p1+p2)/2 and q'=100-p'

Substituting the values of $Z\alpha = 1.96$(level of statistical significance) and $Z_\beta = 0.907$ (power of the study), p1 = 9, p2 = 11, q1 = 100-9 = 91, q2 = 100-11 = 89, p' = 10, q' = 90

Sample size, (each group) n = 60 in each group and total number of patients in the study were 120.

We also conducted a post-hoc power analysis of the number of participants included in the study using G*power software[15]. Assuming a low effect size of 0.3 and type I error probability of 0.5, and degree of freedom of one, the power of the study was computed to be 0.907.

Patients fulfilling the criteria were allowed to choose the route of administration of dinoprostone gel after taking a written and informed consent (English/ Hindi/ Marathi) with 1:1 distribution (60 participants in each group). There was no blinding during the study.

Dinoprostone gel was administered either through PF or IC routes with 0.5 mg gel. During the study period, the 2 mg PF gel was unavailable in India, and hence, the available formulation of IC gel (Cerviprime, Astra IDL, Bangalore, India) was administered through both the routes[14]. First dose of gel (at 0.5 mg) was instilled either IC or PF under all aseptic conditions. The same dose was re-instilled along the same route after an interval of six hours as per the Bishop's score. Induction of labor was considered "failed" in the absence of initiation of uterine contractions post 12 hours of instillation of 3rd

dose of dinoprostone gel.

Post-gel administration monitoring: Continuous Electronic fetal and tocodynamometric monitoring was performed for two hours[16] followed by intermittent auscultation for fetal heart rate along with manual observation of contractions. Successful induction was considered as occurrence of two contractions every 15 minutes along with cervical dilatation of 3 cm.

Fetal monitoring: Fetal hypoxia and/or acidemia was assessed in terms of non-reassuring fetal status, according to the National Institute for Health and Care Excellence (NICE) guidelines[17].

Uterine hyperstimulation was defined as more than five contractions in 10 minutes, measured for 30 minutes and/or each lasting for more than 2 minutes[18] for which preparations for medical management were kept ready (Injection terbutaline 0.25 mg).

Primary outcome was to measure the rates of normal vaginal delivery. Secondary outcomes that were studied included induction-to-delivery interval, rates of operative vaginal deliveries/ need for emergency caesarean section and incidence of maternal complications such as prolonged labour, postpartum hemorrhage, need of blood transfusion, febrile morbidity and urinary retention as well as adverse fetal outcomes such as neonatal asphyxia were compared along the two routes of dinoprostone administration. The indications for the emergency caesarean sections were also noted.

Statistical analysis:

All the data were analysed using Statistical Package for the Social Science (SPSS; SSS Inc., Chicago, IL, USA) version 21. Continuous variables were expressed in terms of mean and standard deviation and discrete variables were represented in frequencies and percentages. T-test and Mann-Whitney U test were used for comparison of normally and non-normally distributed continuous variables. Pearson's Chi square and Fischer's exact tests were used to compare categorical variables.

Results

A total of 120 participants were recruited in the study. Demographic characteristics and pre-induction observations of the participants were noted as in Table 1. The differences in maternal age, gestational age and mean Bishop's score (MBS) between the two groups were non-significant.

Table 1. Characteristics of the sample and indications for induction of labour (n = 120).

Characteristic of the sample	Intracervical group (IC) (n = 60)	Posterior fornix group (PF) (n = 60)	p value
Maternal age (years)	24.5 ± 3.6	25.4 ± 4.1	0.476
Gestational age (weeks)	39.9 ± 1.08	39.6 ± 1.21	0.197
Parity	0.7 ± 0.02	0.8 ± 0.02	0.220
Weight (kg)	51.2 ± 5.2	52.4 ± 5.07	0.351
Height (cm)	151.4 ± 5.3	151.4 ± 5.9	0.756
Pre-delivery Haemoglobin (g%)	11.03 ± 1.18	10.95 ± 1.25	0.801
Modified Bishop's score (on admission)	1.66 ± 0.92	1.9 ± 0.87	0.208
Modified Bishop's score (after 1st administration)	4.12 ± 0.73	4.38 ± 0.71	0.140
Indication for IOL			
Post-dates (n, %)	30 (50%)	34 (56.66%)	0.065
Suspicion of fetal growth restriction (n, %)	9 (15%)	6 (10%)	0.092
Severe Oligohydramnios (n, %)	8 (13.33%)	10 (16.66%)	0.378
Others (n, %)#	13 (20%)	10 (16.66%)	0.081

Data presented as mean ± standard deviation or n (%)
indications included intrahepatic cholestasis of pregnancy, decreased fetal movements, Rh negative pregnancy at 40 weeks
IOL: Induction of labor

Post-dated pregnancy occurring in 50.0% (n = 30) and 56.66% (n = 34) of the participants in IC and PF groups, respectively, was the most common indication for IOL; followed by suspicious fetal growth (in 9 participants (15%) in IC and 6 in PF (10%) groups, each) and others. Induction of labor was successful in 45 participants (75%) and 42 (70%) participants in the IC and PF groups, respectively. Induction to delivery interval was 14.4 ± 3.6 hours in IC group and 14.6±3.6 hours in PF group. Spontaneous vaginal deliveries were observed in 42 participants (93.3%) of IC group and 34 participants (80.95%) of PF group (Table 2).

Table 2. The fetomaternal outcomes of IOL in the two groups (n = 120).

Outcome of IOL	Intracervical group (IC) (n = 60)	Post fornix group (PF) (n = 60)	p value
Mode of delivery			
Spontaneous vaginal delivery	42 (93.33%)	34 (80.95%)	0.125
Operative vaginal delivery	3 (6.66%)	8 (19.04%)	0.079
Emergency cesarean section	15 (25%)	18 (30%)	0.290
Induction to delivery interval (hours)	14.4 ± 3.6	14.6 ± 3.6	0.778
Number of successful inductions of labor	45 (75%)	42 (70%)	0.248
Need for 2nd reinstallation of gel	32 (53.33%)	27 (45%)	0.24
Need for 3rd reinstallation of gel	0	0	
Spontaneous rupture of membranes	12 (20%)	15 (25%)	0.901
Oxytocin augmentation	20 (33.33%)	21 (0.35%)	0.517
Abnormal fetal heart tracings	7 (11.66%)	11 (18.33%)	0.182
Stillbirths	0	0	
Weight of newborns (kg)	2.76 ± 0.29	2.81 ± 0.38	0.294
APGAR Score > 7	56 (93.33%)	57 (95%)	0.231
APGAR Score < 7	4 (6.66%)	3 (5%)	0.871
NICU admissions	4 (6.66%)	3 (5%)	0.609
Vaginal lacerations (traumatic PPH)	2(3.33%)	1(1.66%)	0.790
Atonic PPH	0	4(6.66%)	0.009
Urinary retention	1 (1.66%)	0	0.010
Puerperal pyrexia	1(1.66%)	1(1.66%)	0.290
Maternal mortality	0	0	N/A

Data presented as mean + standard deviation or n (%)
IOL: Induction of labor, NICU: neonatal intensive care units, PPH: postpartum hemorrhage.

Total number of emergency cesarean deliveries required in the study was 33 of total 120 deliveries. Out of which, 15 (25% of total deliveries) were required in IC group and 18 (30% of total deliveries) were required in PF group as noted in Table 3.

In our study, none of the participants experienced hyperstimulation. Majority of the newborns were fullterm with mean weights of 2.76 ± 0.29 kg (IC) and 2.81 ± 0.38 kg (PF) in the two groups (p = 0.29). Amongst those induced for suspicious fetal heart rate (FHR), the birth weights ranged between 1.9 to 2.3 kg. Other fetomaternal outcomes across the two groups are tabulated in Table 3.

Table 3. Indications for emergency cesarean section deliveries in the two groups (n = 33).

Indication for emergency cesarean delivery*	Intracervical group (IC) (n = 15)	Posterior fornix group (PF) (n = 18)	p value
Meconium-stained amniotic fluid with fetal distress	6 (40%)	9 (50%)	0.092
Placental abruption	2 (13.33%)	1 (5.5%)	0.128
Arrest of dilatation in first stage of labor	4 (26.6%)	6 (33.3%)	0.099
Arrest of descent in second stage of labor	3 (20%)	2 (11.1%)	0.267

Data presented as n (%)
*statistical test used was Mann Whitney U test.

Discussion

Induction of labor is a commonly used obstetric intervention aimed to mitigate the possible adverse perinatal outcomes. In this study, the authors have attempted to highlight the differences in the fetomaternal outcomes with the use of 0.5 mg dinoprostone gel through IC and PF routes. This is the first of its kind study from the recently published literature, that mainly have observed the differences using dinoprostone vaginal pessary versus intracervical dinoprostone gel. The two groups did not differ significantly in terms of maternal characteristics. The mean initial MBS at the time of admission was 1.66 ± 0.92 in the IC group and 1.9 ± 0.87 in the PF group ($p > 0.05$). In the study by Perry et al, the mean MBS was 2.5 and 3.0 in IC and PF groups, respectively. Similar to this study, neither the initial scores nor the difference between subsequent scores, assessed within six hours of first dose of PGE2 administration, were statistically significant[19].

Post-datism (53.33% in 120 participants) was the most common indication for IOL in our study. Kemp et al observed post-dates pregnancies to be the second most common in their study (32.9%)[20]. The number of vaginal deliveries in the current study were 45 (75%) in IC group as compared to 42 (70%) in the PF group ($p > 0.05$). This was similar to the study by Grignaffini et al, the PF insertion of dinoprostone lead to 67% successful vaginal deliveries as compared to 66% in the IC route of administration. Thus, indicating that both the routes lead to similar proportion of successful vaginal deliveries[21].

The need for emergency cesarean deliveries across the two groups was also not statistically significant. The most common indications have been failure to progress in the studies of Perry et al and Corrado et al and suspected uterine rupture in IC route by Irion et al, but none were found in the current study[22,23].

The induction-to-delivery interval showed no statistically significance between the two groups similar to findings by Corrado et al[22] but contrary to the findings of Grignaffini et al, where they found induction-to-delivery interval to be shorter in IC gel group as compared to slow-release PF insert of dinoprostone (12 h 54 min IC vs 16 h 59 min IV; $p < 0.05$)[21]. This difference could have probably been due to the difference in the sample size included in the latter study.

Of the total successful vaginal deliveries, 71.11% (32 of 45) participants in the IC group and 64.28% (27 of 42) participants in the PF group required re-instillation of gel, the difference not statistically significant.

Rates of instrumental deliveries increased with the use of dinoprostone induction of labour. Instrumentation was required for three deliveries in IC group and eight in PF group, whereas oxytocin augmentation was required for 20 deliveries and 21 deliveries in the IC and PF groups, respectively. These findings were also not significant, similar to the previous studies mentioned earlier[20-22]. No statistically significant differences were seen in the rates of rupture of membranes, abnormal FHR tracings, APGAR scores and NICU admissions across the two groups.

In our study, there was a statistically significant

differences noted in the incidence of atonic postpartum hemorrhage and urinary retention across the two groups.

In a systematic review by Boulvain et al on 7,738 participants, it was found that although the IC application of PGE2 was an effective route for IOL, it offered no advantage over PF[24]. The findings of our study supported these earlier findings.

Contrary to our study findings, the observations made by Ekman et al and the recent study by Reinhard et al concluded statistically significant differences showing IC route to be superior of the two routes[25, 26].

Conclusion

In conclusion, overall, the differences in the two routes were found to be statistically insignificant in our study; but the authors would like to draw important conclusions relevant to the current practice. Dinoprostone 0.5 mg could be used through both the routes with similar efficacy (not previously studied), unlike recent studies which have used vaginal dinoprostone pessaries that are not widely available. Moreover, it is evident that there still lies controversy in the two modes of application and most of the studies comparing the effect were conducted in the late 1900s and there is a dearth of current studies in this domain. Dinoprostone gel 0.5 mg being more readily and widely available at a reduced costs suggests that it still serves as a promising the 0.5 mg dinoprostone gel serves as a promising agent for cervical ripening during induction of labour at term for both the routes. The recently popular vaginal dinoprostone pessary 2 mg tablet was not available widely during the study period in India.

The limitation of the study was that the observations and conclusions drawn from the current study, being a quazi-experimental, need to be tested in randomized controlled trials on a larger number of participants.

Potential conflicts of interest

The authors declare no conflicts of interest.

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