

# Comparison between Two Preparations of Dinoprostone (PGE<sub>2</sub>)-pessary and Gel for Induction of Labor at Term

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## ABSTRACT

**Background:** There are multiple inducing agents available—pharmacological and non-pharmacological. The search for an ideal inducing agent continues worldwide. An ideal inducing agent should have less induction interval to delivery time, less side effects such as fetal distress and hyperstimulation, patient safety, economical, and have ease of administration. The two preparations of Dinoprostone (PGE<sub>2</sub>) gel and pessary were compared for efficacy in vaginal delivery, induction delivery interval (IDI), and cost effectiveness.

**Materials and methods:** A prospective observational study was done in 100 patients in a tertiary level teaching hospital from 1 November 2019 to 31 March 2021. A total of 50 patients in group A received 0.5-mg PGE<sub>2</sub> gel and 50 patients in group B had insertion of sustained release 10-mg PGE<sub>2</sub> pessary for induction of delivery at term. The two groups were compared for the rate of vaginal delivery and IDI. Other variables, such as need of augmentation, fetal distress, postpartum haemorrhage (PPH), and neonatal intensive care unit (NICU) admission, were also compared.

**Results:** The rate of vaginal delivery in both groups were similar. Mean induction to vaginal delivery interval was significantly lesser in the Dinoprostone pessary group ( $17.72 \pm 6.81$  hours for PGE<sub>2</sub> pessary group vs  $19.57 \pm 5.46$  hours for PGE<sub>2</sub> gel group); duration of augmentation with Oxytocin was significantly lesser in the pessary group ( $5.68 \pm 4.05$  hours in pessary group vs  $7.41 \pm 3.44$  hours in gel group). There was no significant difference in failed induction, uterine hyperstimulation, fetal distress, PPH, and NICU admission in the two groups.

**Conclusion:** Dinoprostone gel and pessary are similar in rate of vaginal delivery. The IDI and need of oxytocin are less with PGE<sub>2</sub> pessary. Failure rate is same for both PGE<sub>2</sub> pessary and gel. In comparison, no marked superiority of pessary was seen over economical gel preparation.

**Keywords:** Dinoprostone, Inducing agents, Induction of labor, PGE<sub>2</sub> pessary, Prostaglandin.

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## INTRODUCTION

Multiple pharmacological, mechanical, and complementary methods are available to induce labor. Dinoprostone is available as gel and sustained release pessary, both approved by the US food and drug administration (FDA), WHO, drug controller general of India (DCGI) for induction of labor.<sup>1,2</sup> An ideal inducing agent should have less induction interval to delivery time, less side effects like fetal distress and hyperstimulation, patient safety, economical, and have ease of administration. The two preparations of PGE<sub>2</sub> gel, and pessary were compared for efficacy in vaginal delivery, IDI, and cost effectiveness.

## MATERIALS AND METHODS

A prospective, comparative observational study was done in 100 women admitted for induction of labor in a tertiary level teaching hospital from November 2019 to March 2021. Informed written consent was taken from all participants. Ethical clearance was taken from institutional ethical committee for the study. Women with single live pregnancy with vertex presentation, at term with unfavorable Bishop score ( $\leq 6$ ) were included while women presenting with premature rupture of membranes, multiple pregnancy, and previous caesarean section were excluded in the study. Fifty patients admitted for inductions of labor were allocated into each group, using simple randomization. In group A, induction was done with PGE<sub>2</sub> gel (0.5 mg) placed intracervically, 8 hourly, with maximum of 3 doses in 24 hours, till patient goes into labor. If Bishop score became favorable ( $> 6$ ) and contractions were not established, Oxytocin was started after 6 hours of gel insertion. In group B, induction was done with sustained release PGE<sub>2</sub> pessary (10 mg) placed in posterior fornix in vagina pessary was removed in active labor or after 24 hours of

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insertion. If the patient did not go in labor with insert, oxytocin was started. Labor was followed as per the standard protocol. The primary outcome variables compared in the two groups were the mean (IDI) in primi- and multigravida, rate of vaginal delivery in primi- and multigravida and induction failure; the secondary outcome variables compared were the duration of oxytocin infusion, mean time taken by patients to go into active stage of labor in primi- and multigravida, hyperstimulation, fetal distress, incidence of PPH, neonatal Apgar score, and NICU admissions. The failed induction was defined as no improvement in Bishop score in 24 hours of using inducing agent.

## Statistical Analysis

The statistical package for social sciences (SPSS), version 21.0 was applied. Qualitative variables were compared using Chi-squared test/Fisher's exact test, with significant value taken as  $p < 0.05$ .

## RESULTS

### Comparison of Demographic Variables in Two groups

The patients in both groups were comparable in age, parity, gestational age, and Bishop's score at time of induction (Table 1).

### Comparison of Primary Outcome Variables

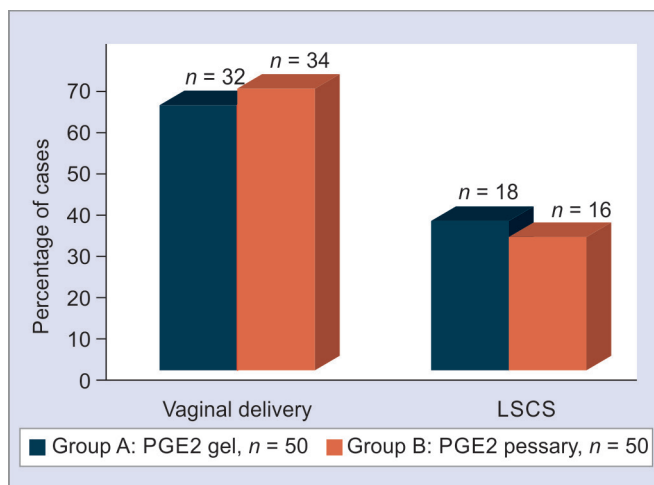
- **Rate of Vaginal delivery:** In group A, 32 patients out of 50 (64%) delivered vaginally (Fig. 1). Out of these 17 (34%) were primigravida and 15 (30%) were multigravida. In group B, 34 patients among 50 (68%) delivered vaginally and out of these, 18 (36%) were primigravida and 16 (32%) were multigravida. There was no significant difference for mode of delivery in both groups value 0.572. No significance was noted when the

parity was considered in comparing vaginal delivery rate in both groups  $p = 0.992$  and  $p = 0.423$  for primigravida and multigravida women, respectively (Fig. 2).

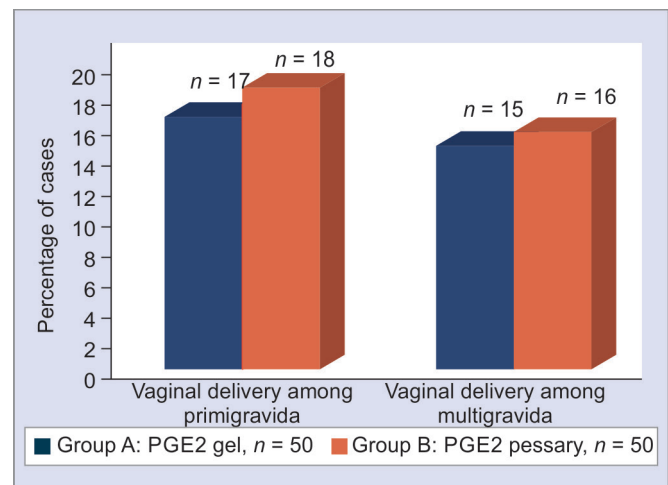
- **Induction to Delivery Interval:** Mean IDI was  $19.57 \pm 5.46$  (range, 10.60–32.40 hours) in group A and  $17.72 \pm 6.81$  (range, 9.4–42.5 hours) in group B. The IDI was seen to be shorter with PGE2 insert in group B. This was of statistical significance with  $p = 0.043$ . However, when the difference was compared in primigravida and multigravida women,  $p$ -value was not significant. The mean IDI was  $21.25 \pm 6.37$  hours in PGE2 gel group while  $19.34 \pm 7.42$  hours in PGE2 pessary group ( $p = 0.287$ ) for primigravida women. For multigravida women, the mean IDI was  $19.08 \pm 6.5$  hours in group A while  $15.68 \pm 4.67$  hours in group B ( $p = 0.062$ ). No statistical difference was noted in IDI in both groups (Fig. 3).

**Table 1:** Comparison of demographic variables in groups A and B

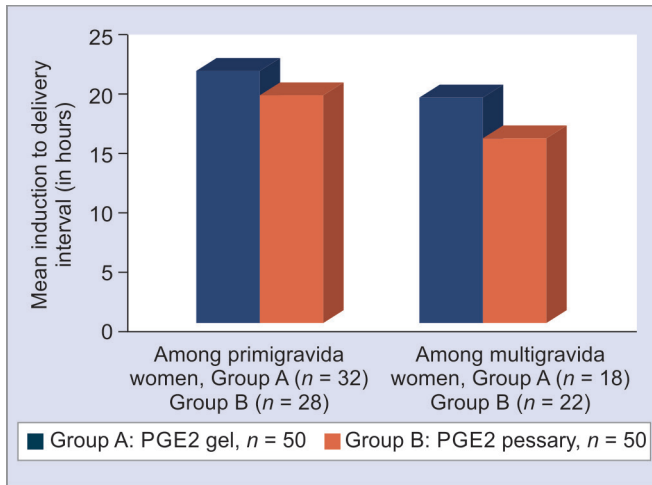
Demographic variable	Group A (PGE2 gel) (n = 50)	Group B (PGE2 pessary) (n = 50)	p
1. Parity			
Primigravida	32 (64%)	28 (56%)	0.414
Multigravida	18 (36%)	22 (44%)	0.324
2. Mean age (in years)			
For primigravida women	$26.84 \pm 4.38$	$27.75 \pm 5.21$	0.467
For multigravida women	$27.33 \pm 4.47$	$26.00 \pm 4.28$	0.343
3. Period of gestation at the time of induction:			
For primigravida women:			
37–38 + 6 weeks	17 (34%)	17 (34%)	1.00
39–40 + 6 weeks	12 (30%)	15 (30%)	0.966
For multigravida women:			
37–38 + 6 weeks	13 (26%)	12 (24%)	0.856
39–40 + 6 weeks	08 (16%)	06 (12%)	0.764
4. Modified Bishop score at time of induction:			
Among primigravida women	$3.50 \pm 2.84$	$3.57 \pm 0.92$	0.755
Among multigravida women	$3.89 \pm 0.68$	$3.41 \pm 1.14$	0.108



**Fig. 1:** Comparison of mode of delivery in two groups



**Fig. 2:** Comparison of vaginal delivery in primigravida and multigravida in two groups



**Fig. 3:** Comparison of IDI for vaginal delivery in primigravida and multigravida women between the two groups

- **Failed Induction:** The rate of induction failure was seen in 5 out of 50 patients (10%) in PGE2 gel group and in 3 patients out of 50 (6%) in pessary group ( $p = 0.249$ ). No statistical difference was seen in the induction failure in both groups. The failed induction patients were taken for caesarean section.

### Comparison of Secondary Outcomes

- **Time Taken to Reach Active Phase:** PGE2 and PGE2 pessary, the time was for primigravida patients ( $13.38 \pm 4.35$  hours vs  $14.00 \pm 7.01$  hours,  $p = 0.735$ ) and for multigravida patients ( $13.00 \pm 6.38$  hours vs  $12.23 \pm 5.26$  hours). No statistical difference was seen in two groups ( $p = 0.691$ ).
- **Need of Oxytocin:** Duration of oxytocin for patients who delivered vaginally was more in group A than in pessary group. In group A, the mean duration of oxytocin infusion was  $7.41 \pm 3.44$  hours but in group B, it was significantly less  $5.68 \pm 4.05$  hours with  $p = 0.012$ . When the difference was studied in parity,  $p$ -value was not significant for primigravida women ( $10.64 \pm 6.71$  hours vs  $10.17 \pm 6.34$  hours,  $p = 0.782$ ), while it was highly significant for multigravida women,  $p = 0.009$  ( $8.76 \pm 5.28$  hours in group A vs  $5.11 \pm 3.03$  hours in group B). All patients in group A required oxytocin for vaginal delivery whereas 15 patients in group B delivered within 24 hours of pessary insert (30%) alone without needing oxytocin.
- **Fetal Distress, Hyperstimulation, PPH, Apgar score, NICU admission:** No statistical difference was seen in both groups. No cases of hyperstimulation were observed in gel group. Hyperstimulation occurred in only one patient in Dinoprostone pessary group in our study. Postpartum hemorrhage occurred in four patients in PGE2 gel group while it occurred in three patients in PGE2 pessary group. The fetal outcomes in terms of Apgar score at birth, NICU stay were of no statistical difference for both groups (Table 2).

### Cost-effectiveness

The distribution of number of gel applications required in group B, 1 patient (2%) required 1 application, 31 (62%) of the patients required 2 gels, and 18 (36%) patients required 3 gel application. As per the protocol, slow-release PGE2 pessary was single application in group B.

**Table 2:** Comparison of hyperstimulation, PPH, fetal distress, Apgar score, and NICU admission in two groups

Variable	Group A (PGE2 gel) (n = 50)	Group B (PGE2 pessary) (n = 50)	p
Hyperstimulation	0.00%	2.00%	0.312
Postpartum haemorrhage	8.00%	6.00%	0.696
Fetal distress	22.00%	20.00%	0.802
APGAR score			
At 1 minute	$7.88 \pm 0.85$	$7.96 \pm 0.45$	0.557
At 5 minutes	$8.86 \pm 0.28$	$8.90 \pm 0.1$	0.656
NICU admission	10.00%	12.00%	0.748

### DISCUSSION

The gel PGE2 is a naturally occurring prostaglandin and is widely used in obstetrics, in gel or pessary form, for induction of labor. Dinoprostone is the only prostaglandin agent approved by FDA for labor induction in nulliparous or parous women with singleton post-term pregnancies. Central drugs standard control organization (CDSCO) approved Dinoprostone gel in 1990 and Dinoprostone pessary in 2001 in India.<sup>2</sup>

In this study, no difference was seen in the two groups in rate of vaginal delivery and induction failure. Shorter IDI was seen with PGE2 insert than with gel but when IDI in primigravida in two groups were compared  $p$ -value was not significant. Similarly, when multigravida IDI was compared, no significant difference was seen. This could be explained as the overall number decreases if considering parity. No difference was seen in other variables such as time to go into active labor, oxytocin augmentation, PPH, or fetal outcome in the two groups.

The advantage of PGE2 insert was seen in form of ease of insertion, ability to remove threads if hyperstimulation occurs and in 30% of patients in group B which delivered vaginally without need of oxytocin, within 24 hours of induction.

Published literature shows no clear advantage of one preparation over other in terms of rate of vaginal delivery and shorter IDI. This could be explained because of variable regimens, indications for induction and Bishop score of the recruited patients. In a study done in London, UK in 2011, PGE2 gel had shorter IDI than pessary and there was more failed induction with pessary than gel.<sup>3</sup> In a Cochrane review, in 2014, no significant difference was found.<sup>4</sup> There are two meta-analyses on the efficacy of Dinoprostone vaginal pessary for labor induction. Sanchez-Ramos et al.<sup>5</sup> reviewed four clinical trials and concluded that the vaginal insert was "less effective than other prostaglandins for cervical ripening and labor induction," whereas the conclusion reached by Hassan et al.<sup>6</sup> was that vaginal insert is equally effective as other prostaglandin routes of administration in terms of delivery by 24 hours, rate of uterine hyperstimulation with fetal heart rate changes and cesarean delivery rate. A study in Saudi Arabia also found no difference in two preparations.<sup>6</sup> Indian studies also find no advantage in IDI and vaginal delivery rate.<sup>7</sup> However, few studies demonstrated more vaginal delivery with insert.<sup>8,9</sup> In a randomized controlled trial, Trigalia found that the pessary achieved a significantly higher rate of spontaneous vaginal delivery.<sup>8</sup> More hyperstimulation has been seen with PGE2 insert than PGE2 gel.<sup>10</sup> Shorter IDI has been seen

with insert in a study done in Jaipur.<sup>11</sup> Another study carried out in ESI Hospital, New Delhi, India found shorter IDI with PGE2 gel than pessary.<sup>12</sup> The heterogeneity of results can be explained partly by different parity and Bishop score in the study population.

In our study, no added advantage of PGE2 pessary over PGE2 gel was found in terms of rate of vaginal delivery, IDI, or less hyperstimulation. There is definitely an advantage of single application and removal of pessary if hyperstimulation occurs and some benefit of shorter IDI and no need of oxytocin infusion, as 30% of our patients in PGE2 insert group delivered with insert alone but the cost factor in developing countries too needs consideration. At present in India, the market price of PGE2 pessary stands at ₹2,450, while it stands ₹250 per PGE2 gel. Syntocinon ampoule cost is ₹14 for five units; so, there is no financial benefit of reduced syntocinon needed with PG pessary. In our study, we did not find any benefit of using the expensive PGE2 preparation over gel preparation.

The limitation of our study was the small sample size for comparison of both preparations of PGE2. Future studies with larger sample size are needed to justify use of one PGE2 preparation over other.

## CONCLUSION

Both formulations of PGE2 (gel and pessary) showed similar outcomes for rate of vaginal delivery, and failure rate. The gel PGE2 pessary had lesser induction to delivery interval and lesser need for oxytocin infusion to establish labor. The gel PGE2 pessary has the advantage of single application and ability to remove by thread in case of hyperstimulation but it is expensive compared to intracervical PGE2 gel.

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