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Original Article

Pre-induction cervical ripening using two different dinoprostone vaginal preparations: A randomized clinical trial of tablets and slow release retrievable insert

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ABSTRACT

Objective: The current study compared the safety and efficacy of two different dinoprostone preparations (dinoprostone vaginal tablets & dinoprostone slow release retrievable vaginal insert) to ripen the cervix at term.

Materials and methods: Women admitted for pre-induction cervical ripening were included in a randomized controlled trial. Eligible women were randomly assigned to receive Dinoprostone either in the form of vaginal tablets or slow release retrievable vaginal insert. Study outcomes included time to vaginal delivery and time to onset of labor intervals and vaginal delivery rate.

Results: No statistically significant difference was found between the two groups regarding the main outcome measures, however, the probability of successful vaginal delivery was independently related to the type of dinoprostone preparation used to ripen the cervix (proportional hazard, 1.366; 95% CI, 1.010−1.847; P, 0.043) and the parity (proportional hazard, 1.412; 95% CI, 1.041−1.915; P, 0.026).

Conclusion: Both dinoprostone preparations were effective and potentially safe. The probability of successful vaginal delivery was higher with dinoprostone vaginal tablets while use of dinoprostone vaginal insert was associated with better patients' acceptability.

clinicaltrials.gov: NCT01635439.

Introduction

The ideal cervical ripening agent has to be effective, safe, easy to be administered and acceptable to the pregnant woman. Utilizing prostaglandins (PG) for cervical ripening during induction of labor (IOL) was first described in the 1960s [1]. Since that time various types of prostaglandins including $PGF_{2\alpha}$, PGE_2 (Dinoprostone) and PGE_1 (Misoprostol) were extensively studied to elicit the best prostaglandin pharmacological agent for pre-induction cervical ripening.

Dinoprostone was found to be superior to the others, as it increases the rates of successful vaginal delivery within 24 h without increasing the operative delivery rates. Vaginal route was found to be a safe and effective approach of bringing on labor. However, the best vehicle for delivering vaginal prostaglandins still needs further research [1].

There are several dosage forms of dinoprostone including tablet, gel and sustained release insert. Dinoprostone sustained release preparations have been developed to reduce the number of applications needed during IOL and subsequently decreasing the number of vaginal examinations. These preparations are easily retrievable in case of uterine tachysystole and/or abnormal fetal heart rate tracing [2]. On the other hand, the tablet form is designed to dissolve in the vaginal cavity and release PGE_2 for several hours; it has the advantage of easy manufacture and application [3].

Only two old studies [4,5] have compared between these two vehicles: the first study [5] was conducted in 1998 and included a very small number of patients with high degree of cross over, it reported a higher vaginal delivery rate and better fetal outcomes with dinoprostone vaginal insert; on the contrary, the second study [4] did not report any difference in the studied maternal and fetal outcomes. Due to the limitations in the previous studies, the current trial was conducted to reevaluate the safety and efficacy of

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dinoprostone vaginal tablets and dinoprostone slow release retrievable vaginal insert in pre-induction cervical ripening at term.

Patients and methods

This randomized controlled trial was conducted in the labor and delivery unit of a tertiary care governmental maternity hospital, after being approved by the local institutional ethics and research committee. This trial has been registered at clinicaltrials.gov (identification number NCT01635439). Women admitted for pre-induction cervical ripening, as per the institutional protocol, were initially enrolled to participate in the study. A written informed consent was obtained from all participants.

Inclusion criteria included the presence of a singleton gestation at ≥37 weeks with unfavorable cervix (Bishop Score < 7), vertex presentation, absence of labor and presence of reassuring fetal heart rate (FHR) pattern. Gestational age was calculated at the time of enrolment according to Naegele's rule and confirmed by reviewing the early pregnancy ultrasound report(s). Women with antepartum hemorrhage, placenta previa, uterine scar, suspected cephalopelvic disproportion, previous use of labor inducing agent during the current pregnancy, contraindications for vaginal delivery and/or known hypersensitivity or contraindication to dinoprostone or any of the other constituents of dinoprostone vaginal tablets or inserts were excluded from the study.

Eligible participants were randomly assigned to have pre-induction cervical ripening using dinoprostone either in the form of vaginal tablets or slow release retrievable vaginal insert, randomization was performed using a computer generated random numbers, and participants were assigned to their groups using sealed envelopes that were opened just before starting the intervention. Women assigned to the vaginal tablets arm, received 3 mg dinoprostone vaginal tablets (Prostin E_2, Pfizer, Sanico NV, Turnhout, Belgium). The tablets were inserted in the posterior vaginal fornix every 6 h with a maximum of four doses. Women assigned to the vaginal insert arm, received the 10 mg dinoprostone slow release retrievable vaginal insert (Propess, Ferring Pharmaceuticals, Copenhagen, DK) as a single dose: the insert is a hydrogel reservoir strip that releases PGE_2 with a controlled and constant rate of 0.3/hour over 24 h.

Pre-induction assessment of Bishop score (BS) [6] was done by the attending physician, presence of normal FHR pattern and absence of uterine activity were assured using cardiotocography (CTG) for 90 min (30 min before dinoprostone insertion and 60 min after), the same assessments were repeated with each new dose of dinoprostone (in dinoprostone vaginal tablets arm) or if labor onset was suspected (in both groups).

Discontinuation of dinoprostone (i.e. no further doses of dinoprostone vaginal tablets versus immediate removal of dinoprostone vaginal insert, according to the assigned group) was done if one of the following events occurred: 1) labor onset, presence of regular uterine contractions occurring every 2–3 min; 2) non-reassuring fetal heart rate pattern; 3) reaching the maximum dose of dinoprostone; or 4) improvement of Bishop score to be ≥ 7. Four hours after the last dose of dinoprostone vaginal tablets or 2 h after the removal of the dinoprostone insert; artificial rupture of fetal membranes (ROM) was considered if there was: 1) no evidence of active labor despite reaching the maximum dinoprostone dose; or 2) poor progress of labor despite the presence of regular uterine contractions. Oxytocin, if needed, was begun 2 h after artificial ROM, using a low dose titration approach with starting dose of 2 mU/minute, increments of 2 mU/minute every 15 min till achieving adequate uterine contractions or reaching the maximum dose (32 mU/minute).

Interpretation of intrapartum fetal heart rate pattern was done according to ACOG guidelines [7]. Failure of IOL was only defined as inability to achieve an active labor within at least 6 h of oxytocin maximum dose administration. Uterine tachysystole was diagnosed when more than five contractions were present in 10 min for at least 20 min [8].

Patient acceptability was assessed via the general questionnaire that is distributed to all patients at the time of discharge from the hospital and recollected during the first postnatal visit. Among the items of this questionnaire four items were added to evaluate pre-induction cervical ripening pharmaceutical preparation; each item was rated as either strongly agree, agree, disagree, or strongly disagree; a total score of ≤50 was categorized as unsatisfactory. The four items were: 1) you are satisfied with the pharmaceutical preparation used in pre-induction cervical ripening; 2) if you need to have pre-induction cervical ripening in the future, you do not mind using the same pharmaceutical preparation again; 3) you are fully satisfied about the frequency of application of the used pharmaceutical preparation; 4) you did not experience any discomfort during the insertion or application of the used pharmaceutical preparation.

The required sample size was estimated using G*Power© v.3.1.0 (Institut für Experimentelle Psychologie, Heinrich Heine Universität, Düsseldorf, Germany). The primary outcome measure was time to vaginal delivery interval. Based on this outcome, and data from previous study [4], it was estimated that a sample size of 100 women in each arm would have a power of 80% to detect an effect size (Cohen's d = 0.4). The test statistic used was the two-samples t test and significance was targeted at an α-error of 0.05. The secondary outcomes included vagina delivery rate, time to labor onset interval, patient's acceptability to the used dinoprostone preparation, uterine tachysystole, adverse maternal outcomes, low APGAR score at 5 min, delivery related neonatal intensive care admission rate and low cord pH.

Whenever possible outcome assessors were kept blinded to the intervention done especially when assessing a subjective outcome (i.e. patient's satisfaction), Additionally, data analysts and the persons in charge of reporting the results of the trial were kept unaware of the identity of the study groups.

Statistical analysis was done on a personal computer using IBM® SPSS® Statistics version 19 (IBM® Corporation, Armonk, NY, USA). Normally distributed numerical data were presented as mean (SD) and the independent-samples t test was used to compare differences between group means. Nominal data were presented as number (%) and differences between the two groups were compared with the chi square test or Fisher's exact test if > 20% of the cells in a contingency table had an expected count of <5. A two-tailed P value of <0.05 was considered statistically significant. Cox proportional hazard regression was used to evaluate the impact of parity, initial Bishop score and type of dinoprostone used in pre-induction cervical ripening on the probability of successful vaginal delivery at all time to vaginal delivery intervals. The simultaneous (enter) method was used for regression to avoid automatic elimination of pertinent predictors from the model.

Results

217 Women were found to be eligible for randomization, 109 were assigned to dinoprostone vaginal tablets arm and 108 were assigned to dinoprostone vaginal insert arm; by the end of the study 200 women were included in the final statistical analysis (Fig. 1).

As shown in Table 1, there were no statistically significant differences as regards the studied maternal and labor data of both groups. The rate of caesarean section was 11% in dinoprostone

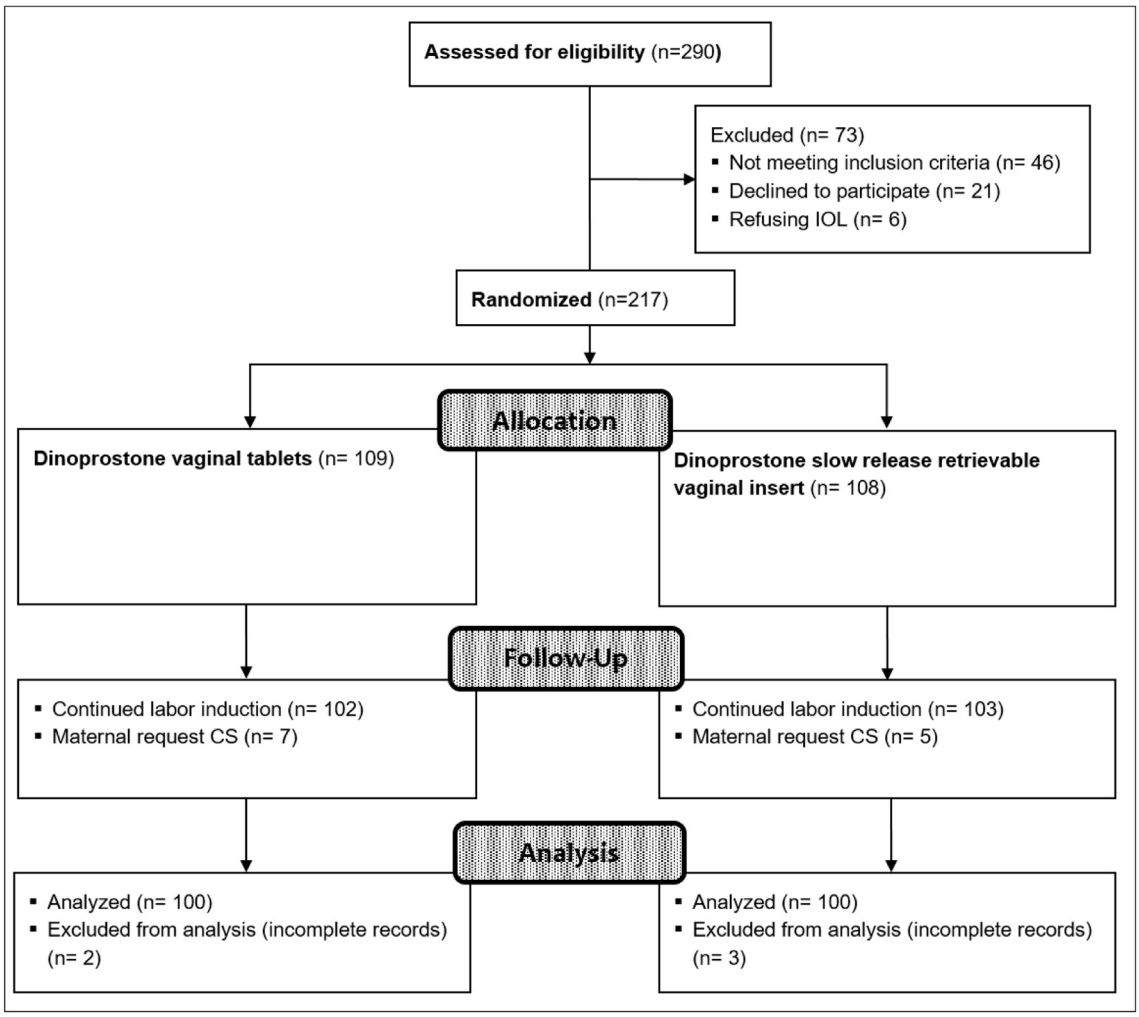

Fig. 1. Participants flow diagram.

vaginal tablets group (four for suspected fetal distress, four for failed IOL, two for failed progress of labor and one for antepartum hemorrhage) and 15% in dinoprostone vaginal insert group (three for suspected fetal distress, nine for failed IOL and three for failed progress of labor). There was no statistically significant difference between both groups, as regards the rate and the indications of cesarean sections. Instrumental deliveries were 4% in dinoprostone vaginal tablets group (two for suspected fetal distress and two for prolonged second stage) and 6% in dinoprostone vaginal insert group (four for suspected fetal distress and two for prolonged second stage). No significant systemic side effects were reported in both groups. No statistically significant difference was observed between the two groups regarding the incidence of uterine tachysystole, neonatal birth weight and adverse fetal outcomes (Table 2). Uterine tachysystole was reported only in five cases, none was associated with pathological FHR changes. In dinoprostone vaginal insert group, reversal of tachysystole occurred within 10–25 min after removal of the insert, one woman in dinoprostone vaginal tablets group needed tocolysis by β2 sympathomimetic to abort the uterine tachysystole. Five patients in dinoprostone vaginal insert group had their pessaries spontaneously expelled before the completion of the 24 h' interval of pre-induction cervical ripening; insertion of another insert was necessary to continue cervical ripening (provided that the total interval of application would not exceed 24 h). The remaining 95 patients had their pessaries removed because of completion of 24 h ($n = 41$), establishment of regular uterine contractions ($n = 49$), occurrence of uterine tachysystole ($n = 2$) or presence of non-reassuring FHR patterns in CTG ($n = 3$).

There was no difference between the 2 groups regarding the mean time to vaginal delivery interval; however, survival analysis showed that the probability of successful vaginal delivery was independently related to type of dinoprostone preparation used for pre-induction cervical ripening and parity; the results of Cox proportional hazards regression are shown in Table 3 and Fig. 2, of the variables included in the model, the treatment group and parity were independent predictors of successful vaginal delivery. On the contrary, there was no statistically significant difference among those with a Bishop score of 4–6 and those with a score of <4 as regards the outcome of interest. The full model had a −2 log likelihood (likelihood ratio statistic, LRS) of 1508.3 which was significantly different from that of the null model (P, 0.034).

Discussion

Findings and interpretation

This randomized trial compared dinoprostone vaginal tablets and dinoprostone vaginal insert in primiparous and multiparous

Table 1
Participants' maternal and labor data.

Variable	Dinoprostone vaginal tablets group (n = 100)	Dinoprostone vaginal insert group (n = 100)	P value
Maternal age (years)	26.8 ± 5.1	26 ± 4.3	0.214
Body mass index (kg/m^2)	23.5 ± 3.5	23 ± 2.7	0.257
Parity			0.818
Primiparous	44 (44%)	49 (49%)	
Multiparous	56 (56%)	51 (51%)	
Gestational age (weeks)	40.4 ± 1.3	40.6 ± 0.9	0.281
Bishop score			0.091
< 4	94 (94%)	87 (87%)	
4 – 6	6 (6%)	13 (13%)	
Indication for induction of labor			0.171
Prolonged pregnancy	54 (54%)	73 (73%)	
Diabetes mellitus	18 (14%)	15 (15%)	
Pre-labor rupture of membranes	8 (8%)	4 (4%)	
Fetal indications	17 (17%)	5 (5%)	
Hypertensive disorders	3 (3%)	3 (3%)	
Syntocinon augmentation	10 (10%)	5 (5%)	0.179
Mode of delivery			0.672
Normal Delivery	85 (85%)	79 (79%)	
Caesarean section	11 (11%)	15 (15%)	
Ventose	4 (4%)	5 (5%)	
Forceps	0	1 (1%)	
Time to labor onset interval (hours)	17.8 ± 5.3	19 ± 5.1	0.117
Time to vaginal delivery interval (hours)	21.2 ± 5.4	22.5 ± 5.3	0.076

Data are presented as mean ± SD or number (%).

women. The study protocol did not allow more than one application of dinoprostone vaginal insert or more than four administrations of dinoprostone vaginal tablets. Dinoprostone had the advantage of better patient tolerability and acceptability as well as easy retrievability in case of uterine tachysystole, while, dinoprostone vaginal tablets was associated with higher probability of successful vaginal delivery.

Differences in results and conclusions in relation to other studies

To the best of our knowledge, only 2 trials [4,5] were conducted before to compare between these two dinoprostone preparations (Table 4). The higher probability of successful vaginal delivery with dinoprostone tablets was not proven in the previous two trials, this can be explained by the different protocols used in these trials that improved the effectiveness of pre-induction cervical ripening in dinoprostone vaginal insert arm on the expense of dinoprostone vaginal tablets arm; Hunter et al. used combined protocol in the dinoprostone vaginal insert arm as they added dinoprostone vaginal tablets 3 mg every 8 h till labor commenced to women who did not initially respond to dinoprostone vaginal insert [5] while Rabl et al. defined failed IOL in their dinoprostone vaginal tablets arm by failure to respond to 2 doses of dinoprostone vaginal tablets each 3 mg given 6 h apart [4]. In the tablets group of this study, the maximum cumulative dose of dinoprostone given was 12 mg (3 mg QID), while in the slow release retrievable vaginal insert group, it was 7.2 mg only (i.e. a 10-mg reservoir releases dinoprostone constantly at a rate of 0.3 mg/h, for 24 h). A higher dinoprostone dose is expected to exert a more powerful therapeutic effect.

Although both preparations were proved to have a comparable safety profile in the current as well as in the previous trials [4,5]; dinoprostone vaginal insert was superior in the point of easy retrievability in case of occurrence of uterine tachysystole [4]. In the current study, all cases of uterine tachysystole with dinoprostone vaginal insert (n = 2) resolved

Table 2
Participants' maternal and fetal outcomes.

Variable	Dinoprostone vaginal tablets group (n = 100)	Dinoprostone vaginal insert group (n = 100)	P value
Uterine tachysystole	3 (3%)	2 (2%)	1.000
Patients' acceptability	44/70 (63%)	61/75 (81%)	**0.016**
Adverse maternal outcomes			0.945
None	87 (87%)	88 (88%)	
Rupture uterus	0	0	
Retained placenta	2 (2%)	1 (1%)	
Coagulopathy	0	0	
Atonic Postpartum hemorrhage	4 (2%)	5 (2%)	
Cervical tear	3 (3%)	2 (2%)	
3rd & 4th degree perineal tear	2 (2%)	1 (1%)	
Perineal hematoma	2 (2%)	3 (2%)	
Birth weight (grams)	3064 ± 417	2997 ± 489	0.298
APGAR score at 5 min < 7	1 (1%)	0	1.000
Meconium stained liquor (grade 3)	10 (10%)	5 (5%)	0.283
Neonatal intensive care unit admission (delivery related)	6 (6%)	3 (3%)	0.498
Cord pH < 7.0 (arterial)	2 (2%)	1 (1%)	1.000

Data are presented as mean ± SD or number (%).
Bold indicates P value <0.05 (Statistcal significance).

Table 3
Cox proportional hazards regression model (probability of successful vaginal delivery).

Covariate	b	SE	P value	Exp(b)	95% CI of Exp(b)	
					Lower bound	Upper bound
Treatment group 0 = Dinoprostone insert 1 = Dinoprostone tablets	0.312	0.154	**0.043**	1.366	1.010	1.847
Parity 0 = Primipara 1 = Multipara	0.345	0.155	**0.026**	1.412	1.041	1.915
Bishop score 0 = Score <4 1 = Score 4–6	0.101	0.252	0.690	1.106	0.674	1.813
Overall model fit						
Null model −2 Log Likelihood			1517.0			
Full model −2 Log Likelihood			1508.3			
Chi-square			8.681			
DF			3			
Significance level			P = 0.034			

CI, confidence interval; **b**, regression coefficient; **Exp(b)**, proportional hazard; **SE**, standard error of regression coefficient.
Bold indicates P value <0.05 (Statistcal significance).

rapidly after removal of the insert; however tocolytic therapy was required in one case to reverse the effects of uterine tachysystole with dinoprostone vaginal tablets (n = 3); the easy removal and potential reversibility of uterine tachysystole can be considered as another potential benefit of using dinoprostone vaginal insert.

Although the previous two trials adopted the policy of removing the dinoprostone sustained release preparations after a maximum of 12 h interval [4,5], in the current study dinoprostone insert was kept inside the vagina for up to 24 h, as per the manufacturer instructions and the local hospital protocol. A previous non-systematic analysis emphasized the benefit of keeping the use of dinoprostone sustained release preparation for 24 h when 12 h exposure does not lead to onset of labor [9].

Patient acceptability was assessed after delivery via answering a questionnaire investigating the discomfort caused by the insertion of dinoprostone preparation. Only 145 women did adequately fill the questionnaire; the rate of dissatisfaction was higher in dinoprostone vaginal tablets group than in dinoprostone vaginal insert group (37% versus 19% respectively); most of the women who reported dissatisfaction in dinoprostone vaginal insert group were concerned about the intensity of pain experienced during the application; while in dinoprostone vaginal tablets group the main concern was the frequency of applications.

The number of applications used and hence the number of required vaginal examinations before onset of labor was significantly less in the dinoprostone vaginal insert group; this advantage allowed us to have a better utilization of labor and delivery unit staff.

Relevance of the findings: implications for clinicians and policymakers

Based on the current study findings; we prefer to afford the women dinoprostone vaginal tablets as a first option for pre-induction cervical ripening and preserve dinoprostone insert as a second option for the women who are much interested to have the minimal number of vaginal examinations.

Strengths and weaknesses of the study

The merits of this study included the use of a standard labor management protocol, and the utilization of regression analysis.

Although the sample size of the current study can be considered relatively large when compared with the aforementioned studies, it is still not adequately powered to confirm the safety of the studied dinoprostone preparations in pre-induction cervical ripening. Another potential point of criticism is the inclusion of multiparous

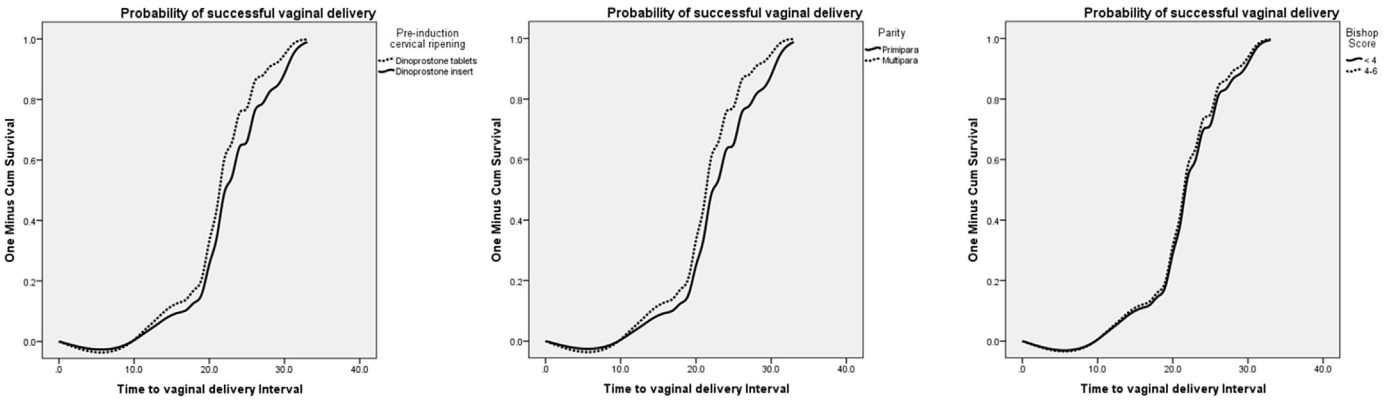

Fig. 2. Survival curves produced by Cox proportional hazard regression. For the treatment groups, dinoprostone vaginal tablets were associated with significantly higher probability of successful vaginal delivery (proportional hazard, 1.366; 95% CI, 1.010 to 1.847; P, 0.043); for parity, multiparity was associated with significantly higher probability of successful vaginal delivery (proportional hazard, 1.412; 95% CI, 1.041 to 1.915; P, 0.026); for the Bishop score, there was no statistically significant difference in the probability of successful vaginal delivery among those with Bishop score of 4–6 and those with a score of <4 (proportional hazard, 1.106; 95% CI, 0.674 to 1.813; P, 0.690).

Table 4
Studies comparing dinoprostone vaginal tablets and dinoprostone vaginal insert in pre-induction cervical ripening (including the current trial).

	Hunter and Parveen 1998	Rabl et al 2002	Present study
Population	55 pregnant women - 26 received dinoprostone vaginal insert (10 mg) - 29 received dinoprostone vaginal tablets (3 mg)	200 pregnant women - 100 received dinoprostone vaginal insert (10 mg) - 100 received dinoprostone vaginal tablets (3 mg)	200 pregnant women - 100 received dinoprostone vaginal insert (10 mg) - 100 received dinoprostone vaginal tablets (3 mg)
Intervention	In dinoprostone vaginal insert group, the insert was removed 12 h after insertion, or before if indicted. If the cervix did not respond to dinoprostone insert, then dinoprostone vaginal tablet (3 mg) was given and further doses were inserted 8 hourly until labor commenced. In dinoprostone vaginal tablets group, 3 mg tablets were given every 8 h as long as the Bishop Score was <6 and regular contractions were not present.	In dinoprostone vaginal insert group, the insert was removed 12 h after insertion, or before if indicated. In dinoprostone vaginal tablets group, 3 mg tablets were given twice six hours apart.	In dinoprostone vaginal insert group, the insert was removed 24 h after insertion, or before if indicated. In dinoprostone vaginal tablets group, 3 mg tablets were given at six-hour intervals with a maximum of 4 doses.
Efficacy outcome measures	Onset of labor within 12 h or an increase in Bishop Score of ≥3: 43% in dinoprostone insert group & 34% in dinoprostone tablets group. Vaginal delivery within 24 h After a single dose of prostaglandin: 50% in dinoprostone insert group & 62% in dinoprostone tablets group. Rate of normal vaginal deliveries: 81% in dinoprostone insert group & 52% in dinoprostone tablets group. Dinoprostone insert resulted in higher rates of normal deliveries & consequently improved fetal outcomes.	Rates of vaginal delivery within 24 h of insertion: No differences were found in terms of vaginal delivery or caesarean section within 24 h. Caesarean section rates: - 21% in dinoprostone insert group - 22% in dinoprostone tablets group. time to onset of regular uterine contractions interval and time to delivery interval: No significant differences were found.	Mode of delivery, time to labor onset interval, time to vaginal delivery interval: No significant differences were found. Cox proportional hazards regression showed that among the variables included: the treatment group and parity (but not Bishop score) were independent predictors of the probability of having a successful vaginal delivery (i.e. dinoprostone tablets and multiparity).
Safety outcome measures	Uterine tachysystole: One patient in dinoprostone insert group and none in dinoprostone tablets group.	Uterine tachysystole: 8% in dinoprostone insert group: removal of the insert was sufficient to reverse the problem in 7 women. 9% in dinoprostone tablets group: 8 needed medical interventions to end hyperstimulation. Abnormal fetal heart rate patterns & fetal outcome: No significant differences were found.	Uterine tachysystole, adverse maternal outcomes: No significant difference was found between the two groups. Low APGAR score at 5 min, delivery related NICU admission, low cord pH < 7.0: No significant difference was found between the two groups.
Conclusion	Pre-induction cervical ripening using dinoprostone vaginal insert was safe, simple and convenient with a high degree of patient acceptability.	The continuous release of prostaglandins from dinoprostone vaginal insert permitted controlled induction of labor and easy removal of the drug in cases of uterine tachysystole.	Although both preparations were effective and potentially safe. There was a higher probability of successful vaginal delivery with dinoprostone vaginal tablets rather than dinoprostone slow release retrievable vaginal insert while dinoprostone inserts had better patients' acceptability.

women in the studied population, as most of the cervical ripening studies usually target the primiparous women with low Bishop scores. In the high-parity communities, like Saudi Arabia, where multiparous women are more prevalent and riskier. The authors believe that it would be more valuable to generalize the results on all women regardless of their parities and Bishop scores. The potential confounding effects of Bishop score and parity on the probability of successful vaginal delivery has been adjusted for using the multivariate analysis.

Finally, it can be concluded that, the studied dinoprostone preparations are effective and potentially safe. There was a higher probability of successful vaginal delivery with dinoprostone vaginal tablets rather than dinoprostone slow release retrievable vaginal insert, while dinoprostone inserts had better patients' acceptability.

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Conflicts of interest statement

No actual or potential conflict of interest in relation to this manuscript exists and the results of this manuscript have not been distorted by research funding.

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