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Effect of vaginal washing before intravaginal dinoprostone insertion for labor induction: A randomized clinical trial

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Abstract

Aim: Prostaglandins have a dual action of cervical ripening and induction of uterine contraction. This study was designed to compare the effectiveness of vaginal washing just before insertion of intravaginal dinoprostone.

Methods: A randomized controlled trial was conducted at the Zeynep Kamil Women and Children's Health Training and Research Hospital. One hundred and ninety-one women with singleton, term pregnancy who underwent labor induction were randomly assigned to two groups: Group 1 consisted of 95 pregnant women with vaginal washing before intravaginal dinoprostone (Propess system for slow release system of 10 mg of dinoprostone) insertion (study group), and 96 pregnant women constituted the control group who did not undergo vaginal washing before intravaginal dinoprostone insertion. A parallel randomized controlled trial was conducted with an allocation ratio of 1:1 to compare the effectiveness of vaginal washing before intravaginal dinoprostone insertion.

Results: The groups had similar mean age, body mass index, gestational age, gravidity, parity and Bishop score before agent insertion ($P > 0.05$). Duration of dinoprostone kept intravaginally, *duration from the beginning of dinoprostone insert vaginally to the active phase of labor* and duration from the time of intravaginal dinoprostone insertion to delivery were significantly longer in the control group ($P < 0.05$). Uterine hyperstimulation rate was significantly higher in study group compared to control group ($P < 0.05$). Meconium passage, fetal infection and neonatal intensive care unit admission were significantly higher in the control group ($P < 0.05$).

Conclusion: Vaginal washing before intravaginal dinoprostone insertion may increase Prostaglandin E2 bioavailability as we found shorter duration and better outcome of labor induction in the present study.

Key words: cervical ripening, dinoprostone, labor induction, propess, safety, vaginal washing.

Introduction

Induction of labor (IOL) is commonly used in obstetrics. In developed countries, 25% of all deliveries at term involves IOL whereas in developing countries the rate of it changes but mostly lower.[1]

Several approaches, including mechanical and pharmacological methods, have been introduced to induce labor in pregnant women who are candidates for delivery. PGE1 (Prostaglandin E1) and PGE2 (Prostaglandin E2, gel, tablet or pessary type) have been used for cervical ripering but only PGE2 (dinoprostone) is approved by US Food and Drug Administration for cervical ripening.[2]

The application of PGE2 to the human cervix increases collagenase activity, regulates hydrophilic

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glycosaminoglycans synthesis and inflammatory response that characterizes cervical ripening and remodeling.[3] Furthermore, dinoprostone have some advantages to be preferred mostly. It could be used as single application, could be administered easily and drug releasing is slow so it allows greater dose control.[4]

Administration of cervical ripening agents are expected to achieve successful cervical ripening for vaginal delivery within the shortest possible time, with a low incidence of failure to achieve vaginal delivery, reduced oxytocin augmentation and with no increase in perinatal morbidity compared to spontaneous labor.

Predictive factors of vaginal delivery in dinoprostone-induced labor varied among the studies. The vaginal surface is normally acidic and this acidity is suggested to influence dinoprostone release, which may result in variable clinical responses.[5]Vaginal pH was shown to be altered with vaginal douching.[6]

In view of these findings, we aimed to compare the effectiveness of vaginal washing just before insertion of intravaginal dinoprostone (Propess).

Methods

Study design

This parallel, randomized controlled trial was conducted with an allocation ratio of 1:1 to compare the effectiveness of vaginal washing before intravaginal dinoprostone insertion. The CONSORT statement was used when reporting this prospective randomized trial.[7]

The study was conducted between February 2017 and December 2017 at Zeynep Kamil Women and Children's Health Training and Research Hospital following study approval by the institutional review board and clinical trial registration (ClinicalTrials.gov #NCT03050684). The study protocol was in compliance with the Declaration of Helsinki and a signed informed consent was obtained from all the voluntary participants before admission to the labor room and they were assured of the option to withdraw from the study at any moment. The randomization sequence was computer generated and the allocation sequence was concealed from the researcher who was enrolling and assessing participants in sequentially numbered order.

Study participants

Patients who were admitted to the labor and delivery unit for IOL were assessed for eligibility and approached to participate in the study. Pregnancies (aged 18–40 years) with singleton, term (defined as >38 weeks), cephalic presentation, reactive fetal heart rate in cardiotocograpy, no contraindication to vaginal delivery, the absence of spontaneous uterine contractions and cervical modified Bishop's score less than 5 were enrolled for the study.

Exclusion criteria were defined as pregnancies with multiple pregnancies, less than 38 weeks, noncephalic presentation, ruptured membranes, nonreassuring fetal heart rate, fetal anomaly and fetal demise, suspected chorioamnionitis, emergency delivery indications, known hypersensitivity to prostaglandins, previous cesarean delivery or other uterine surgery.

Indications for labor induction were defined as: preeclampsia ≥37 weeks, significant maternal disease not responding to treatment, suspected fetal compromise, postdate (>41 + 0 weeks) or post-term (>42 + 0 weeks) pregnancy, diabetes mellitus (glucose control may dictate urgency), alloimmune disease at or near term, intrauterine growth restriction, oligohydramnios and gestational hypertension ≥38 weeks.

Procedures

The same examiner (C. Y. A.) provided an initial cervical assessment and assigned an initial Bishop score to all of the patients. Vaginal washing was applied with sterile 0.9% NaCl serum (20 cc) just before inserting dinoprostone (Propess, slow release system of 10 mg PGE2) vaginal insert in the study group. Dinoprostone (Propess) was inserted without any additional intervention in the control group.

With the onset of active labor, the routine hospital protocol was followed. Continuous fetal heart monitoring and uterine activity monitoring were performed in all patients. Duration of dinoprostone kept intravaginally was determined by calculation of duration from time of agent insertion to the time of manual removal of agent due to the hyperstimulation or confirmed successful labor induction with vaginal examination. Progress and outcome of labor were recorded by the labor room doctor. Hyperstimulation syndrome was defined as tachysystole and/or hypertonus on cardiotocography, with fetal heart rate alterations.[8]

Outcome measurements

Primary outcome was duration from the beginning of intravaginal dinoprostone administration to the active phase of labor which indicates successful labor induction. We defined active phase when effective regular,

coordinated uterine contractions occurred with cervical effacement and dilatation ≥5 cm.[9]

Secondary outcomes were duration of dinoprostone kept intravaginally, duration from the time at intravaginal dinoprostone insertion to total cervical dilatation, route of delivery, presence uterine hyperstimulation, failure of labor induction, presence of labor arrest, fetal distress, meconium discharge and fetal infection.

Sample size and power

Sample size was calculated to be 88 with a 1:1 ratio with 80% power and 95% confidence interval, and mean duration from agent insertion to delivery was assumed to be 25.1 h in the study group and 36.6 h in the control group according to a previously published study.[10]

Statistical analysis

For evaluation of the findings obtained in the study, the IBM SPSS STATISTICS 22.0 program was used for statistical analysis. Student's *t*-test was used for the comparison of two groups of normal distribution parameters in comparison of descriptive statistical methods (mean, standard deviation), and Mann–Whitney *U* test was used for comparison of two groups of parameters without normal distribution. Chi-square test, Fisher's exact test and continuity correction (Yates) test were used for the comparison of qualitative data. Significance was assessed at P less than 0.05 level.

Results

The patient flow chart is listed in detail in Figure 1. Out of 225 eligible patients, 25 patients were excluded because they did not meet the inclusion criteria. Two hundred participants were randomly assigned to the study (n = 100) and control groups (n = 100). Five patients in the study group and four patients in control group were excluded because they declined to participate in the study.

The baseline characteristics of participants in each group were shown in Table 1. The ages of the patients ranged from 18 to 40 years with an average of 28.63 ± 5.44 years. There was no statistically significant difference in the Propess usage indications between the groups ($P > 0.05$). The mean pre-induction Bishop score was 1.82 ± 0.84 in the study group and 1.87 ± 0.80 in the control group. There was no statistically significant difference between groups in terms of birth weight ($P > 0.05$). The most

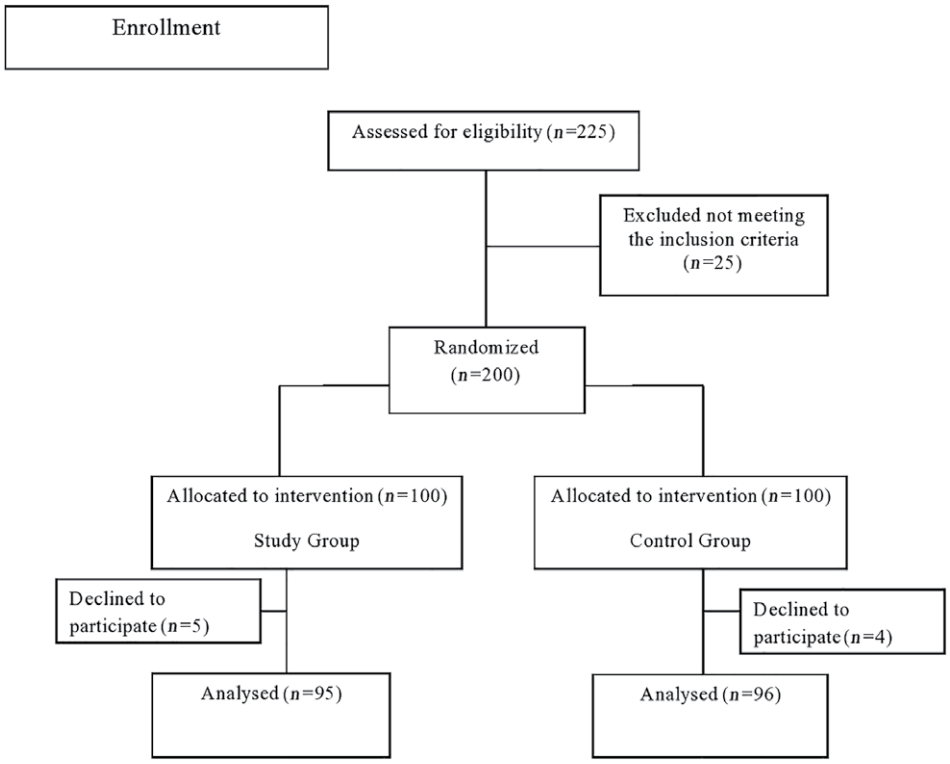

Figure 1 Flow chart of the study population.

Table 1 Evaluation of demographic parameters by the two groups

		Study (n = 95)	Control (n = 96)	P-value*
		Mean ± SD	Mean ± SD	
Age (years)		28.03 ± 4.985	29.24 ± 5.94	0.12†
Gestational age (weeks)		40.02 ± 1.15	40.03 ± 1.33	0.95†
Body mass index (kg/m^2)		28.67 ± 5.96	27.95 ± 7.93	0.50†
		n (%)	n (%)	
Gravidity	1	40 (42.7)	39 (41.2)	0.13‡
	2	29 (30.2)	19 (19.6)	–
	3	15 (16.6)	15 (15.5)	–
	4	4 (4.2)	12 (12.4)	–
	5+	7 (7.3)	11 (11.3)	–
Parity	0	47 (50)	44 (46.4)	0.26‡
	1	27 (28.1)	20 (20.6)	–
	2	13 (13.5)	23 (23.7)	–
	3	8 (8.3)	9 (9.3)	–
No. of miscarriage	0	73 (77.1)	76 (79.4)	0.90‡
	1	15 (15.6)	13 (13.4)	–
	2+	7 (7.3)	7 (7.2)	–

*P < 0.05. †Student's t-test. ‡Chi-square test.

common indication of labor induction was postterm pregnancy in both groups (Table 2).

In the study group, duration of dinoprostone kept in the vagina, *duration from the beginning of dinoprostone insert vaginally to the active phase of labor* and duration from the time at intravaginal dinoprostone insertion to total cervical dilatation were statistically significantly shorter than in the control group (P < 0.05, Table 2).

Table 2 Evaluation of some labor characteristics by the two groups

		Study (n = 95)	Control (n = 96)	P-value*
		Mean ± SD (median)	Mean ± SD (median)	
Duration of dinoprostone kept intravaginally (h)		8.29 ± 4.71 (8)	10.78 ± 7.21 (9)	0.04*,†
Duration from the beginning of dinoprostone insert vaginally to the active phase of labor (h)		10.59 ±7.12 (8)	15.11 ±12.66 (10)	0.01*,†
Duration from the time at intravaginal dinoprostone insertion to total cervical dilatation (h)		13.77 ±8.43 (11)	18.25 ±13.17 (14)	0.03*,†
Prelabor Bishop score		1.82 ±0.84 (2)	1.87 ±0.80 (2)	0.61†
		Median (%)	Median (%)	
Route of delivery	C/S	14 (14.6)	25 (25.8)	0.07‡
	VD	81 (85.4)	71 (74.2)	
Indications for labor induction	Postterm	44 (46.9)	59 (61.9)	0.07§
	GDM	6 (6.3)	9 (9.3)	–
	GHT	11 (11.5)	4 (4.1)	–
	Preeclampsia	10 (10.4)	10 (10.3)	–
	Oligohydroamnios	24 (25)	14 (14.4)	–
Uterine hyperstimulation	(+)	15 (15.8)	2 (2.1)	0.002**,‡
	(−)	80 (84.2)	94 (97.9)	–
Failure of labor induction	(+)	3 (3.1)	10 (10.3)	0.13‡
	(−)	92 (96.9)	86 (89.7)	–
Labor arrest	(+)	4 (4.2)	11 (11.3)	0.11‡
	(−)	91 (95.8)	85 (88.7)	–
Fetal distress	(+)	8 (8.3)	12 (12.4)	0.49‡
	(−)	87 (91.7)	84 (87.6)	–

*P < 0.05. **P < 0.01. †Mann–Whitney U test. ‡Yates continuity correction test. §Chi-square test. C/S, cesarean section; GDM, gestational diabetes mellitus; GTH, gestational hypertension; VD, vaginal delivery.

There was no statistically significant difference in route of delivery between the groups ($P > 0.05$, Table 2). The rate of hyperstimulation in the cardiotocograpy was significantly higher in study group than control group ($P < 0.05$).

There was no statistically significant difference of cases of failed induction between the groups ($P > 0.05$, Table 2). There was no statistically significant difference between the groups in terms of the rate of labor arrest ($P > 0.05$). There was no statistically significant difference in fetal distress cases between the groups ($P > 0.05$).

Comparing the groups, the mean Apgar 1 and Apgar 5 scores did not differ statistically ($P > 0.05$). In the control group, the Neonatal intensive care unit (NICU) admission rate was significantly higher than the study group ($P < 0.01$). The meconium passage rate in the control group was significantly higher than in the study group ($P < 0.05$). There was a statistically significant difference in fetal infection between the groups ($P < 0.01$). The fetal infection rate in the control group was significantly higher than in the study group (Table 3).

Discussion

This prospective RCT investigated the efficacy of intravaginal dinoprostone in labor induction between groups of women with and without vaginal washing before agent insertion. Our data analysis showed that duration of dinoprostone kept in the vagina, *duration from the beginning of dinoprostone insert to the active phase of labor* and duration from the time of dinoprostone insertion to the total cervical dilatation were significantly longer in the control group. The rates of hyperstimulation were significantly higher in the study group than the control group. The rates of meconium passage, fetal infection and NICU admission were significantly higher in the control group.

Several randomized trials have been conducted of different labor induction agents to compare delivery outcome.[11–16] These data showed that different pharmacologic agents with different pharmacokinetic and pharmacodynamic properties may have variable effects on placental perfusion with variable response of the myometrium to these agents.

Application form of the drugs effect pharmacokinetic and pharmacodynamics of the molecule. Vaginal pH is important and interesting area because of understanding the disease and drug development. Döderlein's bacillus produce lactic acid through glycogen fermentation so that healthy human vagina have acidic pH (normal range is 3.8–4.5).[17]

Throughout women life vaginal pH is affected by hormonal and environmental changing. Alkaline pH reduces the viability of the healthy endogenous vaginal microbiota and to cause growing of pathogenic bacterial species.[18] *In vitro* dinoprostone release at pH 7.4, 5.4 and 3.4 was assessed in one study and analysis of the data revealed that vaginal pH could influence dinoprostone release. The authors concluded that release of PGE2 was reduced at lower pH.[5]

Vaginal douching may reduce the density of normal vaginal flora and may turn the vaginal pH to alkaline.[6]

We hypothesized that PGE2 releasing is more effective in alkaline pH so we washed vagina with saline solution just before inserting the dinoprostone vaginal

Table 3 Evaluation of some neonatal characteristics by the two groups

		Study (n = 95)	Control (n = 96)	P-value*
		Mean ± SD	Mean ± SD	
Birth weight (g)		3378.02 ± 492.9	3467.47 ± 443.4	0.18†
Apgar 1		7.94 ± 0.59 (8)	7.65 ± 1.09 (8)	0.06‡
Apgar 5		9.0 ± 0.39 (9)	8.80 ± 0.77 (9)	0.08‡
		n (%)	n (%)	–
NICU admission	(+)	7 (7.4)	22 (22.9)	0.005**,§
	(−)	88 (92.6)	74 (77.1)	–
Gender	Male	51 (54.2)	49 (50.5)	0.71¶
	Female	44 (45.8)	47 (49.5)	–
Meconium passage	(+)	2 (2.1)	10 (10.3)	0.03*,§
	(−)	93 (97.9)	86 (89.7)	–
Fetal infection	(+)	0 (0)	9 (9.3)	0.003**,††
	(−)	95 (100)	87 (90.7)	–

*$P < 0.05$. **$P < 0.01$. †Student's t-test. ‡Mann–Whitney U test. §Yates continuity correction test. ¶Chi-square test. ††Fisher's exact test. NICU, neonatal intensive care unit.

insert. We found the *duration from the beginning of dinoprostone insert vaginally to the active phase of labor* and the duration from the time of intravaginal dinoprostone insertion to total cervical dilatation significantly longer in the control group compared to the study group (vaginal washing group).

Basirat *et al*. measured the vaginal pH and administered dinoprostone vaginal insert for IOL. They found that active phase duration in patients with high pH was significantly shorter than those with low pH ($P = 0.019$) as a result they concluded that high vaginal pH influences the function of prostaglandin tablet as a reduction in duration of the active phase of labor.[19]

One of the prospective observational study was carried out to see the effect of vaginal pH on the efficacy of prostaglandin gel (PGE2) for cervical ripening. They demonstrated a significant change in the Bishop's score over 18 h after commencement of the first dose of PGE2 gel in higher vaginal pH group but no significant difference was found between the groups with respect to time to onset of labor, time to active labor, time to complete dilatation and delivery. In this study, they took the optimal pH value 5.5 and only 47 pregnant women enrolled the study.[20] Our study was the first randomized study about this subject with larger study population and we recommended an easy method to make the vaginal pH alkaline before IOL to get better results.

Consistent with our findings, Ramsey *et al*. found that women with a high vaginal pH (>4.5) had significantly shorter times to active labor, complete dilatation and vaginal delivery compared with women with a low pH (≤4.5).

However, we did not know the optimal pH to get maximum effectivity of the PGE2 vaginal insert. Johnson *et al*. declared the optimal pH of 7.4 for PGE2 release *in vitro*.[5] Another investigator MacDonald and Weirfound declared that increased pH of 6.5 to 7.5 gets better PGE2 releasing *in vitro*.[21]

Uterine tachysystole (hyperstimulation) was shown to occur in more than 10% of spontaneous labors. Some nonreassuring fetal heart tracings with an increased rate of cesarean deliveries and NICU admissions were reported to be secondary findings of uterine tachysystole, however, no relationship was found between uterine tachysystole and low Apgar scores or meconium-stained amniotic fluid.[22] As the agent may result in variable responses based on factors related to altered pharmacokinetic and pharmacodynamic properties, an unexpected complication like tachysystole may be observed with labor induction. In our study population, since the rates of uterine tachsystole were significantly different between the two groups, there must be an explanation for this difference, which was thought to be due to changing the pharmacokinetic and pharmacodynamic properties of the agent secondary to vaginal washing.

A previous study showed a significantly higher rate of cesarean delivery and chorioamnionitis in cases with a prolonged first stage of labor, however in this study, neonatal outcomes were found to be similar.[23] As a result of pharmacokinetic and pharmacodynamic changes with vaginal washing, in our study we found a significantly higher mean duration of the first stage of labor in the control group compared to the study group. Additionally, this decrease in duration of labor may be resulted in lower rate of fetal infection and meconium passage with decreased NICU admission. Bishop score at admission for labor induction was not found to be associated with poor outcome, but a significant association was found between length of the latent phase and Bishop score at admission.[24] Additionally, the number of applications of dinoprostone required to achieve successful induction was shown to be related to parity and cervical status at presentation.[24] Initial Bishop scores in the groups were comparable with a mean number of 1.8 in our study.

In conclusion, this is the first randomized clinical study about this subject in the literature. Vaginal washing before intravaginal dinoprostone insertion may increase the vaginal pH and affect the PGE2 vaginal insert bioavailability. This is also useful and easy applicable method for the obstetricians to get better results about IOL. But the limitation of this study is that we did not assess the vaginal pH before and after vaginal washing so we did not know the exact vaginal pH. In future research, pH assessment for each patient should be performed before and after the procedure to get objective results about the optimal vaginal pH, furthermore, it could help the obstetrician to find out the optimal pH releasing PGE2 *in vivo*.

Disclosure

No authors have any conflict of interest report.

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