CLINICAL STUDY

The Role of Vaginal pH on Efficacy of Controlled-Release Dinoprostone Vaginal Insert for Cervical Ripening/ Labor Induction: A Prospective Double-Blind Study

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Abstract

Objective: To evaluate if vaginal pH has any effect on the efficacy of controlled-release PGE_2 vaginal insert for cervical ripening/labor induction in post-term patients.

Materials and Methods: Sixty-three post-term women with unfavorable cervix (Bishop's score ≤6) undergoing labor induction were enrolled in this prospective, double-blinded trial. All patients received sustained-release dinoprostone vaginal insert for cervical ripening/labor induction during 12 hours, repeated dosing one time 24 hours later.

Results: Women with a low vaginal pH (≤4.5, n=38) and women with a high vaginal pH (>4.5, n=25) were similar in maternal age, parity, body mass index, gestational age or initial Bishop's score. Bishop's score change over the initial 12 hours significantly ($p<0.05$) differed between the low vaginal pH (3.9±3.3) and the high vaginal pH group (5.5±3.4). Time to active labor (14.7±17.3 hrs vs 13.1±9.8 hrs), complete dilation (19.6±20.1 hrs vs 17.1±11.8 hrs) and delivery (20.0±21.4 hrs vs 17.6±12.0 hrs) were comparable between the low and high vaginal pH groups, respectively. Linear regression analysis revealed no significant association between vaginal pH and Bishop's score change over 12 hours, time to active labor, time to complete dilation, or time to delivery.

Discussion: Vaginal pH has significant effect on cervical ripening but has no effect on delivery outcomes in post-term patients with unfavorable cervices, who undergo cervical priming/labor induction using sustained-release dinoprostone vaginal insert.

Keywords: dinoprostone vaginal insert, vaginal pH, cervical ripening, labor induction

Özet

Servical Olgunlaşma/Doğum Eylemi İndüksiyonu İçin Kontrollü Salınan Dinoproston Vajinal Ovülünün Etkinliğinde Vajinal pH'ın Rolü: Prospektif Çift-Kör Çalışma

Amaç: Post-term hastalarda servikal olgunlaşma/doğum eylemi indüksiyonu için kontrollü salınan PGE_2 vajinal ovülünün etkinliğinde vajinal pH'ın etkisini değerlendirmek.

Materyal ve Metot: Uygunsuz servikal skora sahip (Bishop skoru ≤6) 63 post-term kadın bu prospektif çift-kör çalışmaya dahil edildi. Bütün hastalar 12 saat boyunca servikal olgunlaşma/doğum eylemi indüksiyonu için sürekli salınımlı dinoproston vajinal ovülü kullandı. Tekrar dozu 24 saat sonra 1 kez uygulandı.

Sonuçlar: Düşük vajinal PH'a (≤4.5, n=38) sahip kadınlar ile yüksek vajinal pH'a (>4.5, n=25) sahip kadınlar maternal yaş, parite, VKİ, gestasyonel yaş veya başlangıç Bishop skoru açısından benzer bulundular. Bishop skorunda ilk 12 saatte düşük vajinal pH'lı (3.9 3.3) ile yüksek vajinal pH'lı (5.5 3.4) gruplar arasında anlamlı/önemli bir değişiklik ($p<0.05$) olduğu saptandı. Düşük vajinal Ph ile yüksek vajinal pH'lı gruplar arasında elde edilen karşılaştırma sonucunda aktif doğum eylemi (14.7±17.3 saat; 13.1±9.8 saat), tam dilatasyon (19.6±20.1 saat; 17.1±11.8 saat) ve doğum zamanları (20.0±21.4 saat; 17.6±12.0 saat) bakımından yazılan sıraya göre her bir grubun zaman ve tolerans değerleri elde edildi. Doğrusal regresyon analizi sonucunda vajinal pH ile 12 saatlik Bishop skoru değişimi, aktif doğum eylemi zamanı, tam dilatasyon zamanı ve doğum zamanı arasında anlamlı bir ilişki bulunmadı.

Tartışma: Vajinal pH'nın servikal olgunlaşmaya önemli bir etkisi vardır; ancak, uygunsuz serviksi olan post-term hastalarda (doğum eylemi indüksiyonuna doğru giden, sürekli salınımlı dinoproston vajinal ovül kullanan) doğum sonuçlarına etkisi yoktur.

Anahtar sözcükler: dinoproston vajinal ovül, vajinal pH, servikal olgunlaşma, doğum eylemi indüksiyonu

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Introduction

About 20% of pregnant women undergo labor induction. When the uterine cervix is unfavorable (Bishop's score, ≤6), oxytocin, with or without amniotomy, is frequently ineffective for labor induction. The mainstay of induction of labor with an unfavorable cervix is the use of exogenous prostaglandins (1,2), which are effective not only in successfully achieving cervical ripening, but also in activating myometrial contractility.

Prostaglandin E_2 (PGE_2) is available in different formulations for local administration, including vaginal tablets, endocervical gels, vaginal gels and in the slow-release dinoprostone vaginal insert forms. Although efficacy and safety of vaginal insert form of dinoprostone on cervical priming and labor induction for singleton gestations at term were compared with an alternative vaginal or cervical prostaglandin in previous randomized trials (3-10), few studies have characterized factors that affect the relative clinical efficacy of these vaginally administered prostaglandin preparations (11).

Vaginal pH has been investigated (11-16) as a potential factor influencing the efficacy of prostaglandins for cervical ripening and labor induction but the results have been conflicting. Only two studies (11,16) have results on the effects of vaginal pH on the efficacy of controlled-release PGE_2 vaginal insert for cervical priming/labor induction. Ramsey et al. (11) showed that vaginal pH did not appear to influence the efficacy of the dinoprostone vaginal insert for cervical ripening/labor induction. On the other hand, Lyrenas et al. (16) demonstrated that there was a positive relationship between vaginal pH and PGE_2 release. Moreover, time interval from induction to delivery was found to be decreased linearly with increasing vaginal pH in the latter study.

As PGE_2 preparations have been used for vaginal administration, the acidity of the vagina may alter the release and this could result in variable clinical responses. Nonetheless, the effect of vaginal pH on overall efficacy of the cervical ripening/labor induction with dinoprostone vaginal insert has not been well studied (17).

The aim of this prospective observational double-blind trial was to investigate if vaginal pH has any effect on the efficacy of controlled-release PGE_2 vaginal insert for cervical ripening and labor induction in post-term patients with unfavorable cervix.

Materials and Methods

This is an observational study of otherwise healthy pregnant women with prolonged pregnancy (41 or more weeks of gestation), who required induction of labor with an unfavorable cervix (Bishop's score ≤6) between August-September 2005.

All patients were informed about the treatment protocol and informed consent was obtained from all of them after the study was approved by the Local Ethic Committee of the Zekai Tahir Burak Women's Health Education and Research Hospital at Ankara, Turkey.

Inclusion criteria included (1) singleton gestation with cephalic presentation and no contraindication for vaginal delivery (2), parity <4 intact membranes (3), unfavorable cervix (4), defined as a Bishop score ≤6 (as determined by the doctor S.O.) and (5) reassuring fetal heart rate (FHR) pattern without any uterine contraction on cardiotocogram.

Exclusion criteria were (1) previous uterine surgery, active vaginal bleeding (2), placenta praevia (3), estimated fetal weight >4000 g (4), suspicion of cephalopelvic disproportion (CPD) (5), previous attempted labor induction for the present pregnancy (6), suspection of vaginal infection (7), any contraindication to prostaglandin use (history of glaucoma, asthma, preexisting cardiac disease or known hypersensitivity against prostaglandins) (8).

Before other examinations were performed, each participant underwent a speculum examination and vaginal pH value was assessed by using indicator paper (Universalindikator pH 0-14, Merck KGaA, Darmstadt, Germany). The indicator paper was placed on the lateral vaginal wall between the two blades of speculum until it became wet. Color change of the strip was immediately compared with the manufacturer's colorimetric scale and the finding was recorded by a doctor (S.O.) as in the previous study by Günalp and Bildirici (15). Patients were seperated into two groups as "low vaginal pH group" (if vaginal pH ≤4.5) and "high vaginal pH group" (if vaginal pH >4.5).

Women scheduled for induction of labor received vaginal insert which was a hydrogel polymer matrix containing 10 mg dinoprostone. The pessary releases PGE_2 at a constant rate of 0.3 mg/h over 12 hour. It was inserted into the posterior vaginal fornix of the vagina and the patient was asked to remain recumbent for an hour to allow the vaginal insert to swell. Vaginal insert was removed after 12 hours. It was removed earlier only in the case of onset of activ labor (at least 4 cm cervical dilation with regular uterine contractions), the rupture of the membranes, or hyperstimulation syndrome.

The treatment period was followed by 12 hours rest. If the patient did not reach active labor spontaneously even in the rest period, treatment was repeated once more with the same regimen. If the patient was still not in the active phase at 36^{th} hour, treatment was defined as failed induction. In the case of failed induction, after a 12 hour rest, the patient was induced by low-dose oxytocin regimen once more for 12 hours. If active labor was not entered even after the 3^{rd} induction, the patient underwent cesarean delivery.

Continuous external electronic fetal monitoring was used for assessment of FHR and uterine contractions. In the case of hyperstimulation syndrome (abnormal contraction pattern associated with fetal heart rate deceleration) treatment was ceased and it was restarted if the pattern resolved. The diagnosis and treatment of hyperstimulation syndrome were performed as in the previous literature (18).

As PGE_2 insertion and labor management were carried out by a physician in the labor and delivery unit other than initial examining doctor (S.O.), both the patient and the physician were blinded to the vaginal pH measurement and initial Bishop's score.

Primary outcome measure was changes in Bishop's score over initial 12 hours; overall vaginal and cesarean delivery rates, the rate of uterine hyperstimulation syndrome, duration of stages of labor, neonatal complications including fetal weight >4000 g, meconium-stained amniotic fluid, 5-minute Apgar score ≤7 and the rate of admission to neonatal intensive care unit (NICU) were the secondary outcome measures.

A sample size of 24 women was identified to detect a mean 2-point difference (SD=2.4) in Bishop's score change during the initial 12 hours preinduction interval between the low and the high vaginal pH group (a=0.05 and b=0.2). We recruited 63 women totally, 38 in the low vaginal pH group and 25 in the high vaginal pH group.

Numeric values were expressed as mean ±SD and ordinal values were expressed as number (percentage). The normality of distributions of variables was analyzed by the Kolmogorov-Smirnov distribution equality test. The Student's *t*-test was used for statistical significance of differences in variables with normal distribution between groups. The χ^2 test, two-sided difference test between two proportions and the Mann-Whitney *U*-test were used for statistical significance of differences in variables with non-normal distribution between groups. Linear regression analysis was used to reveal significant association between vaginal pH and Bishop's score change over 12 hours, time to active labor, time to complete dilation or time to delivery. A *p* value of <0.05 was considered to be statistically significant. The SPSS 11.0 Statistical Package was used for statistical analysis.

Results

A total of 63 low risk post-term women with an unfavorable cervix were enrolled in this prospective double-blind trial. Median (range) pre-induction vaginal pH was 4 (3-7) for all of the patients; 38 patients in low vaginal pH group (median pH=4) and 25 patients in high vaginal pH group (median pH=5).

As illustrated in Table 1, baseline characteristics of both groups were similar with respect to maternal and gestational age, body mass index, gravidity, parity, pre-induction Bishop's score and amniotic fluid index (AFI).

Primary and secondary outcome measures were compared between the two groups in Table 2. In the high vaginal pH group, Bishop's score change over 12 hour after commencement of the first dinoprostone vaginal insert was statistically significantly higher than those in the low vaginal

Table 1. Baseline characteristics of patients

	Low pH (≤4.5) (n=38)	High pH (>4.5) (n=25)
Maternal age (year)	22.7±4.3	23.0±3.7
Gestational age (day)	291.4±1.3	291.8±1.7
BMI (kg/m²)	27.7±3.1	28.3±4.2
Gravidity (n)	1.5±0.8	1.6±1.0
Parity (n)	0.3±0.6	0.4±0.7
Bishop's score (n)	2.3±1.3	2.6±1.5
AFI <50 (mm)	14 (36.8%)	10 (40%)

Data are presented as mean ±SD or n (%). *P*>0.05 for all comparisons (Student's *t*-test and Mann-Whitney U-test). BMI: body mass index, AFI: amniotic fluid index.

Table 2. Comparison of primary and secondary outcome measures

	Low pH (≤4.5) (n=38)	High pH (>4.5) (n=25)	*p*
Bishop score change over 12 hr	3.9±3.3	5.5±3.4	0.03*
Hyperstimulation syndrome (n)	3 (7.9%)	2 (8%)	0.52†
Time to hyperstimulation syndrome (hr)	3. 2±1.7	2.4±1.2	0.24*
Time to membrane rupture (hr)	13.9±17.4	12.3±8.7	0.52*
Time to active labor (hr)	14.7±17.3	13.1±9.8	0.93*
Time to complete dilation (hr)	19.6±20.1	17.1±11.8	0.89*
Time to delivery (hr)	20.0±21.4	17.6±12.0	0.42*
Need for 2nd dose (n, %)	7 (18.4%)	2 (8%)	0.25†
Failed induction (n, %)	4 (10.5%)	1 (4%)	0.34†

Values are presented as mean ±SD or n (%), *Mann-Whitney U-test, †Fisher's exact test.

Table 3. Comparison of overall delivery outcomes

	Low pH (≤4.5) (n=38)	High pH (>4.5) (n=25)	*p* *
Vaginal delivery ≤24 hr	17 (73.9%)	17 (89.5%)	0.25
Total vaginal delivery	23 (60.5%)	19 (76%)	0.20
Total cesarean delivery	15 (39.5%)	6 (24%)	0.34

Values are presented as n (%), *Fisher's exact test.

Table 4. Comparison of adverse fetal outcomes

	Low pH (≤4.5) (n=38)	High pH (>4.5) (n=25)	*p*
Fetal weight >4000 g	2 (5.3%)	1 (4%)	0.64*
5-min Apgar score ≤7	1 (2.6%)	4 (16%)	0.15†
Meconium-stained amniotic fluid	5 (13.2%)	2 (8%)	0.52*
Admission to NICU	1 (2.6%)	1 (4%)	0.76*

Values are presented as n (%), NICU: neonatal intensive care unit, *Two-sided difference test between two proportions, †Fisher's exact test.

pH group (5.5±3.4 versus 3.9±3.3, $p<0.05$). Time from commencement of the first vaginal insert to hyperstimulation syndrome, time to rupture of membranes, time to active labor, time to complete dilation, time to delivery were not significantly different between the low and the high pH groups, respectively.

Rate of hyperstimulation syndrome (7.9% versus 8%), rate of those women who needed a second dose (18.4% versus 8%) and rate of those patients who failed for induction (10.5% versus 4%) were similar between the low and the high pH groups, respectively (Table 2).

Table 3 shows the comparison of overall delivery outcomes and the indications for cesarean section. Seventeen women (73.9%) in the low vaginal pH group delivered within 24 hours compared to 17 women (89.5%) in the high vaginal pH group ($p=0.25$). No significant differences were noted in the proportions of patients who delivered vaginally (60.5% versus 76%) and by cesarean section (39.5% versus 24%) between the low and the high pH groups, respectively.

Table 4 summarizes the perinatal complications. The percentage of infants with birth weight >4000 g was similar in both groups and no infant had birth weight >4500 g in the present study. Number of infants with Apgar score ≤7 at 5 minute were 1 (2.6%) and 4 (16%) in the low and high pH groups, respectively ($p=0.15$). Meconium was present in 13.2% of the infants of patients with low vaginal pH compared with 8% of the infants of patients with high vaginal pH ($p=0.76$). One infant in the low pH group (2.6%) and one infant in the high pH group (8%) were admitted to the neonatal intensive care unit ($p=0.76$).

Linear regression analysis revealed no significant association between vaginal pH and Bishop's score change over 12 hours ($r=0.246$, $p=0.112$), time to active labor ($r= -0.032$, $p=0.813$), time to complete dilation ($r= -0.039$, $p=0.802$), or time to delivery ($r= -0.031$, $p=0.845$).

Discussion

In this observational double-blinded study, effect of vaginal pH on slow-release dinoprostone vaginal insert was investigated in post-term women with unfavorable cervix undergoing cervical priming/labor induction. A statistically significant change was found in Bishop's score over the 12 hours after commencement of the first dose of PGE_2 vaginal insert to the posterior vaginal cervix, whereas no significant difference was present between the groups with respect to delivery and neonatal outcomes.

In the previous studies, controlled release PGE_2 vaginal insert have been shown to be effective in achieving cervical ripening and shortening the length of labor (19-24). Cervical ripening mechanisms of PGE_2 contain softening the cervix by altering the extracellular ground substance, increasing the activity of collagenase, elastase and total glycosaminoglycan, dermatan sulphate, and hyaluronic acid levels (25,26). This time-dependent collagen degradation by collagenases and other proteases and increase in hyaluronic acid results in a softer and more pliable cervix.

Although clinically effective, wide variability in efficacy of prostaglandins is occasionally noted between patients (14). Since the induction of labor is a challenge against time, factors affecting the therapeutic interval should be verified. From that point of view, vaginal pH has been investigated in several recent studies as a factor that may account for the variability observed clinically with the vaginally administered prostaglandin cervical ripening/labor induction agents (11-16).

In an *in vitro* study by Johnson et al. (12), release from different commercial preparations of PGE_2 was investigated and authors reported an increased prostaglandin release in solutions with a higher pH. MacDonald and Weir (13) later described the role of pH in relation to PGE_2 dissolution *in vitro*, reporting higher PGE_2 release from a hydrogel PGE_2 pessary with increased pH of 6.5 to 7.5.

To the best of our knowledge, there are only three previous studies in the literature; one (14) investigating the effect of vaginal pH on efficacy of dinoprostone gel and the other two (11,16) investigating the effect of vaginal pH on the efficacy of slow-release dinoprostone vaginal insert *in vivo* but giving conflicting results. The first study was carried out by Lyrenas et al. (16), who evaluated the *in vivo* relationship of vaginal pH and efficacy of a controlled-release dinoprostone vaginal insert in a series of 68 women with an unfavorable cervix who were undergoing labor induction. These investigators noted a significant correlation between vaginal pH and PGE_2 release from the insert.

Ramsey et al. (14) evaluated if vaginal pH has an effect on the efficacy of the dinoprostone gel for cervical ripening/ labor induction. In contrast to our study, authors noted a significant association between vaginal pH and time to active labor, complete dilation and delivery; however, pH was not significantly associated with change of Bishop's score during the initial 12 hours of cervical ripening. Recently, authors have carried out a similar study where they investigated if vaginal pH alters the efficacy of the controlled-release dinoprostone vaginal insert (11). In the latter study, they concluded that no significant association was present between vaginal pH and change of Bishop's score during the pre-induction interval, time to active labor, time to complete dilatation, or time to delivery.

We and only two aforementioned studies (11,16) evaluated the effect of vaginal pH on the efficacy of the slow-release dinoprostone vaginal insert for cervical ripening/labor induction. Our results supported the findings of the study of Lyrenas et al. (16) regarding effect of vaginal pH during cervical ripening period where there was a significant decrease in Bishop's score in patients with higher vaginal pH. Moreover, our results also supported the results of Ramsey et al's (11) study with respect to delivery outcomes where there was no relationship between vaginal pH and time to active labor, time to complete dilatation, or time to delivery. However, results of Lyrenas et al's study (16) regarding the effect of vaginal pH on delivery outcomes and results of Ramsey et al's study (11) regarding the effect of vaginal pH on change in Bishop's score were different than the findings of our study.

It was also reported in the two *in vitro* studies that PGE_2 release is raised at higher pH levels, it is predominantly ionized at a pH of 7.5 (pKa, 4.9), which may have diminished the potential for absorption (12,13). Lyrenas et al. (16) further noted that high vaginal pH (6.5-7.5) and therefore increased PGE_2 release would not equate to increased plasma concentrations of PGE_2 and its metabolites. Therefore, why vaginal pH affected the cervical priming but did not affect the labor outcomes in our study may be due to these findings that ionization of PGE_2 in high pH might cause local effects, like change in Bishop's score, and the diminishing of its absorption may decrease its systemic effects and therefore, absence of change in labor outcome.

Ramsey et al. noted a significant association between vaginal pH and time to active labor, complete dilation, and delivery; however, pH was not significantly associated with Bishop's score change during the initial 12 hours of cervical ripening in a study where 32 women received cervical ripening with the dinoprostone gel 5 mg intracervically, with repeated dosing one time 6 hours later (14). Moreover, authors revealed no significant association between vaginal pH and Bishop's score change during the preinduction interval, time to active labor, time to complete dilation, or time to delivery in their latter study where 34 women received preinduction with the dinoprostone vaginal insert 10 mg intravaginally for 12 hours (11). Furthermore linear regression analysis revealed no significant association between vaginal pH and Bishop's score change over 12 hours, time to active labor, time to complete dilation, or time to delivery in our study with 63 women receiving cervical priming/labor induction with the dinoprostone vaginal insert 10 mg intravaginally for 12 hours as in the latter study (11).

Although, there was statistically significant change in Bishop's score between the two groups, it did not seem to be clinically relevant since linear regression analysis showed no significant association between vaginal pH and Bishop's score change over 12 hours. This may be because of the closeness of the median vaginal pH values between the groups in the present study. Effect of vaginal pH on the efficacy of sustained-release dinoprostone vaginal insert could be better established if the vaginal insert had been moistened with solutions having different pH as in the previous studies (16,27).

In conclusion, findings of our small-scale study suggest that vaginal pH has significant effect on cervical ripening but has no effect on delivery outcomes in post-term patients with unfavorable cervices, who undergo cervical priming/labor induction using controlled-release PGE_2 vaginal insert.

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