Effect of vaginal pH on efficacy of dinoprostone gel for labour induction

1Dr. Neha Mourya, 2Dr. Purnima Pachori

1Resident Doctor, Department of Obstetrics and Gynecology, JLN Medical College, Ajmer, Rajasthan, India
2Professor, Department of Obstetrics and Gynecology, JLN Medical College, Ajmer. President FOGSI, Ajmer, Rajasthan, India

Correspondence Author: Dr. Neha Mourya, Resident Doctor, Department of Obstetrics and Gynecology, JLN Medical College, Ajmer, Rajasthan, India

Type of Publication: Original Research Paper

Conflicts of Interest: Nil

Abstract

Background: Induction of labour is defined as an intervention designed to artificially initiate uterine contractions leading to progressive dilatation and effacement of the cervix. Prostaglandin (PGE2) is a well-established agent that has a primary action in softening the cervix. They are organic acids that have diminished solubility in aqueous solution with a low pH. In general vagina maintains a pH between 3.8-4.8. A variety of factors may alter there lease of the drug and this could result in variable clinical response.

Objective: The purpose of this study was to evaluate whether vaginal pH has an effect on the efficacy of the PGE2 dinoprostone gel for labour induction.

Methodology: 150 women with indication for labor induction with Bishop’s score ≤6 were enrolled in this prospective observational study. After initial vaginal pH and Bishop Score assessment all women received dinoprostone gel intracervically for cervical ripening with repeated dosing twelve hours later or oxytocin/misoprost induction were initiated depending on cervical status. Clinical outcomes were evaluated. Statistical analysis was done using SPSS 16.0.

Results: Average initial vaginal pH was 4.75±0.89. No significant differences were noted between those patients with vaginal pH≤4.5 (group 1) compared with those with high pH> 4.5 (group II) with respect to maternal age. Subjects with higher parity were associated with higher vaginal pH parity (55.5% primigravida in group I vs 53.2% primigravida in group II). Higher vaginal pH was associated with a higher Bishop score prior to induction(4.94 in group II vs 3.12 in group II), responded to single induction, and had a higher number of vaginal deliveries than those with lower vaginal pH(41.45 % in group I vs 70.6% in group II.) There was no significant association found in vaginal pH and the time taken to enter into active phase of labour.

Conclusion: Vaginal pH has significant effect on cervical ripening and labour events by PGE2 gel induction.

Keywords – Induction, Vaginal pH, PGE2, Labour

Introduction

Induction of labour is defined as an intervention designed to artificially initiate uterine contractions leading to progressive dilatation and effacement of the cervix and birth of the baby. About 20% of pregnant women will have labour induced for a variety of reasons. There are various medical and surgical methods of Induction/Cervical ripening. Overall, induction of labour using prostaglandins seem to improve the rate of
successful vaginal delivery, lower the rate of caesarean section, lower epidural usage and to be associated with improved maternal satisfaction.[1,11]

Cervical ripening is the process that culminates in the softening and distensibility of the cervix, which facilitates labour and delivery. The cervix contains relatively few smooth muscle cells and derives its rigidity from collagen bundles surrounded by proteoglycans. In pregnancy nearing term, there are various factors that induce certain changes in the cervix leading to cervical ripening. There are agents that can artificially induce these changes if it has not occurred. It is difficult to separate methods of cervical ripening and labour induction.[2]

Prostaglandin (PGE$_2$) is a well-established agent that has a primary action in softening the cervix. Compounds such as IL-8 act synergistically with PGE$_2$ in attracting neutrophils.[3] The human uterine cervix can produce nitric oxide (NO), a free radical with an ultra-short half-life. Nitric oxide in the human uterine cervix acts as an endogenous ripening factor with an unknown mechanism of action. Nitric oxide and PGE$_2$ are the two pathways that, cross activating each other, trigger the cascade of events responsible for cervical ripening.[4]

M. Norman et al studied the metabolism of cervical connective tissue in cervical biopsies from non-pregnant and pregnant cases. The concentration of proteoglycans in the pregnant cervix was found to be approximately one-half of that in the non-pregnant cervix indicating that the turnover of proteoglycans in pregnant cervical tissue was significantly increased. After prostaglandin induction it was found that the decrease in sulfatedGAGS(glycosaminoglycans) could decrease electrostatic interactions that would weaken interfibrillar interaction that would be consistent with a decline in cervical resistance. The involvement of matrix metalloproteinases(MMP) i.e. MMP-2 and MMP-9 in the cervical ripening process has been indicated in cervical ripening.3,4 To summarize, the complex interactions of various cytokines bring about profound changes in the proteoglycans in the cervix which eventually leads to cervical ripening. 14 Recently, vaginal pH has been investigated as a potential factor influencing the efficacy of prostaglandins for cervical ripening and labour induction but the results have been conflicting. Studies have been conducted on the effects of vaginal pH on the efficacy of controlled-release PGE2 vaginal insert and PGE2 gel for cervical priming/labour induction in which overall vaginal pH seemed to influence the PGE2 release. The vaginal pH in pregnancy is known to be acidic and not much is known about the variations in vaginal pH throughout pregnancy. There are studies that mention that pH may change the degree of ionization of a drug and affect the absorption of the drug resulting in variable clinical responses. Vaginal pH changes also have a role in preterm delivery which suggests that it has a role in influencing cervical ripening.5 Nonetheless, the effect of vaginal pH on overall efficacy of the cervical ripening/labour induction with PGE$_2$ gel has not been well studied, thus this study is to evaluate the influence of vaginal pH on the efficacy of PGE$_2$ gel for cervical priming/labour induction which would improve patient selection for PGE$_2$ gel induction and reduce the incidence of failed induction. The purpose of this study is to evaluate the influence of vaginal pH on the efficacy of PGE$_2$ gel for cervical ripening/labour induction and assess its association with various baseline characteristics of patients and labour outcomes.

**Material And Method**

**Study Setting:** Observational Prospective Study was done at Rajkiya Mahila Chikitsalaya, Jawaharlal Nehru Medical College situated at Ajmer, Rajasthan, India. Total number of 150 subjects, for period of ten months from November
2016 to August 2017, who required induction, was enrolled in the study. Written and informed consent was obtained from all the patients after the study was approved.

**Inclusion criteria:** An unfavourable cervical Bishop score of < 6, Singleton pregnancy with vertex presentation, Reassuring fetal heart rate, Absence of spontaneous uterine contractions, no contraindications for induction.

**Exclusion criteria:** Known hypersensitivity to prostaglandins, Placenta Praevia, Suspected chorioamnionitis, A previous caesarean delivery or a history of uterine surgery, Cephalopelvic disproportion.

1. Each participant underwent a speculum examination and vaginal pH value was assessed by using pH indicator paper (both broad & narrow spectrum) after performing cardiotocography to rule out uterine contractions and to assess fetal status. The indicator paper was placed on the lateral vaginal wall between the two valves of Cusco’s speculum until it became wet. Colour change of the strip was immediately compared with the manufacturer’s colorimetric scale and the finding was recorded.

2. Patients were divided into two groups as Group I & Group II on basis of their vaginal pH. 
   - **Group I** included patients with vaginal pH <4.5
   - **Group II** included vaginal pH >4.5

   A vaginal examination was then performed to determine the Bishop’s score. Bishop score was assessed:

<table>
<thead>
<tr>
<th>SCORE</th>
<th>Cervical dilatation,(cm)</th>
<th>Cervical effacement</th>
<th>Cervical consistency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0-30%</td>
<td>firm</td>
</tr>
<tr>
<td>1</td>
<td>1-2</td>
<td>40-50%</td>
<td>medium</td>
</tr>
<tr>
<td>2</td>
<td>3-4</td>
<td>60-70%</td>
<td>soft</td>
</tr>
<tr>
<td>3</td>
<td>&gt;4</td>
<td>&gt;80%</td>
<td></td>
</tr>
</tbody>
</table>

The highest possible score is 13 and <6 is unfavourable that needs induction.

4. After ruling out all contraindications Dinoprostone gel was applied endocervically. The patient is then continuously monitored.

**Statistical Analysis**

The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics included computation of percentages, means and standard deviations. The independent t test (for quantitative data within two groups) was used for quantitative data comparison of all clinical indicators. Chi-square test used for qualitative data whenever two or more than two groups were used to compare. Level of significance was set at \( P \leq 0.05 \).

**Results:**

A total of 150 women with unfavourable cervix were enrolled with 75 cases in each group.

**TABLE 1: Vaginal pH and subjects baseline characteristics:**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (&lt;4.5)</th>
<th>Group II (&gt;4.5)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal pH</td>
<td>3.72±0.45</td>
<td>5.24±0.42</td>
<td></td>
</tr>
<tr>
<td>Age(years)</td>
<td>24.08±3.83</td>
<td>3.32±3.51</td>
<td>0.208</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.53±2.3</td>
<td>40.14±1.2</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Obstetric score | 55.5% primi | 53.2% primi | 0.02
--- | --- | --- | ---
Initial Bishop score | 3.12±1.59 | 4.64±0.48 | 0.49

Table 1 showed that there was no statistically significant association between the two groups with respect to maternal age, gravidity and gestational age but difference in mean initial bishop’s score was slightly significant being 0.49.

**Figure 1: Vaginal ph and Indication of Induction.**

PROM : prelabour rupture of membranes
TP: term pregnancy

Figure 1 showing Subjects with Post datism (56%) and term patient with Rh negative (28%) as indication of induction were found to have lower vaginal pH as compared to subjects with PROM (44% had higher vaginal pH.) Which would have been attributed due to basic nature of amniotic fluid.

Following induction, it was found that:

**FIGURE 2: Vaginal Ph Andmean Bishop Change Over 12 Hr.**

\[ X^2 = 12.85, \text{df}=2, \text{ p value}=0.002 \ (S) \]

**Figure 3: Vaginal Ph and Requirement of Augmentation:**

Figure 2 and 3 showing mean change in bishops score over 12 hours after 1st induction with PGE2 gel was higher in subjects with higher vaginal pH (0.69 in group I vs 2.04 in group II) and responded to a single induction (41.45% in group I vs 70.6% in group II) Table 3 showing that the mean time between the initial induction by PGE2 gel and delivery (irrespective of mode of delivery), was high in lower vaginal pH subjects (14.98
hours in group I vs 11.07 hours in group I) with p value = 0.001.

On assessment of delivery outcome among both the groups, it was found that:

Vaginal Ph and Mode of Delivery

<table>
<thead>
<tr>
<th>VAGINAL pH</th>
<th>Mode of delivery</th>
<th>FTLSCS</th>
<th>FTVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP I ≤4.5</td>
<td>N</td>
<td>42</td>
<td>71.1%</td>
</tr>
<tr>
<td>GROUP II &gt;4.5</td>
<td>N</td>
<td>17</td>
<td>28.8%</td>
</tr>
<tr>
<td>Total</td>
<td>N</td>
<td>59</td>
<td>100%</td>
</tr>
</tbody>
</table>

X²=23.98, df=2, p value=0.001 (S)

Vaginal Ph and Indication of LSCS: Comparison of Groups

<table>
<thead>
<tr>
<th>Vaginal pH</th>
<th>Failed induction</th>
<th>NPOL + NRFHR</th>
<th>NRFHR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP I ≤4.5</td>
<td>9 (81.8%)</td>
<td>15 (65.2%)</td>
<td>18 (72%)</td>
<td>42</td>
</tr>
<tr>
<td>GROUP II &gt;4.5</td>
<td>2 (18.1%)</td>
<td>8 (34.7%)</td>
<td>7 (28%)</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>11 (100%)</td>
<td>23 (100%)</td>
<td>25 (100%)</td>
<td>59</td>
</tr>
</tbody>
</table>

X²=40.69, df=7, p value=0.04 (S)

Subjects with lower vaginal pH were associated with more number of LSCS( 71.1% in group I vs 28.8% in group II). Among indications of LSCS, lower vaginal pH was more associated with failed induction (81.1% in group I vs 18.1% in group II).

Feto-maternal outcome: comparisons of group

<table>
<thead>
<tr>
<th>Vaginal pH</th>
<th>MS</th>
<th>NICU</th>
<th>NNJ</th>
<th>Observation</th>
<th>LSCS wound</th>
<th>Puerperal seps</th>
<th>PPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP I ≤4.5</td>
<td>38</td>
<td>4</td>
<td>3</td>
<td>33</td>
<td>5</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>GROUP II &gt;4.5</td>
<td>57</td>
<td>2</td>
<td>3</td>
<td>13</td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

X²=32.11,df=4,p value=0.09

X²=17.14, df=4, p value=0.09

Total there were only 6(4%) NICU admissions while 6 (4%) had neonatal hyperbilirubinemia „with overall 19 cases of post partum maternal complications , but none of fetomaternal outcome was associated with vaginal pH.

Discussion

Observations from the present study suggest that parity influences vaginal pH and vaginal pH itself has a significant effect on cervical ripening and the Bishop Score prior induction. With high vaginal pH, there is better chance of posotitive Bishops score change, often responds to a single induction and is more often associated with vaginal deliveries than LSCS and also reduced time to enter into active phase of labour and shorter delivery interval more so in multipara. Lowr vaginal pH is more associated with failed induction.

Vaginal pH has been investigated in several studies as a factor that may account for the variability observed clinically with prostaglandin used as cervical ripening/labor induction agents.

Johnson et al studied in vitro release of PGE from many commercially available preparations and reported higher release of prostaglandin in higher pH [6]

The first study was carried out in 2001 by Lyrenas et al, who evaluated the effect of vaginal pH and efficacy of a controlled-release PGE vaginal insert in 68 subjects with an unfavourable cervix who were undergoing labor induction and shown that the PGE2 release rate in women with PROM was not linear.[7]
Two in vitro studies by Johnson et al. and MacDonald and Weir describes an increased PGE2 release in solutions with a higher pH (6.5 to 7.5). It was also reported that along with the increased release of PGE2, it is also predominantly ionized at a pH of 7.5 (PKa, 4.9), which diminishes the potential of its systemic absorption.

Ramsey PS et al (2002) showed that vaginal pH was not significantly associated with bishop score change over initial 12 hours but had significantly shorter time to active labor and vaginal delivery in women with high vaginal pH > 4.5 [8].

AVG Taylor in response to Johnson et al pointed out that the acidic environment encountered at term delays PGE release and a significant increase in pH could explain the occasional case of uterine hyperstimulation associated with this preparation [13].

Basirat Z et al (2007) in their study found that the average duration of latent phase between individuals with low and high pH was not significantly different, but the duration of active phase in patients with high pH was lower than low pH which was significant (p=0.019). In the study the cesarean section rate in women with low or high vaginal pH showed no difference [9].

Onen et al (2008) in their study found that in the high vaginal pH group, bishop’s score change over 12 hour after commencement of the first Dinoprostone vaginal insert was statistically higher than those in the low vaginal pH group (5.5±3.4 versus 3.9±3.3, p<0.05). But there was no significant difference in time to active labor and time to complete delivery between the high and low pH groups [10].

**Conclusions**

The findings of the present study showed that vaginal pH can be an important predictor for success of PGE2 gel induction.

The pH is important in terms of the design and the efficacy of vaginal drug delivery systems.[16] The effect of vaginal pH on the efficacy of sustained-release PGE vaginal insert could be better established if the vaginal insert had been moistened with solutions having different pH as in the previous studies. Hence knowing the vaginal pH prior induction could prove to be a useful tool in assessing the labour outcome of a patient undergoing labour induction with PGE2 gel.

**Recommendation of This Study:** Further research is required to know about vaginal pH in pregnancy, cause of variation, and study of various agents that would increase the vaginal pH thereby creating a favourable environment for PGE2 gel induction, thereby decreasing incidence of failed induction and associated maternal morbidity.

**Abbreviations:**

PGE2 : prostaglandins E2  
PGE1 : prostaglandins E1  
IL : interleukins  
NO: nitric oxide  
ACOG: American College of Obstetricians and Gynaecologists  
WHO: World Health Organization  
NPOL: non progression of labour  
NRFHR: Non reassuring fetal heart rate  
LSCS: lower segment cesarean section  
MAS : meconium aspiration syndrome  
PROM: Prelabour rupture of membrane  
FTVD: full term vaginal delivery

**References**