A Randomized Trial Comparing Vaginal and Cervical Prostaglandin Gel for Cervical Ripening and Labor Induction

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Objective: To compare the effectiveness of intravaginal and intracervical prostaglandin \( E_2 \) (PGE\(_2\)) gel for cervical ripening, defined as an increase of 3 or greater in the Bishop score, and for induction of labor.

Methods: Women with Bishop score 4 or less were assigned randomly to receive either 2 mg PGE\(_2\) intravaginally \((n = 125)\) or 0.5 mg intracervically \((n = 122)\). If the Bishop score was 4 or less, another dose of PGE\(_2\) was given after 6 hours, and up to two additional doses were given 6 hours apart on the second day. An oxytocin infusion was begun when the Bishop score was 5 or greater in absence of spontaneous labor, or if labor had not begun on the third day.

Results: Baseline characteristics of the two groups were similar. Survival analysis showed that time from PGE\(_2\) application to obtain an increase of 3 or greater in the Bishop score, to vaginal delivery was significantly shorter with intravaginal PGE\(_2\) (logrank test: \( P = .003 \) and < .001 after stratification for parity, respectively). Thirty-one percent of women in the intravaginal gel group required oxytocin for labor induction compared with 63% in the intracervical group \((P < .001)\). There were no significant differences in relation to cesarean delivery rate, Apgar scores at 5 minutes, and arterial umbilical cord pH, although the power of our study was limited to detect differences in proportions of adverse outcomes.

Conclusion: Vaginal PGE\(_2\) gel is more effective than intracervical gel for cervical ripening and labor induction. (Obstet Gynecol 1998;91:65-71. © 1998 by The American College of Obstetricians and Gynecologists.)

When there is an indication for delivery and the Bishop score is low, the risk of failure to induce labor with oxytocin is high. This results in discouraged parturients and obstetricians, long occupation of delivery rooms, and a potential increase in unnecessary cesarean deliveries. Prostaglandin \( E_2 \) (PGE\(_2\)) is used commonly in local application (cervical or vaginal gels or tablets) to ripen an unfavorable cervix or to induce labor. However, the optimal dose and route of PGE\(_2\) application is controversial. Few studies have compared the efficacy of an intravaginal with that of an intracervical PGE\(_2\) gel. Previous studies included small numbers of women treated with different dosages and preparations of PGE\(_2\), and their results were sometimes conflicting.\(^1\)\(^-\)\(^6\)

We conducted a randomized trial to compare the effectiveness of an intravaginal with that of an intracervical PGE\(_2\) gel. The purpose of each method was to ripen the uterine cervix and to induce labor in women with singleton pregnancies and cephalic presentation who required induction of labor.

Materials and Methods

From June 1994 to October 1995, 247 women with singleton pregnancies admitted for induction of labor were allocated randomly to receive either intravaginal or intracervical PGE\(_2\) gel. The study was approved by the local ethics committee, and written informed consent was obtained from each participant. The study was conducted in the Department of Obstetrics and Gynecology of the Geneva University Hospital. In this institution, approximately 4000 women were delivered during the study period, with a cesarean delivery rate of 12%.

Women admitted for induction of labor were examined by one of the three senior faculty members to assess the Bishop score. Inclusion criteria to the trial were gestational age greater than 30 completed weeks, cephalic presentation, Bishop score 4 or less, intact membranes, absence of spontaneous labor, and reassuring electronic fetal monitoring. Women with known asthma were not eligible. Gestational age was calculated according to the date of the last menstrual period and first or second trimester ultrasound examination.
The randomization list was generated by computer with blocks of random length without stratification. Randomization of women was performed centrally immediately before beginning the induction. The randomization list was not available to the physicians examining the women or to the midwives in charge of their labor. Co-interventions in both groups were performed according to uniform guidelines.

Women were assigned to receive one of two commercially available forms of PGE2 gel (dinoprost): either 2 mg intravaginal PGE2 gel (Prostin), or 0.5 mg intracervical PGE2 gel (Prepidil). Both gels were supplied by Upjohn (Dübedorf, Switzerland). The intracervical gel was applied under direct vision during a speculum examination, using a syringe with a plastic catheter. The intravaginal gel was applied in the posterior vaginal fornix. Women in both groups were treated according to a uniform protocol. Fetal heart rate (FHR) was recorded electronically for 1 hour after gel administration. After this, the woman was allowed to ambulate. If uterine contractions were observed, the FHR was monitored for 30 minutes every hour. Another digital examination of the cervix was performed 6 hours after gel administration, or sooner if regular uterine contractions had started. If the woman was not in labor after 6 hours, and if the Bishop score was still 4 or less, a second PGE2 gel dose (vaginal or cervical as initially randomized) was given; if the Bishop score was 5 or greater, an oxytocin infusion was begun. The PGE2 gel administration and cervical assessments at 6 and 12 hours, respectively, were performed by the same resident in charge of the labor and delivery room. If necessary, up to two additional doses of the same PGE2 gel were given on the second day after the same protocol, for a total of four gel applications. On the third day, if labor had not begun, an oxytocin infusion was started.

The prespecified main outcomes of the trial were 1) the delay to obtain cervical ripening, defined as an increase of 3 or greater in the Bishop score and 2) the time to vaginal delivery. The time to vaginal delivery is an unambiguous outcome that can be measured objectively and precisely. A sample of 220 women was required to have a power of 0.80 to detect a difference of 3 hours from the first PGE2 gel application to delivery between the two groups, assuming a standard deviation of 8.0, at a two-sided α level of .05. This time difference was chosen because it was thought to be clinically relevant. Other outcomes measured included the number of PGE2 doses given, the proportion of women to whom oxytocin was given for induction or augmentation, the time to onset of cervical dilatation, and duration of cervical dilatation. The labor curve was graphed for each woman. The onset of cervical dilatation was defined as progressing cervical dilatation of 1 cm with regular painful uterine contractions. We also recorded epidural analgesia, cesarean delivery and intramuscular delivery rate, the neonatal 5-minute Apgar score, and arterial umbilical cord pH value. However, with a study group of 247 women, we had only a power of .70 to detect an increase in the cesarean delivery rate from 20% in one treatment group to 35% in the other group.

Side effects (fever, nausea, vomiting, and diarrhea) were recorded by the attending midwife in the research record. Fever was diagnosed when maternal axillary temperature was higher than 38°C on two separate readings. Maternal hemoglobin was measured shortly before inclusion and on postpartum day 3. The length of maternal hospital stay was calculated in days from the day of admission.

Data were analyzed with BMDP Statistical Software (BMDP Inc. Los Angeles, CA). The statistician was blinded to treatment details. No interim analysis was performed. Intent-to-treat analyses were done. Results are presented as medians with quartiles or 95% confidence intervals (CIs) or numbers (%). Statistical analyses included the Mann-Whitney U test, the χ2 test, the Fisher exact test, or the Mantel-Haenszel test. Time to events (an increase of 3 or greater in the Bishop score, full cervical dilatation, vaginal delivery) was described by means of Kaplan-Meier survival curves, and the two treatment groups were compared by the Mantel-Cox logrank test with and without stratification for parity. Women with cesarean delivery were censored at the time of surgery. Reflected CIs for the median survival times based on censored data were calculated. All tests were two-sided. A P value < .05 was considered statistically significant.

Results

Two hundred forty-seven women were allocated randomly to receive either 2 mg intravaginal PGE2 gel (n = 125) or 0.5 mg intracervical PGE2 gel (n = 122). The two groups were similar with respect to maternal and gestational age, parity, indication for labor induction, Bishop score, hemoglobin value, fetal gender, and weight (Table 1). No woman was excluded from analysis.

Cervical ripening, defined as the time to obtain a difference of 3 or greater in Bishop score after the first PGE2 application, was significantly shorter with intravaginal gel than with intracervical gel (P = .005 without stratification; P = .003 after stratification for parity) (Figure 1). In the intravaginal group, the median delay to obtain a difference of 3 or greater in Bishop score was 15 hours (95% CI 12, 19) for nulliparous women com-
Table 1. Baseline Characteristics of Groups Receiving Vaginal Gel and Cervical Gel

<table>
<thead>
<tr>
<th></th>
<th>Vaginal gel (n = 125)</th>
<th>Cervical gel (n = 122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td>30 (27–35)</td>
<td>31 (27–34)</td>
</tr>
<tr>
<td>Gestational age (wk + d)</td>
<td>40 (38 + 5–41 + 1)</td>
<td>40 (38 + 5–41 + 0)</td>
</tr>
<tr>
<td>&lt; 36 completed wk</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>&lt; 38 completed wk</td>
<td>15 (12%)</td>
<td>19 (16%)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>56 (45%)</td>
<td>57 (47%)</td>
</tr>
<tr>
<td>1</td>
<td>51 (41%)</td>
<td>48 (39%)</td>
</tr>
<tr>
<td>≥2</td>
<td>18 (14%)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>Bishop score before PGE₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (6%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>1</td>
<td>41 (33%)</td>
<td>35 (29%)</td>
</tr>
<tr>
<td>2</td>
<td>43 (34%)</td>
<td>42 (34%)</td>
</tr>
<tr>
<td>3</td>
<td>22 (18%)</td>
<td>23 (19%)</td>
</tr>
<tr>
<td>4</td>
<td>12 (10%)</td>
<td>14 (11%)</td>
</tr>
<tr>
<td>Indication for labor induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected fetal</td>
<td>58 (46%)</td>
<td>48 (39%)</td>
</tr>
<tr>
<td>macrosomia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 42 completed wk</td>
<td>24 (19%)</td>
<td>29 (24%)</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>17 (14%)</td>
<td>12 (10%)</td>
</tr>
<tr>
<td>IUGR</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (2%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Maternal fatigue</td>
<td>7 (6%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Others</td>
<td>14 (11%)</td>
<td>18 (15%)</td>
</tr>
<tr>
<td>Hemoglobin value (g/dL)</td>
<td>11.9 (11.1–12.6)</td>
<td>12.1 (11.3–12.8)</td>
</tr>
<tr>
<td>Female fetuses</td>
<td>55 (44%)</td>
<td>61 (50%)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3720 (3300–3970)</td>
<td>3570 (3150–3930)</td>
</tr>
</tbody>
</table>

IUGR = intrauterine growth retardation (< 10th centile for gestational age); PGE₂ = prostaglandin E₂.
Data are presented as median (quartile) or n (%).

pared with 9 hours (95% CI 8, 13) for parous women. In the intracervical group, the median time to obtain a difference of 3 or greater in Bishop score was 22 hours (95% CI 13, 28) for nulliparous women versus 17 hours (95% CI 12, 24) for parous women.

The time from the first PGE₂ administration to vaginal delivery was significantly shorter with intravaginal gel (median 21 hours, 95% CI 18, 31) than with intracervical gel (median 36 hours, 95% CI 30, 42) (P < .001). The time to vaginal delivery was shorter with intravaginal gel than with intracervical gel, both for nulliparous and for parous women (P < .001 after stratification for parity) (Figure 2). In the intravaginal group, the median time to vaginal delivery was 32 hours (95% CI 21, 36) for nulliparous women and 18 hours (95% CI 14, 25) for parous women. In the intracervical group, these intervals were 44 hours (95% CI 35, 65) for nulliparous women and 30 hours (95% CI 24, 37) for parous women.

The time from the first PGE₂ gel application to the onset of cervical dilatation was shorter after intravaginal PGE₂ gel than after intracervical PGE₂ (P = .001; P < .001 after stratification for parity). In the intravaginal group, the median time from the first PGE₂ application to onset of cervical dilatation was 18 hours (95% CI 13, 24) for nulliparous women and 12 hours (95% CI 9, 15) for parous women. In the intracervical group, these intervals were 29 hours (95% CI 26, 33) for nulliparous women and 22 hours (95% CI 14, 29) for parous women.

The time from the onset of cervical dilatation to full dilatation is represented in Figure 3. This interval of time was significantly shorter for parous than for nulliparous women (P < .001) but is similar for the two groups that received intravaginal and intracervical gels (P = .21 without stratification; P = .19 after stratification for parity).

In the intravaginal group, 40 women delivered after one PGE₂ gel application, 67 after two applications, 11 after three applications, and 7 after four applications. In the intracervical group, 27 women delivered after one PGE₂ gel application, 65 after two applications, 10 after three applications, and 20 after four applications. This difference in the number of PGE₂ doses received before

Figure 1. Kaplan-Meier survival analysis of time from the first prostaglandin E₂ application to an increase of 3 or greater in Bishop score comparing intravaginal and intracervical prostaglandin E₂ gels. Intracervical gel, nulliparous women (closed circles); intravaginal gel, nulliparous women (open circles); intracervical gel, parous women (closed squares); intravaginal gel, parous women (open squares). Mantel-Cox logrank test for comparison of intravaginal and intracervical gels after stratification for parity: P = .003.
delivery is statistically significant, with women in the intravaginal group requiring fewer doses of PGE$_2$ than women in the intracervical group ($P = .015$).

Oxytocin infusion, epidural analgesia, cesarean deliveries with their indications, and instrumental deliveries are shown in Table 2. Significantly fewer women in the intravaginal group required oxytocin for labor induction compared with the intracervical group ($P < .001$). This difference remained statistically significant after adjustment for parity ($P < .001$, Mantel-Haenszel test): 18 nulliparous women (32%) in the intravaginal group compared with 38 (67%) in the intracervical group, and 21 parous women (30%) in the intravaginal group compared with 39 (60%) in the intracervical group received oxytocin for labor induction. Three cesarean deliveries were performed for suspicion of uterine rupture. Two were performed in the intravaginal gel group, but rupture was not confirmed at laparotomy. One was performed in the intracervical gel group, and uterine rupture was confirmed at laparotomy; however, in this case, oxytocin was used for labor induction in women with previous cesarean delivery. Maternal and neonatal recovery was uneventful. Maternal side effects, hemoglobin loss, and length of hospital stay, as well as neonatal 5-minute Apgar score less than 7, arterial cord blood pH, and length of infant hospital stay are presented in Table 3. None of these outcomes differed significantly between the two treatment groups. Only one case of uterine hyperstimulation was reported in the intravaginal group.

**Discussion**

Compared with placebo, intravaginal PGE$_2$ has proved to be effective in promoting cervical ripening at term. There are few randomized studies comparing the intravaginal and the intracervical routes of application of PGE$_2$ for cervical ripening and labor induction. These studies have included relatively small numbers of women (60–125). Proper randomization is required to generate unbiased comparison groups. Ekman et al. studied 60 women at term and found...
that the intracervical route (0.5 mg PGE2 gel) was more effective than the intravaginal route (4 mg PGE2 gel) in women with a Bishop score 3 or less but not in women with a Bishop score of 4–5. They suggested that maternal side effects were more likely to occur with intravaginal gel and observed no noticeable neonatal complications. Zanini et al2 studied 100 women at more than 35 pregnancy weeks with Bishop score less than 6. They reported that the 3 mg PGE2 intravaginal gel had a greater effect on cervical ripening than the 0.5 mg PGE2 intracervical gel but that it had a significantly higher incidence of side effects. In a double-blind comparison of 2.5 mg intravaginal and 0.5 mg intracervical custom-made PGE2 gels, Hales et al3 found that the intravaginal gel resulted in a Bishop score change greater than 3 in significantly more women. However, they saw no difference in the occurrence of active labor or in the need for oxytocin induction or augmentation. Their sample size (100 women) was too small to have a reasonable power to show clinically important differences. These authors noted that the gel did spill out of the cervix during intracervical application in 85% of cases. They found no differences in maternal side effects or in neonatal Apgar scores.

In a study by Seeras,4 68 women were randomized to receive intravaginal or intracervical PGE2 gel, but three women who had received the PGE2 treatment who underwent cesarean delivery were excluded from analysis. This author found that the induction-labor and induction-delivery intervals were shorter with the intravaginal gel and reported no differences in perinatal outcome. In their study, Nuutila and Kajanoja5 compared the application of 1 mg intravaginal PGE2 gel, 2 mg intravaginal PGE2 gel, and 0.5 mg intracervical PGE2 gel in 110 women. They found no differences in the number of gel applications required or in the ripening time, labor time, cesarean delivery rate, or neonatal outcome. Lyndrup et al6 randomized 125 women to either 2.5 mg PGE2 vaginal pessaries or 0.5 mg intravaginal gel. They found that pessaries applied twice a day were more effective in inducing delivery than was one dose of cervical gel. They reported no differences in 5-minute Apgar scores or in the umbilical artery pH value.

In the present trial, we found that the administration of the intravaginal PGE2 gel resulted in a shorter interval from the first PGE2 application to cervical ripening and to vaginal delivery than did the administration of the intracervical PGE2 gel. The interval to vaginal delivery is shorter by about 12 hours in the intravaginal group compared with the intracervical group. This difference remains significant after stratification for parity, as illustrated by the Kaplan-Meier survival curve in Figure 1. Analyzing time to events as survival data allows one to take into account the results of women who underwent a cesarean delivery and thus avoids potential biases. For example, such a bias would have occurred if more women in one group had an early cesarean delivery for fetal distress or in case of a differential surgery rate. It is of interest that the intravaginal gel curve for nulliparous women is superimposable to the intracervical curve for parous women. The higher probability of an earlier delivery with the intravaginal PGE2 gel compared with the intracervical gel is of the same magnitude as the advantage offered by parity.
The time from the first PGE₂ gel application to labor after intravaginal PGE₂ gel is clinically and statistically significantly shorter than after intracervical PGE₂. More women went into labor after a lower number of PGE₂ gel doses in the intravaginal than in the intracervical group. Although PGE₂ applications were limited to three in some studies, we did give up to four gel applications when necessary, according to our previous clinical experience that this provides additional vaginal deliveries. In our study, 40 of 247 women had not been delivered after 4 gel applications. Eighteen of them subsequently were delivered vaginally.

It must be stressed that only 31% of women receiving the intravaginal gel versus 63% of women receiving the intracervical gel required oxytocin for induction.

In contrast, once cervical dilatation had begun, these differences were no longer observed: the proportion of women requiring oxytocin for augmentation and the duration of dilatation were similar with the two routes of PGE₂ administration. The number of women with epidural analgesia was also similar in both groups. The proportion of women who were delivered by cesarean, the indication for surgery, and the instrumental delivery rate also were similar. The absence of differences in the duration of labor, the need for oxytocin augmentation, and the rate and indications of cesarean or instrumental deliveries suggest that once labor has begun, the pattern of uterine activity is similar after intravaginal or intracervical PGE₂ gel application. This is reflected by the lack of statistically significant differences in median 5-minute Apgar scores, in the proportion of neonates with 5-minute Apgar score less than 7, in the median arterial cord blood pH, or in the proportion with pH less than 7.10 or less than 7.0. However, all four 5-minute Apgar scores less than 7, 14 of 22 arterial cord blood pH samples less than 7.10, and 3 of 4 pH samples less than 7.0 were among neonates in the intravaginal PGE₂ group. Our study did not have the power to detect clinically important differences in neonatal outcomes.

No differences in maternal side effects and postpartum hemoglobin loss were seen between the two routes of administration. Three women (2.4%) in the intravaginal group complained of vaginal discomfort. Hyperstimulation is sometimes reported with oxytocin or with prostaglandin use. This complication was not a prespecified outcome in our study, because of the difficulty in defining hyperstimulation objectively, and was reported only once, for a woman included in the intravaginal group.

The length of postpartum hospital stay may be used as a proxy for the presence of complications. The maternal and neonatal lengths of hospital stay were not statistically different between the intravaginal and the intracervical groups and were similar to the usual length of stay in Switzerland. The slightly longer maternal stay in the intracervical gel group reflects the longer induction period in this group.

Previous studies that compared vaginal PGE₂ tablets with intracervical or intravaginal PGE₂ gel failed to show significant improvement in labor outcome. Our randomized trial shows that intravaginal PGE₂ gel is more effective than intracervical PGE₂ gel in cervical ripening and labor induction. The reduced efficacy of the intracervical gel may be due to its lower dosage and to the spilling of the gel out of the cervical canal into the vagina. The difference in the effect of these treatments is large and has implications for obstetric practice. In addition, the intravaginal gel is easier to apply because speculum examination is not required, and it is associated with less discomfort for the woman.

References


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