

Pre-Induction Cervical Ripening: A Randomized Comparison of Two Methods

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Objectives: To compare two methods of pre-induction cervical ripening in a randomized clinical trial.

Methods: A single intracervical prostaglandin E₂ (PGE₂) gel application was compared with a single insertion of hygroscopic dilators in 441 women at term with unfavorable cervical scores. Induction success was defined as entry into active labor within 6 hours of oxytocin infusion.

Results: There was no statistical difference in pre- or post-ripening cervical scores. In the group receiving hygroscopic dilators, only 28% entered the active phase of labor within 6 hours of oxytocin infusion compared with 45% ($P < .001$) in the PGE₂ group. Thus, in this study, a change in cervical score did not directly predict induction success. There was a higher rate of postpartum endometritis (24 versus 14%; $P = .007$) and suspected neonatal infection (10 versus 5%; $P = .03$) in the dilator group.

Conclusions: Pre-induction ripening by hygroscopic dilators and intracervical PGE₂ was equivalent as measured by changes in the cervical score. The change in cervical score, however, was not predictive of successful induction, and PGE₂ was more frequently associated with induction success. Hygroscopic dilators were associated with a higher incidence of postpartum maternal and neonatal infection because of a longer duration of labor. Hospital charges for intracervical PGE₂ gel totaled \$522 compared with \$91 for the insertion of three dilators. (*Obstet Gynecol* 1995;85:614-8)

Delivery may be indicated when the cervix is unfavorable for induction. In such cases, cervical ripening before induction often results in a successful vaginal delivery. Techniques such as prostaglandin E₂ (PGE₂) gel^{1,2} and the insertion of intracervical hygroscopic tents³⁻⁵ have been used to accomplish this purpose. Although both methods are superior to placebo use, we are unaware of a large clinical trial comparing intracervical PGE₂ gel to hygroscopic mechanical dilation. Therefore, we initiated a randomized trial to compare

these two methods for pre-induction cervical ripening and subsequent successful induction of labor. We chose successful induction as one of the outcome variables examined because it is not clear that the post-ripening cervical score is as effective in predicting the success of induction as described for the initial cervical score.

Materials and Methods

The study was performed on patients delivered by residents and faculty of the University of South Florida at Tampa General Hospital from June 1, 1991, through December 31, 1993. The study design was approved by the institutional review boards of both the University of South Florida and Tampa General Hospital. Patients admitted for induction of labor who had a Bishop score⁶ of 8 or less on admission were potential candidates. Inclusion criteria included term gestation (greater than 37 weeks) by the best dating criteria available as per ACOG guidelines⁷; fetal well-being documented by nonstress test, contraction stress test, or biophysical profile; the absence of labor; no contraindication to labor; and the ability to render informed consent.

Based on an estimated 30% success rate of entry into the active phase of labor and expecting a 50% increase when intracervical PGE₂ gel was used, we estimated that a sample size of 175 patients was necessary for each group (with 95% confidence and 80% power). Based on an estimation of an overall 50% cesarean delivery rate in this group of patients, we looked for a decrease of 15% when intracervical PGE₂ gel was used, with 80% power and 95% confidence. By this calculation, we estimated that a sample size of 182 patients was needed in each group. Estimating a 10% drop-out rate, we set out to recruit approximately 200 patients in each group.

We randomized the patients into two groups with blocks of computer-generated random numbers. The

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blocks were stratified by gestational age, parity, and the pre-induction cervical score. One group received synthetic hygroscopic dilators (Dilapan; Gynotech, Middlesex, NJ). The second group received 0.5 mg of PGE₂.

The dilators used measured 4 × 65 mm. They were inserted in a sterile manner under direct visualization by a physician. We applied as many dilators as the cervix could accommodate and left them in place for 6 hours. The post-ripening cervical score was determined on removal of the dilators.

The gel was supplied by the hospital pharmacy in 2 mL syringes and frozen at -20°C for no longer than 14 days. The gel was prepared from suppositories that contained 20 mg of PGE₂ (Upjohn, Kalamazoo, MI). After formation of a paste through immersion in a warm water bath, this was combined with 40 mL of sterile hydrophilic gel (K-Y Jelly; Johnson & Johnson Medical Incorporated, Arlington, TX) to form a gel containing 0.5 mg/mL of PGE₂. One milliliter of the gel was inserted into the endocervical canal under direct visualization.

Whenever possible, the same physician evaluated the cervix both before and after cervical ripening. In all cases, each component of the score was recorded on a form detailing each component and the assigned score. External fetal monitoring was performed for 1 hour after insertion and at the discretion of the physicians thereafter. Oxytocin infusion at 1 mIU/minute was begun 6 hours after the ripening agent was applied. An oxytocin infusion protocol was used in a uniform manner by doubling the infusion rate at 30–40 minute intervals until a rate of 16 mIU/minute was reached, after which the infusion was increased by 2 mIU/minute at the same interval. The infusion rate was not increased above 30 mIU/minute.

If the patient had not entered the active phase of labor after 12 hours of oxytocin infusion, serial induction was undertaken at the discretion of the attending physician. Serial induction consisted of an overnight rest period followed by 12 hours of induction by oxytocin infusion. In some cases, this was done over a 3-day interval. When calculating the latent phase interval, we took into account the hours of oxytocin infusion. Artificial rupture of membranes was not performed before entry into the active phase of labor unless internal fetal monitoring was considered necessary. Artificial rupture of membranes was performed before entry into the active phase of labor in 15 of 202 patients (7.4%) receiving intracervical PGE₂ gel and 19 of 214 patients (8.9%) in the dilator group. Because they were randomly distributed in these groups, we included these patients in the statistical analysis.

Successful induction was defined as entry into the active phase of labor within 12 hours after the start of

cervical ripening (6 hours of oxytocin infusion). Chorioamnionitis was defined as persistent intrapartum fever of 100.4°F or greater, in the absence of any other known focus of infection. Neonatal infection was considered to be present when the infant had positive blood cultures or had a poor clinical course necessitating 7–10 days of intravenous (IV) antibiotic therapy. Postpartum maternal infection was defined according to accepted criteria (two febrile episodes 6 hours apart, with a clinical picture consistent with endometritis).

We used the SPSS (SPSS, Inc., Chicago, IL) statistical package to perform the data analyses. Parametric data were analyzed using unpaired Student *t* tests, whereas nonparametric data were compared using Pearson χ^2 analysis or Fisher exact test as appropriate, as well as forward stepwise logistic regression analysis. *P* < .05 was considered significant.

Results

Four hundred forty-one subjects were randomized to the study. Two hundred twenty-four patients received cervical ripening with dilators, and 217 patients underwent PGE₂ insertion.

Twenty-five (5.6%) patients were excluded from complete further statistical analysis after the initial epidemiologic analysis. In the dilator group, eight patients were excluded because of protocol violations, and two patients entered spontaneous labor before ripening. Ten patients in the gel group were excluded because of protocol violations, and three patients entered spontaneous labor before ripening. Two subjects who delivered before the completion of the 6-hour ripening interval in the gel group were excluded as well.

Inclusion of these subjects (intention to treat analysis) did not alter the results. Two hundred fourteen patients remained in the group receiving dilators, and 202 patients remained in the group undergoing intracervical gel insertion. Eight women who were discharged after a diagnosis of failed induction were included in the failure groups, but were not included in the analysis for mode of delivery.

There was no statistical difference between the groups in age, race, parity, height, weight, gestational age, or indication for delivery. Indications for induction included gestational hypertension, preeclampsia, chronic hypertension, diabetes mellitus, post-dates pregnancy (more than 42 weeks), oligohydramnios, suspected macrosomia or fetal growth retardation, non-reassuring fetal status, maternal cardiac disease, sickle cell disease, collagen vascular disease, and antiphospholipid syndrome (Table 1). There were no differences in neonatal birth weight, neonatal length, incidence of

Table 1. Clinical Characteristics

	Dilator group (N = 224)	PGE ₂ group (N = 219)
Maternal age (y)	23.8 ± 0.39	24.4 ± 0.43
Maternal height (in)	64.5 ± 0.19	64.8 ± 0.19
Maternal weight (lb)	190 ± 3.13	195 ± 3.10
Gestational age (d)	278 ± 1.05	279 ± 1.08
Nulliparity (%)	60.5	56.6
Previous cesarean birth (%)	9.4	9.6
Fetal birthweight (g)	3207 ± 43.19	3241 ± 41.79
Indications* (%)		
Post-dates/ oligohydramnios	53	54
Preeclampsia/chronic hypertension	60	59
Other	16	13

PGE₂ = prostaglandin E₂.

Data are presented as mean ± standard error of the mean.

Data did not reach the level of significance.

* Patients may have several indications.

previous cesarean birth, initial cervical score, or initial cervical dilation (Table 2).

Cervical score change in the dilator group (mean ± standard error of the mean 2.14 ± 0.11) and in the gel group (2.34 ± 0.15) was not significantly different ($P = .26$) (Table 2). The post-ripening cervical dilations in the dilator group (2.0 ± 0.07) and in the gel group (1.88 ± 0.13) were not significantly different ($P = .30$), either. Entry into the active phase of labor within 12 hours of ripening was more frequently achieved in the PGE₂ gel group than in the dilator group (44.6 versus 28.0%; $P < .001$).

The rate of cesarean delivery in the group receiving PGE₂ gel was 23.5 versus 31.8% in the group undergoing hygroscopic dilation ($P = .06$). Indications for cesarean delivery were similar in both groups. Arrest of dilation during the active phase occurred in 13.3% in the PGE₂ gel group and in 22.4% of the dilator group (P

Table 2. Ripening Characteristics

	Dilator group (N = 214)	PGE ₂ group (N = 202)	P
Admission cervical score	4.1 ± 0.12	4.2 ± 0.13	NS
Post-ripening cervical score	6.2 ± 0.14	6.5 ± 0.19	NS
Change in cervical score	2.14 ± 0.11	2.34 ± 0.15	NS
Contractions during ripening	24.9%	47.1%	<.001

PGE₂ = prostaglandin E₂; NS = not significant.

Data are presented as mean ± standard error of the mean or %.

Table 3. Labor Kinetics

	Dilator group (N = 214)	PGE ₂ group (N = 202)	P
Oxytocin use (h)	15.3 ± 0.6	13.3 ± 0.7	.048
Maximum infusion rate (mIU/min)	20.0 ± 0.6	16.3 ± 0.7	<.001
Total oxytocin (U)	12,995 ± 791	10,263 ± 740	.012

PGE₂ = prostaglandin E₂.

Data are presented as mean ± standard error of the mean.

= .06). Arrest of descent occurred in 4.2% of the gel group and 4.8% of the dilator group.

The cesarean delivery rate in the successful induction group was 3.3% ($N = 3$) in the intracervical PGE₂ gel group; none of the patients in the dilator group underwent a cesarean.

There were significant differences between the PGE₂ and dilator groups in the length of labor (13.3 ± 0.7 hours for the PGE₂ group versus 15.3 ± 0.7 hours for the dilator group; $P < .05$), maximum oxytocin infusion rate (16.3 ± 0.7 mIU/minute for the PGE₂ group and 20.0 ± 0.6 mIU/minute for the dilator group; $P < .0001$) and total oxytocin used (10,263 ± 710 U for the PGE₂ group and 12,995 ± 791 U for the dilator group; $P < .02$) (Table 3).

The groups experienced similar rates of vaginal examinations; chorioamnionitis; fetal tachycardia; repetitive, variable, or late decelerations; fetal distress; meconium stained amniotic fluid; and scalp pH determination. Use of IV narcotics, epidural anesthesia, and episiotomy were similar. The incidence of spontaneous rupture of membranes was similar between the two groups, as well (173 [36.1%] of patients in the PGE₂ gel group versus 64 [29.9%] in the dilator group; $P = .21$).

The Apgar score distribution was similar, as was the cord blood pH value. The rates of neonatal intensive care unit admission directly from the labor and delivery suite were comparable, but the rates of neonatal infection (4.5 and 10.0% for the PGE₂ and dilator groups, respectively; $P = .03$) and the postpartum maternal infection rate (13.8 and 24.2% for the PGE₂ and dilator groups, respectively; $P = .007$) were higher in the dilator group than in the PGE₂ group (Table 4). Maternal hospital stay was also longer in the dilator group (3.6 and 4.5 days for the PGE₂ and dilator groups, respectively; $P = .001$).

Logistic regression analysis was performed with postpartum infection as the dependent variable, correlating this with factors such as parity, ripening agent, length of labor, and delivery route. Analysis included first- and second-degree interactions between these factors. These variables were chosen based on the

Table 4. Maternal and Neonatal Outcomes

	Dilator group (N = 214)	PGE ₂ group (N = 202)	P
Neonatal infections	21 (10.0%)	9 (4.5%)	.03
Maternal hospital stay (d)	4.5 ± 0.19	3.6 ± 0.13	.001
Endometritis			
All patients	51 (24.2%)	28 (13.8%)	.007
Vaginal delivery	16 (11.2%)	8 (5.2%)	.06
Cesarean delivery	35 (52.2%)	20 (42.6%)	.31

PGE₂ = prostaglandin E₂.

Data are presented as N (%) or mean ± standard error of the mean.

previous findings of univariate analysis. A forward stepwise inclusion methodology was used. A final model included the delivery route, length of labor, and ripening agent used as accounting for the best correlation with postpartum infection. Cesarean delivery ($r = 0.37$, $P < .001$), length of labor ($r = 0.16$, $P < .001$), and cervical dilator use ($r = 0.08$, $P < .001$) influenced the rate of postpartum endometritis.

The factors affecting neonatal infection were examined in the same manner. Using neonatal infection as the dependent variable, logistic regression analysis included parity, ripening agent used, length of labor, delivery route, chorioamnionitis, postpartum infection, and first- and second-degree interactions as independent variables. Once again, these factors were chosen based on the previous findings during univariate analysis. A final model included the interaction of cervical dilator use and the presence of maternal infection ($r = 0.31$, $P < .001$).

Uterine activity during the ripening interval was more frequent in the PGE₂ gel group (24.9 and 47.1% for the PGE₂ and dilator groups, respectively; $P < .001$). During ripening, 13 (3.1%) patients in the PGE₂ group entered spontaneous labor, but none in the dilator group did so ($P < .12$). Three patients, all in the PGE₂ group, experienced an episode of hypertonicity. In each, this occurred within the first hour of ripening and did not result in an emergent abdominal delivery. All three women were induced because of oligohydramnios.

Discussion

The results of our study indicate that a single intracervical application of PGE₂ gel and hygroscopic dilators result in similar changes in cervical score, but vary in the rate of subsequent successful induction of labor with IV oxytocin. Patients ripened with PGE₂ gel had a greater chance of being in active labor after 6 hours of oxytocin infusion. However, the overall cesarean rates

in the two groups were not statistically different. In order for a difference of this magnitude to be statistically significant with 95% confidence and 80% power, we would need 478 patients randomized to each group.

The rate of maternal postpartum infectious complications was increased in the dilator group. Logistic analysis revealed that this increase was primarily due to the longer duration of labor in the hygroscopic dilator group because the rates of cesarean delivery in both groups were comparable.

The rate of diagnosis of neonatal infection was greater in the dilator group. The clinical diagnosis of neonatal infection is rather loosely defined, but the clinical effect is a prolonged neonatal hospital stay for IV antibiotic treatment. By logistic regression analysis, this higher rate seemed to be related to the same factors found to be significant in the increase of postpartum endometritis associated with dilators.

We should note that these effects were seen despite the lack of a significant difference in the cervical scores. This may indicate that intracervical PGE₂ more closely reproduces the physiologic cervical changes that occur before the spontaneous onset of labor. Cervical histologic studies, however, have shown similar changes with either of these agents.⁸⁻¹⁰

There are differences in hospital charges between the two methods. Labor and delivery charges, speculum tray, fetal monitoring for about 1 hour post-insertion, and the pharmacy charge totaled \$522 per patient for the intracervical PGE₂ gel group. Labor and delivery, fetal monitoring, and pharmacy charges were not incurred when we used dilators. The charges in our hospital totaled about \$91 per patient for insertion of three dilators.

Experience must also be considered. When a cervical hygroscopic mechanical dilator is used as a pre-induction ripening agent, this method will not be effective unless the internal os is entered. Virtually no experience is needed to effectively insert intracervical gel.

In this large study, there were no clinically significant episodes of uterine hypertonia or fetal bradycardia during the ripening phase in either group.

In summary, intercervical PGE₂ gel was equivalent to mechanical cervical dilation as measured by the change in cervical score. However, the post-ripening cervical score was not a reliable indicator of the relative efficacy of these two pre-induction ripening methods as measured by the successful achievement of active labor within 12 hours of ripening. It is important to note that successful induction of labor did not translate into a decrease in the overall cesarean rate.

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