Prostaglandin E_2 gel for cervical ripening and labour induction: a multicentre placebo-controlled trial

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Objective: To determine the effect of a single intracervical dose of prostaglandin E_2 (PGE_2) gel on cervical ripening and the need for subsequent labour induction with oxytocin.
Design: Multicentre randomized, double-blind, placebo-controlled study.
Setting: Tertiary care hospitals.
Patients: A total of 397 women met the inclusion criteria: gestational age of at least 36 weeks, parity of 3 or less, a Bishop score of 4 or less, intact membranes, an indication for induction, no contraindication to vaginal delivery, no history of cesarean section or major uterine surgery, no hypersensitivity to prostaglandins, no previous attempt at cervical ripening or induction, no vaginal bleeding and no fetal abnormalities.
Intervention: The experimental group (203 women) received a low dose (0.5 mg) of PGE_2 in 2.5 mL of gel and the control group (194) 2.5 mL of a placebo gel intracervically. The observation period was 12 hours before further induction (with oxytocin) was attempted.
Outcome measures: Ripening effect of gel, need for induction with oxytocin, rate of labour induction, time from gel administration to delivery.
Results: Seventeen women could not be evaluated because induction was not attempted after the first 12 hours (in nine cases) or the induction attempt was delayed for 24 hours (in six); in the other two cases the gel was in place for only 2½ and 4 hours respectively before cesarean section was required. The Bishop score 12 hours after the gel administration and the difference in the score from the time of admission to the end of the 12-hour observation period were significantly higher in the experimental group than in the control group ($p < 0.001$). In all, 91 (46%) of the 196 patients in the experimental group went into labour within the 12-hour observation period, as compared with 21 (11%) of the 184 in the control group ($p < 0.001$). When the women who required further induction were included the rate of successful induction was 85% (166 women) and 72% (132) respectively ($p < 0.004$). The mean interval from the time of gel administration to delivery was smaller in the experimental group than in the control group (19.8 v. 24.1 hours respectively) ($p < 0.001$).
Conclusions: A single, low dose of PGE_2 gel administered intracervically is a safe and reliable method of dealing with indicated but potentially difficult inductions.

Objectif : Déterminer l'effet d'une seule dose intracervicale de gel de prostaglandine E_2 (PGE_2) sur le mûrissement cervical et la nécessité de déclencher par la suite le travail à l'aide d'oxytocine.
Conception : Étude aléatoire multicentres, en double anonymat et contrôlée par placebo.
Contexte : Hôpitaux de soins tertiaires.
Patientes : Au total, 397 femmes ont satisfait aux critères d'inclusion : 36e semaine de

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gestation ou plus, 3e parité ou moins, cotation de Bishop de 4 ou moins, membranes intactes, déclenchement indiqué, aucune contre-indication à l'accouchement vaginal, aucun antécédent de césarienne ou de chirurgie utérine importante, aucune hypersensibilité aux prostaglandines, aucune tentative antérieure de mûrissement cervical ou de déclenchement, aucun saignement vaginal, aucune anomalie foetale.

Intervention : Les 203 femmes du groupe expérimental ont reçu une faible dose (0,5 mg) de PGE_2 sous forme de 2,5 mL de gel et les 194 femmes du groupe témoin ont reçu 2,5 mL d'un gel de placebo par voie intracervicale. La période d'observation a été de 12 heures avant qu'on procède à un autre essai de déclenchement (à l'aide d'oxytocine).

Mesures des résultats : Effet mûrissant du gel, nécessité de provoquer un déclenchement à l'oxytocine, taux de déclenchement du travail, temps écoulé entre l'administration du gel et l'accouchement.

Résultats : Dix-sept femmes n'ont pu être évaluées parce qu'on n'a pas essayé de déclencher l'accouchement après les 12 premières heures (dans neuf cas) ou parce que la tentative de déclenchement a été retardée de 24 heures (dans six cas); dans les deux autres cas, le gel n'avait été appliqué que depuis 2½ heures et 4 heures respectivement avant le moment où il a fallu procéder à une césarienne. La cotation de Bishop 12 heures après l'administration du gel et l'écart entre la cotation au moment de l'admission et la cotation 12 heures après l'administration du gel étaient beaucoup plus élevés chez les femmes du groupe expérimental que chez celles du groupe de contrôle ($p < 0,001$). Au total, le travail a commencé chez 91 (46 %) des 196 patientes du groupe expérimental au cours de la période d'observation de 12 heures et chez 21 (11 %) des 184 patientes du groupe de contrôle ($p < 0,001$). Si l'on inclut celles chez qui il a fallu déclencher l'accouchement, le taux de déclenchement réussis a atteint 85 % (166 femmes) et 72 % (132) respectivement ($p < 0,004$). L'intervalle principal entre le moment de l'administration du gel et celui de l'accouchement était moindre chez le groupe expérimental que chez le groupe témoin (19,8 c. 24,1 heures respectivement) ($p < 0,001$).

Conclusions : Une seule dose faible de gel de PGE_2 administrée par voie intracervicale est une façon sécuritaire et fiable de traiter des déclenchements indiqués mais qui peuvent présenter des difficultés.

Spontaneous labour and vaginal delivery in uncomplicated parturition follow a cascade of synchronous events, which include the softening and effacement of the cervix. If this "ripening" fails to occur attempts at induction may be prolonged, if not completely unsuccessful.[1]

Prostaglandin E_2 (PGE_2) has been widely reported in the literature as an effective and safe method for cervical softening and labour induction when induction is medically indicated.[2-4] Of all the reported routes of prostaglandin administration (e.g., into the posterior fornix and extramniotically) direct application into the cervical canal appears to be the most advantageous in terms of increased efficacy and diminished side effects.[5]

The objective of this study was to determine the effect of a single intracervical dose of PGE_2 gel on cervical ripening and the need for subsequent labour induction with oxytocin.

Methods

From July 1, 1985, to June 30, 1986, patients were enrolled in nine hospitals throughout Canada. The eligibility criteria were as follows: gestational age of at least 36 weeks, parity of 3 or less, a Bishop score of 4 or less (Table 1), intact membranes and a medical or obstetric indication for induction, as decided by the attending physician. Women were not included if they had any contraindication to vaginal delivery, a history of cesarean section or major uterine surgery, a known hypersensitivity to prosta-

Table 1: Cervical scoring chart[6]

	Score		
Characteristic	0	1	2
Dilatation, cm	0	1–2	3–4
Degree of effacement, %	0–30	40–50	60–70
Station	−3	−2	−1/0
Consistency	Firm	Medium	Soft
Position of the cervix	Posterior	Middle	Anterior

glandins, any previous attempt at cervical ripening or induction, suspected or clinically evident fetal compromise, vaginal bleeding, ruptured membranes or fetal death in utero.

Eligible patients were then randomly assigned in a double-blind fashion to receive PGE_2 gel (203 women) or placebo gel (194). Prepackaged preparations were used that had been coded by the pharmacy. The packages were similar in appearance, and the code was broken only after the study period ended.

On admission to hospital the patients were observed for 30 minutes before gel insertion. During this time their vital signs were recorded, the fetal heart rate and uterine activity were assessed with the use of a non-stress test, and the initial laboratory tests (complete blood count, renal and liver function tests and urinalysis) were performed. Evidence of any abnormalities or labour was sufficient for exclusion from the study. No record was kept of the number of patients who were excluded or who refused to give consent.

A Bishop score was assigned to the remaining patients who signed a consent form. Under direct cervical visualization 2.5 mL of gel containing either 0.5 mg of PGE_2 or placebo was injected with the use of a prepared syringe and a sterile 2.5-mm clear plastic catheter into the cervical canal to the level of the internal os.

The patients were kept in the delivery suite, and cardiotocographic monitoring was performed continuously for 1 hour and intermittently thereafter depending on the amount of uterine activity. The maternal vital signs were recorded every 15 minutes for 1 hour, every hour for 3 hours and then once every 4 hours thereafter.

If labour began patients were managed and monitored by the attending physician as deemed appropriate. Amniotomy was not performed until the cervix had dilated to 3 cm or more. Under no circumstances were any other uterotonic drugs such as oxytocin administered until at least 6 hours after the gel had been inserted unless delivery had occurred.

If labour did not ensue 12 hours after the gel administration, another Bishop score was obtained by the initial examiner. Patients not in labour at this time were induced with oxytocin according to the induction protocol in each institution. Continuous electronic fetal monitoring was then initiated, and the maternal vital signs were recorded regularly throughout labour. Unless contraindicated by a particular medical problem (fetal or maternal), induction with oxytocin was continued either until labour started or for a maximum of 12 hours. Management of patients who could not be induced and of labour was left to the discretion of the attending physician.

The newborn was examined immediately after birth, the Apgar score being determined at 1 and 5 minutes. Any fetal abnormalities occurring in hospital were noted. All maternal side effects were recorded, as was the administration of all drugs including analgesics, tranquillizers, anesthetics and antiemetics. It must be emphasized that strict surveillance techniques were used to monitor fetal and maternal side effects.

Statistical analysis

Analysis of variance (ANOVA) was used for most of the quantitative variables (i.e., weight, Bishop score change and leukocyte count) and for differences in treatment effects, investigator effects and treatment by investigator interaction (differing treatment effects by different investigators).[7] If a statistically significant interaction was found the treatment and investigator effects could not be tested; in that case, the variable of interest was examined separately for each investigator. For quantitative variables with a skewed distribution, a nonparametric two-way ANOVA (in which the ranks of the variable of interest replace the actual values) was used.

The analysis of qualitative factors (i.e., the achievement of labour during induction and the method of delivery) began with a logarithmic odds ratio test for heterogeneity in 2×2 tables for different investigators. If the test results differed significantly (indicating a treatment by investigator interaction) the 2×2 tables were examined separately for each investigator. If the test results were not significantly different the Mantel–Haenszel statistic[7] was used to determine whether there was an overall association between the treatment and the variable of interest.

Statistical significance for a test of interaction was defined as a p value of less than 0.10. For other tests significance was defined as a p value of less than 0.05.

Results

Study population

A total of 397 patients were enrolled in the study. The number at each centre treated with PGE_2 gel or placebo gel is indicated in Table 2. The two groups were similar in terms of age, weight, gestational age, gravidity or parity and initial Bishop score (Table 3). Table 4 summarizes the indications for labour induction, both primary and secondary.

Of the 397 patients 17 could not be evaluated because induction was not attempted after the first 12 hours (in 9 cases) or the induction attempt was delayed for 24 hours (in 6). In another two

cases the gel was in place for only 2½ and 4 hours respectively before cesarean section was required. In the first case there was deceleration of the fetal heart rate with mild contractions; in the second case the woman had gestational hypertension and abruptio placentae at 36 weeks. These two patients received PGE_2 gel.

Bishop scores

The mean Bishop score at the beginning of the study period was similar in the two groups (Table 5). After 12 hours the increase in the mean score and the absolute change from the original score were statistically significant in the two groups. For the

Table 2: Distribution of patients by treatment group and study site

Study site	Group; no. of patients: Experimental (PGE_2 gel)*	Control (placebo gel)	Total
Mount Sinai Hospital, Toronto	46	44	90
Ottawa Civic Hospital, Ottawa	3	3	6
Henderson General Hospital, Hamilton, Ont.	4	3	7
Toronto Hospital (General Division), Toronto	10	8	18
Hôpital Sainte-Justine, Montreal	34	36	70
McMaster Hospital, Hamilton, Ont.	30	25	55
Cité de la santé de Laval, Laval, Que.	26	24	50
Grace Hospital, Vancouver	32	34	66
Health Sciences Centre, Winnipeg	18	17	35
Total	203	194	397

*PGE_2 = prostaglandin E_2.

Table 3: Characteristics of patients by treatment group

Characteristic	Group; mean value: Experimental	Control
Age, yr	28.3	28.0
Gestational age, wk	40.3	40.1
Weight, kg	76.8	75.7
Gravidity/parity	1.9/0.5	1.7/0.4
Bishop score on admission	2.7	2.8

Table 4: Most common primary and secondary indications for labour induction by treatment group

Indication	Group; no. (and %) of patients†: Experimental (n = 203)	Control (n = 194)	Total (n = 397)
Overdue	83 (41)	84 (43)	167 (42)
Hypertension			
Gestational	48 (24)	39 (20)	87 (22)
Chronic	2 (1)	6 (3)	8 (2)
Cause unspecified	22 (11)	27 (14)	49 (12)
Diabetes*	37 (18)	25 (13)	62 (16)
Intrauterine growth retardation	14 (7)	18 (9)	32 (8)
Previous obstetric complications	8 (4)	8 (4)	16 (4)
Oligohydramnios	6 (3)	6 (3)	12 (3)
Other	16 (8)	25 (13)	41 (10)

*This included women with gestational diabetes and those with diabetes mellitus.
†There was more than one indication in some cases.

purpose of analysis a patient who went into labour and delivered was assigned a post-treatment Bishop score of 6.

Labour induction

During the 12 hours after the gel administration 91 (46%) of the 196 women in the experimental group and 21 (11%) of the 184 in the control group went into spontaneous labour ($p < 0.001$). Seventy-five (71%) of the 105 women given oxytocin in the experimental group and 111 (68%) of the 163 in the control group went into labour; this difference was not significant. However, when the numbers of women who went into labour are combined (166 [85%] in the experimental group and 132 [72%] in the control group) the difference is significant ($p < 0.004$).

The median interval from gel administration to delivery, including the interval for the patients who had to undergo cesarean section, was 19.8 hours in the PGE_2 gel group and 24.1 hours in the control group ($p < 0.001$). There was no statistically significant difference between the two groups in the interval from oxytocin administration to delivery (10.2 and 11.6 hours respectively).

Cesarean section

A total of 56 (28%) of the 203 patients in the PGE_2 gel group and 65 (34%) of the 194 in the placebo gel group underwent cesarean section ($p = 0.166$). The indications for cesarean section were evenly distributed throughout the two groups, the commonest being cephalopelvic disproportion, failure to progress, fetal distress and failed induction. The cesarean section rates were above average, possibly because the patients being induced were at high risk.

Infant and maternal outcomes

There was no statistically significant difference between the two groups in the infant Apgar scores at 1 and 5 minutes or in the incidence of neonatal jaundice. Also, there was no difference in the maternal vital signs or laboratory test results before and after the gels were administered.

The difference between the two groups in the incidence rate of fetal heart rate abnormalities was not significant ($p = 0.07$) (Table 6). If only contractile abnormalities were included the rate decreased to 1% in the experimental group and

Table 5: Mean Bishop scores on admission and at 12 hours after gel treatment

Time	Group; Bishop score (and standard deviation)		
	Experimental (n = 196)	Control (n = 184)	*p* value
On admission	2.7 (1.1)	2.8 (1.1)	0.43
12 h after treatment	5.3 (2.1)	4.3 (1.9)	0.01
Change in score	2.7 (2.0)	1.5 (1.5)	0.01

Table 6: Summary of fetal heart rate abnormalities*

Abnormality	Group; no. (and %) of patients	
	Experimental (n = 203)	Control (n = 194)
Bradycardia	4 (2)	4 (2)
Decelerations in heart rate		
Late	4 (2)	1 (0.5)
Variable	1 (0.5)	1 (0.5)
Unspecified	4 (2)	1 (0.5)
Poor beat–beat variability	1 (0.5)	0
Fetal distress		
During midforceps delivery	1 (0.5)	0
Unspecified	2 (1)	1 (0.5)
Total	17 (8)	8 (4)

*The difference between the two groups in the incidence of fetal heart rate abnormalities was not significant ($p = 0.07$).

2% in the control group. Uterine hypercontractility was reported in five (2%) and six (3%) of the patients respectively; an associated change in the fetal heart rate was noted in two and four of these patients respectively.

One of the two PGE_2 gel recipients with a change in the fetal heart rate had a Bishop score of 2 at 40 weeks' gestation as well as diabetes mellitus and hypertension. Fifteen minutes after the gel was administered uterine hypertonia was reported, followed by fetal bradycardia. The patient was observed closely, and cesarean section was performed 5.6 hours later; the infant's Apgar score was 9 at 1 and 5 minutes. The second patient had a Bishop score of 0 at 39 weeks' gestation and diabetes mellitus. At 45 minutes after the gel was administered excessive uterine activity was recorded along with a decreased fetal heart rate. This effect subsided satisfactorily, and she delivered vaginally 8.7 hours after the gel administration; the infant's Apgar scores were 6 and 10 at 1 and 5 minutes. The remaining three cases of hypercontractility after PGE_2 gel administration were all transient, and the women went on to deliver vaginally with normal outcomes.

In the control group four of the five cases of uterine hypercontractility were associated with a change in the fetal heart rate; three of the women had been receiving oxytocin. In the fifth case the fetal heart rate was normal and the hypertonia was mild and transient during the oxytocin administration.

Discussion

The ability of PGE_2 to facilitate and even initiate induction of labour has been demonstrated repeatedly.[1-5] Its action involves both a local "ripening" effect on the uterine cervix and the promotion of uterine contractile activity.[8] Initially the use of PGE_2 for this purpose met with resistance because of the unpredictable response and the systemic toxic effects associated with early high-dose preparations. Recent reports have demonstrated that lower doses applied locally can minimize maternal side effects without decreasing the drug's efficacy as a cervical ripening agent.[1,2]

In this study the use of commercially prepared low-dose (0.5 mg) PGE_2 stabilized in a viscous methylcellulose gel was successful in inducing labour. The drug appears to be free of major side effects for mother and fetus.

PGE_2 gel may occasionally result in uterine hypertonia. Because of the high-risk situation encountered when induction is an indication in cases with a low Bishop score, the administration of the gel must be followed by careful fetal monitoring throughout the latent period and especially in the first 1 to 2 hours after administration. I believe that PGE_2 gel can be safely used in any setting in which facilities to perform cesarean section exist.

Some questions remain unanswered. What is the optimal observation period after PGE_2 gel administration and before oxytocin induction — 4, 8 or 12 hours? The use of additional doses of the gel in refractory cases has been evaluated by Mainprize and associates;[9] however, such use has only recently been examined in a large clinical trial, the results of which have yet to be published.

In summary, a single low dose of PGE_2 gel applied intracervically is a safe and reliable aid in dealing with indicated but potentially difficult inductions. The product has the advantages of being uniformally prepared, accurate in dosage, stable, easy to apply and associated with minimal side effects for mother and fetus.

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References

1. Prins RP, Bolton RN, Mark C et al: Cervical ripening with intravaginal prostaglandin E_2 gel. *Obstet Gynecol* 1983; 61: 459-464
2. Trofatter KF, Bowers D, Gall SA et al: Pre-induction cervical ripening with prostaglandin E_2 gel. *Am J Obstet Gynecol* 1985; 153: 268-272
3. Yonekura MD, Songster G, Smith-Wallace T: Pre-induction cervical priming with PGE_2 intracervical gel. *Am J Perinatol* 1985; 2: 305-310
4. Bernstein P, Leyland N, Gurland P et al: Cervical ripening and labor induction with prostaglandin E_2 gel — a placebo controlled study. *Am J Obstet Gynecol* 1987; 156: 336-340
5. Ulmsten U, Wingerup L, Ekmar G: Local application of prostaglandin E_2 for cervical ripening or induction of term labour. *Clin Obstet Gynecol* 1983; 26: 95-99
6. Bishop EH: Pelvic scoring for elective induction. *Obstet Gynecol* 1964; 24: 266-268
7. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; 22: 719-748
8. Forman A, Ulmsten U, Banyai J et al: Evidence for a local effect on intracervical prostaglandin E_2 gel. *Am J Obstet Gynecol* 1982; 143: 756-761
9. Mainprize T, Nimrod C, Dodd G et al: Clinical utility of multiple-dose administration of prostaglandin E_2 gel. *Am J Obstet Gynecol* 1987; 156: 341-343

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