

# Outpatient Use of Prostaglandin Gel for Ripening of the Cervix and Induction of Labor

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*This case series reports the experience in a family practice center with the outpatient use of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) gel in patients with a medical or obstetric indication for induction. A retrospective medical record review of a 15-month period was completed for 45 women receiving intravaginal PGE<sub>2</sub> gel for cervical ripening before the induction of labor. A change in Bishop score was seen following application of the first gel in 21 women (54%). Six women (13%) had labor onset 1 to 16 hours after the initial gel placement, and an additional 19 women (42%) had labor onset within 48 hours of the final gel placement. Twenty-one women (47%) gave birth without the use of oxytocin, and only 11 women (24%) required oxytocin induction of labor. No significant differences were seen in type of delivery, delivery complications, or newborn outcome between categories of labor onset (spontaneous, PGE<sub>2</sub> gel, oxytocin). Two complications followed gel insertions, one case of uterine hyperstimulation and one case of a brief episode of fetal bradycardia. Both women were identified within the monitoring period and subsequently were delivered of healthy term infants. This case series demonstrates the usefulness and lack of adverse effects of outpatient PGE<sub>2</sub> gel as an adjunct in labor induction. J FAM PRACT 1990; 30:656-664.*

The onset of labor, defined as uterine contractions that bring about progressive cervical dilation and effacement with descent of the presenting part,<sup>1</sup> is a complex process involving altered hormonal levels and interaction between both oxytocin and prostaglandins.<sup>2-6</sup> Before the onset of labor, the cervix undergoes a gradual process of ripening, involving a rearrangement of rigid collagen fibers into a more flexible configuration.<sup>7</sup> Hormonal factors, in association with increasing prostaglandin concentration, appear to play an important role. Bishop's description of pelvic scoring<sup>8</sup> and a more recent report by Lange et al<sup>9</sup> of the value of prelabor cervical condition in predicting the inducibility of labor led to the use of various methods for cervical ripening.<sup>10-13</sup> Of these methods the most physiologic and successful were those using prostaglandins.<sup>7</sup>

While the use of oxytocin as a uterine stimulant gained widespread acceptance in the early 1960s, it was not until 15 to 20 years later that prostaglandin use before induction as a cervical ripening agent underwent investigation in

randomized placebo-controlled trials.<sup>14-20</sup> In addition to demonstrating successful cervical ripening, these studies reported a 30% to 60% rate of labor onset after either intracervical or intravaginal prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) gel placement with few adverse effects. Several additional studies investigated dosing intervals of every 6 hours to every 12 hours but found no advantage to sequential gel application.<sup>19,21-23</sup>

While these studies demonstrate the effectiveness of prostaglandin gel in preinduction ripening, the dosage, frequency, and method of gel application remain controversial. A recent placebo-controlled trial of outpatient cervical ripening with intravaginal PGE<sub>2</sub> gel in prolonged pregnancies demonstrated the safety and efficacy of a single gel application in both ripening and induction of labor, with 25% of 55 women in the gel group admitted in labor within 8 hours after gel placement.<sup>24</sup>

The purpose of the present study is to report the experience in a family practice outpatient center with the use of intravaginal PGE<sub>2</sub> gel for cervical ripening among patients with a medical or obstetric indication for induction. In compiling these data, specific attention was directed toward the indications for use of PGE<sub>2</sub> gel, the efficacy of cervical ripening or induction of labor through the use of single or repetitive PGE<sub>2</sub> gel placements, the subsequent

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need for oxytocin induction or augmentation of labor, and the safety of the protocol presented for the administration of the PGE<sub>2</sub> gel in the outpatient setting.

## METHODS

Forty-five patients received PGE<sub>2</sub> gel for outpatient cervical ripening between July 1, 1987, and October 30, 1988, in the family practice center of the University of Michigan Department of Family Practice. The practice is located in a community of 3850 people, with an additional 14,000 people living in the surrounding townships. The community is part of a standard metropolitan statistical area within Washtenaw County and is therefore considered urban. The population is 98% white and the median household income is \$22,499. Patients are seen by family practice faculty and residents for prenatal care, and their deliveries are attended by these physicians at the University of Michigan Hospital in Ann Arbor, Michigan. The decision to use PGE<sub>2</sub> gel was made on a case-by-case basis by the family practice resident or faculty physician with consultation with either the attending family physician or a university obstetric consultant.

The PGE<sub>2</sub> gel was prepared by grinding a whole 20-mg suppository (Prostin, Upjohn Company, Kalamazoo, Mich) and mixing it with 100 mL of sodium carboxymethylcellulose 2% gel. Samples of prostaglandin (2 mg) were drawn up into 5-mL plastic syringes and kept frozen. The gel was thawed at room temperature just before use.

The protocol for all PGE<sub>2</sub> gel insertions was as follows: (1) Before gel insertion, all patients underwent a nonstress test, which was considered reactive if two fetal accelerations (15-beat acceleration for 15 seconds or at least 10% of baseline) were seen associated with fetal movement within 10 minutes. (2) After a reactive nonstress test, the cervix was examined and a Bishop score assigned. A 16-gauge angiocatheter tube was then connected to a gel-filled syringe, and the thawed gel was placed into the posterior vaginal fornix. (3) Patients were continuously monitored for an additional 30 minutes with an external fetal heart rate monitor and a uterine tocodynamometer. (4) Patients were instructed to call or return if contractions occurred as often as 5 minutes apart. An assessment of cervical change was performed on the return visit, as arranged by the physician, or at admission to the hospital in labor.

At the end of the study period, maternal office and hospital medical records and hospital records for the newborns were reviewed for outcome information. Data were analyzed statistically by Student's *t* test and analysis of variance for continuous outcome measures, and a chi-square test was used for categorical outcome measures.

## RESULTS

The 45 women who received PGE<sub>2</sub> gel over the study period represented 86% of all women undergoing an induction procedure ( $n = 45/52$ ) and 14.7% of the total number of women who were cared for by family physicians and who were delivered of liveborn infants during the study period. Of the seven women who underwent induction without prior outpatient use of PGE<sub>2</sub> gel, six underwent oxytocin induction: four with prolonged rupture of membranes (>24 hours), one who had a Bishop score of 6 and pregnancy-induced hypertension, and one who was transferred to the university hospital because of a nonreactive nonstress test before the planned outpatient insertion of gel. The latter woman underwent inpatient gel placement after a negative contraction stimulation test and subsequent oxytocin induction. The remaining woman was induced by amniotomy alone for polyhydramnios. Characteristics of the study population are presented in Table 1. There were 21 nulliparous women.

Indications for PGE<sub>2</sub> gel use are listed in Table 2. The number of PGE<sub>2</sub> gel applications for cervical ripening ranged from 1 to 10, with a mean of 2.6 ( $\pm 1.8$ ) per woman. There was no relationship between the number of gel placements and delivery complications (fetal distress, meconium staining, or need for resuscitation). The frequency of gel application ranged from daily to weekly. There were too few cases with consistent dosing frequency ( $n = 20$ ) to observe any patterns, but women receiving daily gel insertions appeared no more likely to be induced by gel alone ( $n = 4/9$  compared with 5/11). A change in Bishop score<sup>8</sup> was seen following the first insertion of gel in 21 women (54%). Mean Bishop score before gel placement was 3.48 (range 0 to 6) and mean Bishop score following gel placement was 4.22 (range 0 to 9). There was no relationship between either cervical change after the first gel application or initial Bishop score and whether the patient underwent oxytocin induction or augmentation. Gestational age at initial and final gel application is shown in Table 2.

Six women (13%) had labor onset 1 to 16 hours after the initial gel placement. An additional 19 women (42%) had labor onset within 48 hours of the final gel placement (Table 2). Twenty-one women (47%) were delivered without use of oxytocin, nine women (20%) were delivered who received oxytocin augmentation of labor, and 11 women (24%) required oxytocin induction of labor (two after a previous failed oxytocin induction) (Table 3). Four women failed an initial oxytocin induction but were delivered without further use of oxytocin. Two women gave birth spontaneously (over 48 hours after oxytocin or PGE<sub>2</sub> gel use), and two had onset of labor within 24 hours and 48 hours, respectively, after an additional gel placement.

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION (N = 45)

	No.	Percent	Mean
Demographics			
Age (y)	15-38		23.6
Race			
White	43	96	
Other	2	4	
Gravida	1-6		2.2
Para	0-2		0.87
Abortus	0-4		0.5
Risk factors			
Obesity*	8	18	
Poor psychosocial†	7	15	
Smoking	7	15	
Presentation >20 wk	7	15	
Chronic hypertension	3	7	
Prior cesarean section	1	2	
Other‡	4	4	
Pregnancy complications			
Pregnancy-induced hypertension/preeclampsia	10	22	
Vaginal bleeding after 1st trimester	4	9	
Anemia (hematocrit <0.30)	2	4	
Gestational diabetes	2	4	
Herpes in pregnancy	1	2	
Pelvic inflammatory disease in pregnancy	1	2	
Premature rupture of membranes >24 h	1	2	

\*Obesity defined as 30% over ideal weight.

†Poor psychosocial defined as current marital discord, single without support, and/or poverty.

‡Includes carcinoma-in-situ of the cervix, seizure disorder, positive tuberculin test, and inguinal hernia.

Type of delivery and pregnancy outcomes are presented in Table 4. Thirty-three women (77%) had normal spontaneous vaginal deliveries, two (4%) had deliveries assisted by low forcep or vacuum extraction, two (4%) had vaginal deliveries about which further information is not available, and eight (18%) had primary cesarean sections. While numbers are low, no significant differences were seen in type of delivery, delivery complications, or newborn outcome between category of labor onset. There were three newborn complications that included two infants with transient tachypnea of the newborn and one with a fractured clavicle.

Two complications followed gel application. One woman, induced for pregnancy-induced hypertension, had a 4-minute tetanic contraction with no change in fetal heart rate from baseline. This woman had spontaneous onset of labor 4 days later with vaginal delivery of a healthy term infant at 39 weeks' gestation by dates and 42 weeks, large for gestational age, on newborn examination. The remaining woman, induced for gestational diabetes, had a 60-second fetal heart rate deceleration to 90 beats per minute

within 30 minutes after gel placement. This woman was transferred to the university hospital for an oxytocin challenge test, which was normal, and subsequent oxytocin induction resulting in a vaginal delivery of a healthy term infant at 41 weeks' gestation by dates and newborn examination.

There were no differences in labor duration between groups by type of labor onset. There was a significant difference between multiparas and nulliparas only in duration of second stage labor ( $t = 2.37, P < .05$ ). While multiparous women had no greater chance of developing onset of labor after a single gel insertion, they were significantly more likely than nulliparas to respond to PGE<sub>2</sub> induction after multiple gel insertions ( $\chi^2 = 8.98, P = .02$ ).

## DISCUSSION

### Indications

Prolonged pregnancy was the most common indication for cervical ripening and labor induction in this study, with

TABLE 2. INDICATIONS FOR PGE<sub>2</sub> GEL PLACEMENT, PROCEDURES, AND RESULTS OF FINAL GEL PLACEMENT

Indications	No.	Mean No. of Gel Insertions	Gestational Age, 1st Gel (wk)	Gestational Age, Last Gel (wk)	Onset of Labor*		
					<12 h	12-24 h	25-48 h
Prolonged pregnancy	25	2.3	41.4	41.8	7	6	4
Pregnancy-induced hypertension/preeclampsia	10	3.1	38.9	39.9	0	0	1
Suspected intrauterine growth retardation	2	6	38.1	39.6	0	0	0
Gestational diabetes mellitus	2	3	38.4	40.1	1	0	0
Chronic hypertension†	2	1.5	39	39.5	0	1	1
Other‡	4	2	40.3	40.7	1	2	0

\*Onset of labor in hours after final gel placement.

†Hypertension prior to pregnancy.

‡Includes painful inguinal hernia (1), suspected large infants (2), and grade III placenta seen on ultrasound (1).

maternal hypertension, including pregnancy-induced hypertension and preeclampsia, being the second most common indication. It should be noted that the PGE<sub>2</sub> gel was applied specifically for the purpose of cervical ripening, recognizing that induction of labor might also ensue. The intention was to effect cervical ripening, thereby allowing for a more successful induction should it become necessary. Nevertheless, this study presents an aggressive approach to prolonged pregnancy with gel application beginning before 42 weeks' gestation in the majority of patients. While this policy led to few postterm infants, no dysmature infants, and few adverse effects, the current literature is not clear on whether the benefits outweigh the risks in routine induction at or after 42 weeks' gestation.<sup>25-29</sup> In fact, with the exception of Dyson et al,<sup>28</sup> no benefits were seen from an induction over an expectant management policy in the remaining studies. While these studies include only a few women, it seems reasonable to conclude that either approach to management appears safe, and the decision to induce might be based on other factors.

No patient presenting with ruptured membranes to the family practice center was deemed to be a candidate for gel placement. Ekman-Ordeberg et al,<sup>30</sup> in a randomized

study of 20 women with premature rupture of the membranes and unfavorable cervixes given either intravenous oxytocin or a 4-mg prostaglandin E<sub>2</sub> gel, found the application of gel resulted in more effective labor progression with fewer instrument or operative deliveries and without any apparent added risk of infection. This finding was later confirmed in a larger study by Goeschen.<sup>31</sup>

**Efficacy**

Previous randomized clinical trials and case series on PGE<sub>2</sub> gel application have demonstrated benefits in terms of induction without use of oxytocin, fewer instrument or operative deliveries, fewer failed oxytocin inductions, and shorter duration and dose of oxytocin in labor induction.<sup>15,18,20,21,24,32</sup> The present study, although as a small case series it can do little to expand on these data, demonstrates the positive effects of the PGE<sub>2</sub> gel on cervical ripening and induction of labor, which occurred in the majority of women in this study. Similarly, the greater effectiveness, at least of multiple gel placement, on prostaglandin-associated labor in multiparas in this series is also confirmed in the literature.<sup>32,33</sup>

TABLE 3. INDICATIONS FOR PGE<sub>2</sub> GEL USE AND USE OF OXYTOCIN

Indication	No.	Oxytocin Augmentation	Oxytocin Induction
Prolonged pregnancy	25	7 (15%)	7* (15%)
Pregnancy-induced hypertension/preeclampsia	10	1	6†
Suspected intrauterine growth retardation	2	0	1
Gestational diabetes mellitus	2	0	1
Chronic hypertension	4	1	0

\*Three women failed induction with subsequent spontaneous onset of labor in two and onset of labor within 48 h in one.

†One woman failed induction and had onset of labor within 24 h.

TABLE 4. PREGNANCY OUTCOMES (N = 45) BY TYPE OF LABOR ONSET

Outcome	Spontaneous Onset of Labor* (n = 9)	PGE <sub>2</sub> gel Induction† (n = 25)	Oxytocin Induction (n = 11)
Delivery type			
Vaginal	7	19	10
Cesarean section CPD	2	2	1
Cesarean section FD	0	2	0
Cesarean section breech	0	1	0
Data missing	0	1	0
Meconium	1	9	2
Fetal distress	1	3	0
Normal newborn	8‡	22‡	11
Data missing	0	1	0
Birthweight, g, mean	3577.0	3749.4	3599.2
Apgar 1-min, mean	8.1 (≤5 = 0)	7.8 (≤5 = 1)	7.3 (≤5 = 2)
Apgar 5-min, mean	8.9 (<7 = 0)	8.9 (<7 = 0)	8.5 (<7 = 0)
Resuscitation			
Bag/mask	0	1	1
ET/meconium	0	5	0

\*Spontaneous onset of labor was labor beginning 48 h or more after gel placement or failed oxytocin induction.

†PGE<sub>2</sub> gel induction was onset of labor within 48 h of gel placement.

‡Abnormal newborns included transient tachypnea of the newborn (2), and fractured clavicle (1).

CPD—cephalopelvic disproportion; FD—fetal distress; ET—endotracheal suctioning for meconium.

One interesting finding in this study is the time frame of 48 hours from gel insertion to ripening and subsequent labor onset without oxytocin induction. Most study protocols induced women with intravenous oxytocin after 12 hours in the absence of labor following prostaglandin E<sub>2</sub> application. While local cervical effect (that is, ripening) appears to occur relatively rapidly (within 5 hours in the majority of cases),<sup>22,34</sup> Ulmsten et al<sup>14</sup> noted a change in Bishop score after intracervical gel placement for up to 24 hours after treatment, and Ekman et al<sup>34</sup> found that an immature cervix reached maturity in 90% of women after 30 hours. Wiqvist et al,<sup>19</sup> in considering an observed latency after a second dose of PGE<sub>2</sub> gel before the onset of "spontaneous" contractions, hypothesized that the gel might be releasing endogenous prostaglandins or oxytocin that required some time for results. Protocols that begin induction 12 hours after gel placement may not be allowing sufficient time for the full effects of the ripening-to-induction process to be realized. Finally, the intravaginal route of gel administration may not be so effective as the intracervical route in cervical ripening and induction for an unfavorable cervix.<sup>35</sup> The intracervical route may also offer advantages in less systemic absorption, although both altering the vehicle for vaginal drug administration and lowering the dose may further limit side effects without lowering efficacy.

### Safety

In a recent review of prostaglandin E<sub>2</sub> gel for cervical ripening and induction of labor, Rayburn<sup>36</sup> concluded that the benefits as noted above, along with few maternal side effects and favorable neonatal outcomes, offer a major therapeutic advantage in the induction of labor. Concerns have been raised, however, regarding both uncontrolled labor induction, as opposed to cervical ripening, and the dangers of uterine hyperstimulation.<sup>15,37</sup> In fact, the stimulation of contractions following the application of PGE<sub>2</sub> indicated to the authors of one study the inappropriateness of using prostaglandin for local cervical ripening, especially in patients with uteroplacental insufficiency.<sup>38</sup> Uterine hyperstimulation, with an incidence of 0.6% to 8%, has been reported with both intracervical and intravaginal gel placement.<sup>14,15,18,20,32</sup> This effect, however, is dose related, rapid in onset (immediately,<sup>20</sup> 15 minutes,<sup>18,24</sup> soon after gel placement<sup>15</sup>), likely related to parity, being more common in multiparous women, and quickly abolished with betamimetic tocolytic agents. This rate is not thought to be more common than that seen with oxytocin administration and is minimal with either the 0.5-mg intracervical dose<sup>39</sup> or intravaginal gels of 3 mg or less.<sup>32,33</sup> The exception for intravaginal administration may involve the use of triacetin or Tylose gels in the preparation of prostaglandin E<sub>2</sub> gel, which appears to

result in more rapid absorption and therefore potentially greater systemic effects than the sodium carboxymethylcellulose gel used in this study.<sup>35,37</sup> Fetal bradycardia, felt to be related to uterine hyperstimulation, occurs in less than 1% of reported cases and is seen most commonly in the first half hour of observation.<sup>36</sup> Macer et al,<sup>33</sup> however, reported an episode of fetal bradycardia 1.25 hours after placement of the prostaglandin suppository before any uterine activity was appreciated. As the infant at birth had Apgar scores of 9 and 9 at 1 and 5 minutes, the significance of this episode is unclear. In this study, fetal bradycardia did not appear to be related to uterine hyperstimulation. While the 30-minute monitoring period following gel placement seems sufficient for the detection of uterine hyperstimulation, it may be more prudent to monitor for an additional hour, particularly when contractions occur in response to the gel. Monitoring longer would also avoid problems with gel leakage following placement. Other systemic effects such as maternal vomiting, fever, and diarrhea are thought to occur in 0.2% of cases.<sup>36</sup> As PGE<sub>2</sub> gel induction of labor is believed to be a systemic effect as well, it is possible that vomiting, fever, and diarrhea may be early markers of women at risk for adverse effects and in need of additional monitoring.

Overall, the experience in this study with the use of PGE<sub>2</sub> gel in an outpatient setting revealed an apparent benefit for both cervical ripening and labor onset without use of oxytocin and with good patient and newborn outcomes. Of the two adverse effects attributed to the gel application, both were detected within the monitoring period, and no poor outcomes occurred. Outpatient PGE<sub>2</sub> gel is a helpful adjunct in labor induction and may be best used in relatively nonurgent situations in which sufficient time can be allowed for a local cervical effect to occur. Monitoring before and after the gel has been inserted, as described in this study, seems to be effective in the identification of complications that may be caused by myometrial stimulation. With the ease of administration of PGE<sub>2</sub> gel intravaginally, physicians are urged to apply careful clinical criteria to all cases before induction to avoid the risks of unnecessary intervention.

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## Commentary

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In January 1987 the Fertility and Maternal Health Drugs Advisory Committee of the Federal Drug Administration held hearings on a prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) gel called Prepidil. The manufacturer, Upjohn, presented results from a phase II double-blind, randomized, placebo-controlled study conducted in seven medical centers in Canada. The study consisted of 300 patients, one-half of whom received Prepidil endocervically. Forty-two percent of study patients and 12% of control patients went into labor within 12 hours. Prepidil shortened labor and also lowered the cesarean section rate, but not to statistical significance. No contractile abnormalities were noted, but there were some fetal heart rate changes.<sup>1</sup>

The committee concluded that Prepidil made a contribution to labor induction despite an apparent lack of effect on the cesarean section rate. The committee, however, was concerned about safety. They expressed concern about hypercontractability, noting that there is no specific antagonist to PGE<sub>2</sub>. They were particularly concerned about the lack of evidence that there is no ill effect, short term or long term, on the fetus.

The committee unanimously recommended disapproval of Prepidil. They recommended well-defined, blinded, placebo-controlled studies taking into account many obstetric variables to address the efficacy issue.

They recommended development of a more controllable method of administration. Finally they called for neonatal studies including hemodynamics, blood gases, and prostaglandin levels in short-term studies, and growth and development and behavioral studies for long-term follow-up.<sup>2</sup>

The American College of Obstetricians and Gynecologists is tracking PGE<sub>2</sub>. It acknowledges potential efficacy<sup>3</sup> but feels that at present there are insufficient data for the obstetrics committee of ACOG to issue a committee opinion favoring clinical applicability of PGE<sub>2</sub> (personal communication, April 1990).

The Upjohn Company has provided me with the following statement for publication: "After recent discussions with the Food and Drug Administration, The Upjohn Company has begun the process of conducting follow-up studies with the intention of resubmitting the NDA (New Drug Application) in 1990. Because this is still an investigational drug, The Upjohn Company cannot promote its use for any indication, claim, dosage, or route of administration at this time" (personal communication. The Upjohn Company, April 1990). Prepidil is currently available in Canada and throughout Western Europe for cervical ripening. PGE<sub>2</sub> in 20-mg suppository form is available in accredited American hospitals. Ambitious

physicians or pharmacists who wish to compound their own gel are not constrained by law from doing so. If the preparation is to be used, patients must be informed of its nonapproved status.

## THE STUDY

This study by Smith et al<sup>4</sup> purports to show benefit from the use of PGE<sub>2</sub> gel for pre-induction cervical ripening. The results and conclusions are generally concordant with many previous reports.<sup>5</sup> Nevertheless, the study is small (45 patients), retrospective, and uncontrolled. Among some of the more interesting results, it was found that the primary cesarean section rate was 18% in the study population, Bishop scores changed 0.74 after PGE<sub>2</sub> gel administration, 55% of women went into labor spontaneously within 48 hours of their last gel dose, and 47% of women required no oxytocin for delivery. Outcomes as measured by Apgar scores were reassuring, but there was a 26.7% rate of meconium staining. Analysis of these results is somewhat hampered by absence of a control population.

The administration protocol for the PGE<sub>2</sub> includes instructions for compounding the gel, then describes a non-stress test, Bishop score assignment, intravaginal administration, and 30 minutes of postadministration monitoring. Curiously missing from the protocol are the timing and frequency of return visits for cervical assessment and reapplication of gel. The timing appears to have been from daily to weekly. A more regular protocol for administration timing would have aided in drawing valid conclusions about efficacy.

Although the study claims an aggressive approach to the prolonged pregnancy problem by beginning gel administration before 42 weeks, the authors admit that substantial evidence justifying this aggressive approach is lacking. In fact, for most other indications for induction, the approach is really rather nonaggressive. Although the interval between first and last gel application in cases of prolonged pregnancy is only 0.4 weeks, for most other indications the interval was considerably longer, up to 1.0 week for pregnancy-induced hypertension or preeclampsia, 1.5 weeks for suspected intrauterine growth retardation, and 1.7 weeks for gestational diabetes mellitus. To this commentator, such intervals indicate a commendable low-intervention attitude, but this approach does raise the issue of just how urgent or indicated was induction in some of these patients.

The protocol also does not clearly specify where the gel was administered. Presumably it was administered at a family medicine center at some distance from the hospital, since reference is made to outpatient administration and

to transfer of patients. What is the distance between the outpatient center and the university hospital, and what is the approximate time required for transfer? Is administration of PGE<sub>2</sub> gel safe at a distance from the hospital? Is it safe for patients to go home after only 30 minutes of monitoring after gel application? Only two complications were noted after gel administration (a tetanic contraction and an episode of fetal bradycardia), but the authors admit that a longer observation period might be prudent.

There are two fairly interesting and unique aspects of this study. First is the schedule of administration. The authors point out that the dosage, frequency, and method of gel application remain unsettled, and that most previous studies have called for oxytocin induction within a short time after PGE<sub>2</sub> gel administration. This study employed a leisurely approach to the timing of gel administration, yet generated results comparable in efficacy and safety to other more aggressive protocols. The explanation offered by the author may well be true, that the full ripening effect may take up to 48 hours. Equally interesting is the administration of gel in an out-of-hospital facility, with only 30 minutes of monitoring before the patients were discharged to home. Most other studies, perhaps all, have featured inpatient administration with more intensive monitoring. Certainly a demonstration that this more relaxed style of gel administration is safe and efficacious would be of great significance if PGE<sub>2</sub> gel ever becomes generally available in the United States.

## IMPLICATIONS FOR THE FUTURE OF PGE<sub>2</sub> GEL IN PRIMARY CARE

What does PGE<sub>2</sub> gel hold for the future for the family physician who wishes to do obstetrics? Of course, predictions are hazardous given the stance of the FDA and unanswered questions about the drug itself. It does seem quite possible that Prepidil will become available in the United States within the foreseeable future. The independent medical literature seems to support the drug and the concept of cervical ripening.<sup>5</sup>

While waiting for FDA approval, what is the family physician to do? Oxytocin frequently fails on the first or even second attempt when the cervix is unripe. Various alternative techniques exist to attempt to ripen the cervix.

Breast stimulation has been studied and advocated. Elliot and Flaherty<sup>6</sup> and Salmon et al<sup>7</sup> have developed such protocols. Salmon studied 100 patients in a controlled crossover study. Patients who stimulated their breasts for 3 days experienced a Bishop score change of 3.96 compared with 1.04 in the control group ( $P < .00001$ ). Chayen et al<sup>8</sup> went one step further: they induced women



with breast stimulation and found the method to be as effective as oxytocin.

Membrane stripping is a time-honored method whose physiology has been clarified to involve endogenous prostaglandins. Mitchell et al<sup>9</sup> showed an increase in endogenous plasma prostaglandins (13,14-dihydro-15-keto prostaglandin F) following membrane stripping and amniotomy. Weissberg and Spellacy<sup>10</sup> showed a modest increase in the onset of labor within 48 hours when the membranes were stripped in women with an unfavorable Bishop score (0-5). There was no effect when the Bishop score was favorable.

Laminaria has been used to promote cervical ripening. Rosenberg et al<sup>11</sup> reported a controlled study of preinduction cervical ripening in patients with low Bishop scores in whom laminaria was inserted in the cervix, removed 12 hours later, and induction with oxytocin begun. Bishop score increased by a mean of 3.2 ( $P < .0005$ ) and the success rate of oxytocin induction was 75.5% in the laminaria group, but only 11% in the matched controls ( $P < .001$ ). A very recent report compares laminaria with Dilapan, a synthetic hygroscopic cervical dilator, in their cervical ripening effects.<sup>12</sup> Both devices were found to increase Bishop scores, and to allow intervals from induction to complete dilatation comparable to "ripe" controls. Cesarean section rates were comparable. The authors found Dilapan superior to laminaria for a variety of reasons.

These techniques have some advantages over PGE<sub>2</sub> gel. They are nonpharmacologic and easy to use, and breast stimulation can be applied by the patient at home. They involve devices or techniques that are readily available and inexpensive. Safety, although always an issue, appears to be good. Certainly research should be conducted examining and directly comparing all of these methods of preinduction ripening.

If PGE<sub>2</sub> gel is deemed the method of choice for cervical ripening, then family physicians may compound the preparation in a manner similar to that described. The FDA does not regulate the practice of medicine and cannot prevent a licensed physician from using an approved drug even for an unapproved indication. Many examples of this behavior occur in the practice of medicine, most notably, in obstetrics and gynecology, the unapproved applications of terbutaline for premature labor prophylaxis, and depomedroxyprogesterone for contraception. Of course, if an untoward result occurred, one's medicolegal status would be questionable. It is illegal, however, to transport an unapproved drug into the country for clinical use. For example, Prepidil gel cannot legally be brought into the United States from Canada for use in ripening the cervix.

## CONCLUSIONS

The ideal preinduction cervical ripener, as well as being safe and effective, should be easy to apply, even for the patient herself. Intravaginal PGE<sub>2</sub> gel may prove to be the best of the cervical-ripening techniques, and it certainly lends itself well to self-application. In the future we may see women applying a small dose of PGE<sub>2</sub> gel at home under a physician's supervision, at some frequency determined to be optimal, to ripen their cervixes for induction or to shorten their pregnancies. PGE<sub>2</sub> gel may prove to be a boon to family physicians, obstetricians, and their patients who hope to avoid high-technology testing and interventions by shortening pregnancy and easing induction.

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