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A randomized trial of prostaglandin E2 in a controlled-release vaginal pessary for cervical ripening at term

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A randomized trial of prostaglandin E_2 in a controlled-release vaginal pessary for cervical ripening at term

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OBJECTIVE: The purpose of this study was to determine if prostaglandin E_2 in a controlled-release vaginal pessary can produce cervical ripening at term.
STUDY DESIGN: This was a double-blind, randomized, placebo-controlled study conducted at a university center and involving 81 patients with 42 receiving active agent. Categoric data were analyzed by Pearson's χ^2 or logistic regression. Continuous variables were analyzed by analysis of variance and the F test.
RESULTS: Prostaglandin E_2 was significantly better than placebo at cervical ripening and at decreasing the time to rupture of membranes, the time to onset of labor, the need to give oxytocin, and the time to vaginal delivery. Multiparous women benefitted more than primiparous ones. The cesarean section rate decreased only for multiparous women. Uterine hyperstimulation occurred only with prostaglandin E_2 and after the onset of labor.
CONCLUSIONS: Prostaglandin E_2, when administered in a controlled-release vaginal pessary, is affective in producing cervical ripening at term. This agent should be used on inpatients who are under continuous monitoring and it should be removed at the onset of labor. (Am J Obstet Gynecol 1992;166:830-4.)

Key words: Pregnancy, cervical ripening, induction of labor, PGE_2, prostaglandin

Prostaglandin E_2 (PGE_2) has been suggested as an agent to ripen the unfavorable cervix for induction of labor at term. It has several properties that might make it a likely candidate for this task. It can relax the smooth muscle of the cervix[1] and induce an increase in the production of glycosaminoglycans by cervical fibroblasts.[2] The increased glycosaminoglycans may be involved in cervical softening unrelated to uterine contractions, and such softening and increased extendibility have been associated with exogenous PGE_2 application.[3]

Unfortunately, for its role as a cervical ripening agent, PGE_2 is also a uterotonic agent for the pregnant uterus and there are concerns about production of hyperstimulation with its use.[2] PGE_2, when applied in a gel intracervically, has been documented to produce cervical ripening and occasional hyperstimulation.[4] Because PGE_2 is rapidly metabolized in the tissues of origin and by the lungs and gastrointestinal tract, if it were possible to remove the exogenous PGE_2, hyperstimulation could be rapidly reversed. A readily removable solid intravaginal dosage form would be welcome. This report describes a blinded, placebo-controlled trial of a new controlled-release intravaginal PGE_2 pessary for preinduction cervical ripening at term.

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Material and methods

This study was approved by our institutional review board for human trials and consisted of a randomized, blinded, placebo-controlled trial of an intravaginal PGE_2 pessary for cervical ripening. Change in cervical status before induction was assessed by the Bishop score, as described in Bishop's classic article.[5]

The pessary is made of a cross-linked polymer hydrogel that releases PGE_2 at a near-constant rate of approximately 1 mg/hr in vitro. The total reservoir contained in the pessary was 10 mg. It was supplied together with placebo pessaries in foil wrappers, which were kept at $-20°$ C until immediately before use.

The patients were recruited from women to be delivered at our hospital who were to have labor induced at term and who fulfilled the eligibility criteria listed in Table I.

After giving informed consent, the patient underwent a 30-minute observation period in which a nonstress test was performed. If this test was reactive and the patient met all other criteria, she entered the study and was randomly assigned to receive either active or placebo pessary. At the time of pessary insertion, a Bishop score was obtained and the thawed pessary was inserted into the posterior fornix of the vagina with its long axis transverse to the long axis of the vagina. The patient was asked to remain recumbent for the first 2

Table I. Eligibility criteria

1. Informed consent
2. Singleton pregnancy of ≥37 weeks' gestation
3. Cephalic presentation
4. Nulliparous or multiparous with ≤3 previous viable infants
5. A medical or obstetric indication for induction
6. Bishop score of ≤4 on admission
7. Reactive fetal nonstress test
8. No previous uterine scars
9. No vaginal bleeding
10. Intact membranes or premature rupture of membranes for ≤4 hours at insertion of pessary
11. No fever
12. No allergy to prostaglandins
13. No history of asthma or glaucoma, except for childhood asthma without adult recurrences
14. No evidence of fetal distress
15. No evidence of spontaneous labor
16. No evidence of clinical hydramnios, confirmed by ultrasonography
17. No use of aspirin, nonsteroidal antiinflammatory drugs, or acetaminophen within 4 hours before insertion of pessary and any time thereafter
18. No underlying maternal cardiac lesion that might put patient at risk from potential hypotensive effects of PGE_2

Table II. Demographic variables of patients enrolled

	Placebo	*Active agent*	*p Value**
Race			
Black	21	29	0.3230
White	16	13	
Native American	1		
Oriental	1		
Age (yr)			
Mean ± SD	23.1 ± 5.79	23.7 ± 5.35	0.6496
Range	15-40	14-33	
Height (m)			
Mean ± SD	1.6 ± 0.07	1.6 ± 0.05	0.2245
Range	1.5-1.8	1.5-1.8	
Weight (kg)			
Mean ± SD	86.1 ± 17.13	84.6 ± 17.61	0.7048
Range	55-132	48-125	

*p Values for categoric data from Pearson's χ^2 test. p Values for continuous data from one-way analysis of variance F test.

hours after insertion and then was allowed to get up as needed. The pessary was to remain in situ for 12 hours, during which continuous electronic monitoring was used to observe uterine activity and fetal heart rate. Repeat Bishop scores were performed by the same individual if possible at 6 and 12 hours after insertion. If, for any reason, the pessary had to be removed before 12 hours after insertion, a repeat Bishop score was obtained at removal. All pessaries still in situ at the time of the 12-hour Bishop score were removed at that time. After removal of the pessary, any patient who was not in labor underwent induction of labor with oxytocin. Amniotomy was performed at the discretion of the attending physician.

Eighty-one patients entered the study. Thirty-nine received placebo and 42 received the active agent. Of the original 81 patients, 36 placebo and 41 active-agent patients could be evaluated for cervical ripening. To be evaluated for cervical ripening the patient must have been eligible for the study and have had at least one Bishop score after the initial one. Of the placebo patients who could not be evaluated, one never received a pessary when it was determined after randomization that she had a uterine scar and was ineligible, the second patient had insufficient data to analyze because she had a cesarean delivery at 7½ hours after insertion for worsening severe preeclampsia, and the third had ruptured membranes for >4 hours at pessary insertion and was ineligible. The active-agent patient who could not be evaluated was ineligible because she had onset of labor at pessary insertion.

In addition to cervical ripening, the labor parameters that were of interest included time to rupture of membranes, time to onset of labor, length of the first stage of labor, length of the second stage of labor, and the time to vaginal delivery. Labor was defined as uterine contractions occurring at least every 3 minutes and lasting at least 45 seconds or cervical dilatation of 5 cm with any contraction pattern. All times were measured from pessary insertion, with the exception of the first and second stages of labor. Thirty placebo patients and 39 active-agent patients could be evaluated for these

Table III. Obsteric history of patients enrolled

	Placebo	*Active agent*	*p Value**
Gestational age (wk)			
Mean ± SD	39.9 ± 1.69	39.6 ± 1.38	0.3034
Range	37-43	37-42	
Prior pregnancies			
0	32	26	0.0810
1	4	12	
2	3	2	
3		2	
Initial Bishop score			
Mean ± SD	2.9 ± 1.08	2.8 ± 1.03	0.8704
Range	0.0-4.0	1.0-4.0	

*p Values for categoric data from Pearson's χ^2 test. p Values for continuous data from one-way analysis of variance F test.

Table IV. Primary indication for induction*

	Placebo	*Active agent*
Decreased amniotic fluid	5	5
Decreased fetal movement	1	0
Diabetes mellitus	4	2
Elective	2	1
Hypertension	7	11
Impending macrosomia	1	3
Intrauterine growth retardation	3	5
Postterm	11	11
Premature rupture of membranes	1	2
Sickle cell disease	1	0
Preeclampsia	3	2

*p = 0.8300 by Pearson's χ^2 test.

Table V. Measures of successful cervical ripening*

	Placebo	*Active agent*	*p Value†*
Treatment outcome			
Success	10	30	0.0012
No success	26	11	
Change in Bishop score ≥3			
Yes	8	23	0.0041
No	28	18	
Bishop score ≥6			
Yes	10	25	0.0062
No	26	16	
Vaginal delivery within 12 hr			
Yes	0	12	0.0615
No	36	29	
Onset of labor within 12 hr			
Yes	0	24	0.0005
No	29	11	
Not available	7	6	

*Patients may meet more than one measure of success.
†p Value from logistic regression.

labor parameters. Of the placebo patients who could not be evaluated for labor parameters, two had delays from pessary removal to initiation of induction of labor, one failed to go into labor after an extended induction and had a primary cesarean section, and three underwent serial attempts at induction with overnight rests between oxytocin administrations. The two active-agent patients who could not be evaluated had serial attempts at induction with overnight rests between oxytocin administration.

Statistical analysis was done with the Statistical Analysis System.[6] Categoric data were analyzed by either Pearson's χ^2 or logistic regression. Continuous variables were analyzed by analysis of variance and the F test.

Results

Demographic data (Table II), obstetric history (Table III), initial Bishop score (Table III), and primary indication for induction (Table IV) did not differ between the placebo and active-agent groups. This balance was not disturbed when the patients were stratified into those evaluable for cervical ripening and those evaluable for labor parameters or when these evaluable groups were substratified into multiparous and primiparous patients.

The primary outcome variable for this study was cervical ripening. Successful treatment outcome was defined as a change in Bishop score of ≥3, a Bishop score of ≥6, or vaginal delivery within 12 hours of pessary insertion. Table V lists several possible ways to gauge success in cervical ripening for evaluable patients. The results were unchanged when primiparous women were considered separately. When multiparous women were analyzed, only treatment outcome and onset of labor within 12 hours remained statistically different between the placebo and active agent.

Timing for labor events for evaluable patients is presented in Table VI. When primiparous patients were analyzed separately, only the time to rupture of membranes and the time to onset of labor remained statis-

Table VI. Summary of labor timing data for evaluable patients

	Placebo	*Active agent*	*p Value**
Time to rupture of membranes†			
Mean ± SD	23.9 ± 7.56 (n = 28)	15.2 ± 8.32 (n = 35)	0.0002
Range	15-46	3.5-42.8	
Time to onset of labor			
Mean ± SD	21.3 ± 7.46 (n = 26)	11.0 ± 9.76 (n = 34)	0.0002
Range	14-45	0.83-43.50	
Length of first stage of labor			
Mean ± SD	9.6 ± 5.80 (n = 21)	9.3 ± 5.38 (n = 29)	0.4348
Range	0.25-20.50	0.67-23.25	
Length of second stage of labor			
Mean ± SD	1.3 ± 1.08 (n = 20)	1.1 ± 1.25 (n = 30)	0.8012
Range	0.18-4.82	0.05-5.98	
Time to vaginal delivery			
Mean ± SD	32.3 ± 9.92 (n = 20)	20.9 ± 12.90 (n = 30)	0.0093
Range	18-75	5.0-55.7	

*p Values from analysis of variance F test.
†Three patients with pessary insertion after membrane rupture not included.

tically different. For primiparous patients, the mean time to vaginal delivery with placebo was 32.9 hours and with active agent was 27.0 hours (p = 0.1633, analysis of variance F test). When multiparous patients were analyzed separately, in addition to the significant differences seen in the overall group, the mean length of the second stage of labor was significantly shorter with the active agent, 0.4 versus 0.9 hour with placebo (p = 0.0411, analysis of variance F test). For multiparous patients, the mean time to vaginal delivery was 29.7 hours with placebo and 14.0 hours with the active agent (p = 0.0016, analysis of variance F test).

Data for method of membrane rupture, type of analgesia in labor, method of delivery, and occurrence of episiotomy are listed in Table VII for evaluable patients. No statistically significant differences appeared when primiparous women were analyzed separately. The cesarean rate for primiparous women was 33% in both placebo and active-agent groups. When the multiparous women were analyzed separately, a statistically significant difference appeared in cesarean section rate, 33% for placebo versus 7% for active agent (p = 0.0100, Pearson's χ^2 test).

Data on oxytocin administration are given in Table VIII for evaluable patients. The results were unchanged when primiparous patients were analyzed separately. When multiparous patients were analyzed separately, the amount of oxytocin administered was no longer statistically different between the placebo and active agent. This may have been due to the small sample size, because all of the multiparous patients in the placebo group (n = 6) required oxytocin averaging 7.2 U total, whereas only 20% (n = 3) of the multiparous patients in the active-agent group required oxytocin averging 2.4 U total.

Three patients receiving the active agent had uterine hyperstimulation. No patient who received placebo had

Table VII. Summary of labor and delivery events for evaluable patients

	Placebo	*Active agent*	*p Value**
Rupture of membranes			
Spontaneous	7	12	0.7120
Amniotomy	22	25	
Unspecified	1	2	
Analgesia†			
Epidural	22	28	0.5790
Intramuscular	0	1	
Intravenous	11	13	
Local-pudendal	0	1	
Spinal	1	0	
Type of delivery			
Cesarean	13	9	0.2770
Low-forceps	5	4	
Mid-forceps	1	0	
Spontaneous	11	24	
Vacuum extraction	3	2	
Episiotomy			
No	15	26	0.1620
Yes	15	13	

*p Values from Pearson's χ^2 test.
†Some patients received more than one type of analgesic.

uterine hyperstimulation. Uterine hyperstimulation was defined as uterine contractions lasting ≥2 minutes or a contraction frequency of five or more in 10 minutes with evidence that the fetus was not tolerating this contraction pattern, as demonstrated by late decelerations, severe variable decelerations, or fetal bradycardia.

The incidence of hyperstimulation in patients receiving the active agent was 7% in this study. These episodes occurred between 1 hour and 8 hours 50 minutes after pessary insertion. All resolved rapidly after removal of the pessary, and no further therapy was required. All episodes of hyperstimulation occurred after the onset of labor.

Table VIII. Oxytocin administration for evaluable patients

	Placebo	*Active agent*	*p Value**
Oxytocin administered			
No	0	18	0.0000
Yes	30	21	
Induction	26	10	
Augmentation†	4	11	
Amount of oxytocin administered (U)			
Mean ± SD	11.0 ± 8.49	5.7 ± 6.52	0.0213
Range	0.68-32.96	20-60	

**p* Value for categoric data from Pearson's χ^2 test. *p* Value for continuous data from one-way analysis of variance F test.
†Defined as the use of oxytocin to enhance uterine contractions already present.

Comment

The PGE_2 pessary, which released PGE_2 at a near-constant rate of approximately 1 mg/hr in vitro, tested in this study is effective in producing cervical ripening when compared with placebo. It has a distinct advantage over PGE_2 gel or suppositories in that it releases a small amount of PGE_2 over a prolonged period rather than the entire dose rapidly.

The active agent results in significantly more patients going into labor during its 12-hour administration period than placebo. These findings are observed for both primiparous and multiparous patients. When we look past cervical ripening to benefits from pessary use in the subsequent labor, we find that the active pessary shortens the time to rupture of membranes and to onset of labor. It also decreases the need to administer oxytocin.

Additional benefits achieved by multiparous women are a shortened second stage of labor, a shortened time to vaginal delivery, and a decreased cesarean section rate.

The primiparous women gained some additional benefits. The average total amount of oxytocin needed to be administered was cut almost in half, from 12.0 to 6.3 U. Twenty-five percent of the primiparous women given the active agent required no oxytocin, as opposed to all of those given placebo. Additionally, those patients receiving the active agent who also received oxytocin were more likely to require only augmentation (50% vs 8% with placebo). Thirty-eight percent of the primiparous women given the active agent went into labor during the 12-hour period of pessary insertion, whereas none of those patients on placebo did. The time from pessary insertion to vaginal delivery was not shortened by active agent (27.0 hours, range 7.2 to 55.7 hours, vs placebo 32.9 hours, range 18 to 53 hours). The failure to achieve statistical significance is probably due to the wide range of time taken to achieve vaginal delivery. This should not be surprising as Bishop[5] in reporting his scoring system cautioned against elective induction of primiparous patients, because, even in the presence of apparently favorable circumstances, the duration of labor is unpredictable.

Uterine contractions were frequently produced by the active pessary. Irregular contractions and frequent mild contractions compatible with the diagnosis of uterine irritability (not perceived as painful, ≤20 seconds' duration, every 1 to 2 minutes) were the most frequent patterns. Uterine hyperstimulation as defined previously had an incidence of 7% in this study among patients receiving PGE_2. Hyperstimulation resolved immediately on removal of the pessary and resulted in no emergency deliveries. The solid dosage form of the pessary allows for easy removal of the PGE_2 when compared with other dosage forms. All patients with hyperstimulation were multiparous women in labor at the time of the incident. Because of this risk of hyperstimulation that could occur at any time during the administration of the pessary, PGE_2 pessaries should be administered only to inpatients who are having continuous external electronic fetal monitoring and should be removed at the onset of labor as defined here.

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