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Improved Intravaginal Controlled-Release Prostaglandin E_2 Insert for Cervical Ripening at Term

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Abstract The purpose of this study was to determine if prostaglandin E_2 (PGE_2) in a controlled-release vaginal insert with retrieval system can produce cervical ripening at term. This was a multicenter, double blind, randomized, placebo-controlled study involving 206 patients with 102 receiving active agent. A successful outcome was defined as a change in Bishop score of ≥ 3, or a Bishop score of ≥ 6 at 12 h or delivery within 12 h of the insert placement. Analysis was by Fisher's exact test, Wilcoxon's two-sample rank-sum test, and Student's *t*-test where appropriate. One hundred ninety-three women completed the protocol. Initial Bishop scores were 2.6 ± 1.2 and 2.5 ± 1.4 in the PGE_2 and placebo groups, respectively. The incidence of cesarean delivery was identical in the two groups. Uterine hyperstimulation lasted 2–13 min in 5 PGE_2 patients (4.9%) with 1 patient requiring tocolysis. More patients in the PGE_2 group had a change in Bishop score of ≥ 3 (62% vs. 40%; $P = 0.002$), a Bishop score ≥ 6 after 12 h (46% vs. 34%; $P = 0.11$), and vaginal delivery within 12 h (6.5% vs. 1%; $P = 0.055$). Sixty-five percent of PGE_2 group patients had a successful outcome vs. 44% of control patients ($P = 0.001$). In conclusion, when administered in a controlled-release vaginal insert with a retrieval system, PGE_2 is effective in promoting cervical ripening at term.

Key Words: Pregnancy, Cervical ripening, Labor induction, PGE_2, Prostaglandin

INTRODUCTION

Prostaglandin E_2 (PGE_2) is an agent used to ripen the unfavorable cervix at term for induction of labor. It can relax cervical smooth muscle [1] and induce an increase in the production of glycosaminoglycans by cervical fibroblasts [2]. This increase in glycosaminoglycans may be involved in cervical softening unrelated to uterine contractions seen with exogenous PGE_2 application [3]. PGE_2 is also an oxytocic agent for the pregnant uterus and can produce hyperstimulation [4–6]. PGE_2 in a controlled-release vaginal insert has been shown in controlled trials to produce cervical ripening, decrease the time to onset of labor, decrease the need to give oxytocin, and decrease the time to vaginal delivery [5,6].

Because PGE_2 is rapidly metabolized, the removal of the source of exogenous PGE_2 will lead to rapid reversal of its effects including hyperstimulation. Indeed, in previous studies [5–7] removal of the controlled-release vaginal insert resulted in rapid reversal of hyperstimulation in the rare cases where it occurred. As the retrieval system might change the efficacy of the device, its efficacy needed to be reexamined. This report describes a multicenter, blinded, placebo-controlled trial of the controlled-release intravaginal PGE_2 insert with a new

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TABLE 1. Eligibility Criteria

Informed consent
Singleton pregnancy of ≥37 weeks gestation
Cephalic presentation
Nulliparous or multiparous with ≤3 previous viable infants
A medical or obstetric indication for induction
Bishop score of ≤4 on admission
Reactive fetal nonstress test
No previous uterine scars
No vaginal bleeding
Intact membranes
No fever of ≥38°C
No allergy to prostaglandins
No history of asthma or glaucoma, except for childhood asthma without adult recurrences
No evidence of fetal distress
No evidence of spontaneous labor
No evidence of clinical hydramnios confirmed on ultrasonography
No use of aspirin, nonsteroidal anti-inflammatory drugs, or acetaminophen within 4 h before insertion of pessary and anytime thereafter
No underlying maternal cardiac lesion that might put the patient at risk from potential hypotensive effects of PGE_2
Has not been administered a tocolytic or oxytocin within 24 h of insertion of pessary

retrieval system for preinduction cervical ripening at term. This insert with its retrieval system has recently been marketed in the United States under the trade name Cervidil®.

SUBJECTS AND METHODS

This multicenter, randomized, placebo-controlled study was conducted at 10 centers after approval by the Institutional Review Boards of each participating center. The participating centers were the University of Oklahoma Health Sciences Center, East Bay Prenatal Medical Associates, Thomas Jefferson Hospital, The Johns Hopkins University Medical Center, Medical College of Virginia, The University of Southern California School of Medicine, the University of Tennessee-Memphis, Statesville Medical Group, the University of Cincinnati College of Medicine, and the University of Nebraska Medical Center.

Study patients included women admitted for induction at term who fulfilled the eligibility criteria listed in Table 1. The Bishop score used to assess eligibility and cervical ripening was that described in Bishop's [8] classic article.

Patients underwent a 30-min 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 randomized to receive either active or placebo insert with retrieval system. Computer-generated randomization sequences for each site were prepared centrally by the sponsor and used to produce sequentially labeled prepackaged inserts containing either placebo or active agent. The pharmacy at each site was able to break the blind for medical necessity. No one involved directly with the patient's care or evaluation was aware of the study group to which the patient was assigned. The insert is made of a cross-linked polymer hydrogel that releases PGE_2 from a 10 mg reservoir at a controlled rate of approximately 0.3 mg/h in vivo. It measures 0.8 × 9.5 × 29 mm on insertion. The retrieval system is Dacron® polyester with a net proximally around the insert and a long ribbon end which extrudes distally from the vagina. The ribbon is 4 mm wide and 1 mm thick. The total length of the net plus the ribbon is 31 cm. The entire system came preassembled and prepacked in sterile foil packets which were stored at −20°C until immediately before use. The thawed insert was placed in the posterior fornix of the vagina with its long axis transverse to the long axis of the vagina. The ribbon end of the retrieval system was allowed to extrude distally from the vagina, but was tucked into the vagina so that only a few centimeters actually extruded. An initial Bishop score was done at insert placement. The patient was asked to remain recumbent for the first 2 h after insertion and then was allowed to get up as needed. The insert was to remain in situ for 12 h during which

TABLE 2. Demographic Variables of Patients Enrolled

	Placebo	Active agent	P
Race			
Black	33	37	0.452*
White	38	32	
Hispanic	29	32	
Other	4	1	
Age			
Mean ± SD	25.9 ± 5.65 years	24.3 ± 5.29 years	0.043**
Range	16–40 years	16–38 years	
Height			
Mean ± SD	1.6 ± 0.08 m	1.6 ± 0.08 m	0.549**
Range	1.3–1.8 m	1.4–1.8 m	
Weight			
Mean ± SD	85.6 ± 23.86 kg	88.4 ± 26.38 kg	0.446**
Range	47.7–184.5 kg	54.9–220.0 kg	
Gestational age			
Mean ± SD	39.9 ± 1.85 weeks	40.0 ± 1.72 weeks	0.810**
Range	37–46 weeks	37–45 weeks	
Initial Bishop score			
Mean ± SD	2.5 ± 1.41	2.6 ± 1.21	0.911**
Range	0.0–8.0	0.0–5.0	

*P value from Fisher's exact test.
**P value from Student's *t*-test.

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 h after insertion. If, for any reason, the insert had to be removed before 12 h after placement, a repeat Bishop score was obtained at the time of removal. The inserts were removed at the onset of active labor, following rupture of membranes, and if hyperstimulation occurred. All inserts still in situ after 12 h were removed and a Bishop score was performed.

After removal of the insert, any patient who was not in labor underwent induction of labor with continuous oxytocin infusion. Oxytocin was begun at 1 mu/min and increased 1 mu/min every 30 min to a maximum of 30 mu/min. Amniotomy was performed at the discretion of the attending physician.

Treatment success was defined as a Bishop score at 12 h of ≥ 6, a Bishop score increase of ≥ 3 at 12 h, or vaginal delivery within 12 h of insert placement. The times from insert placement to vaginal delivery and the incidence of cesarean section were also compared between the study groups. Labor was defined as uterine contractions occurring at least every 3 min and lasting at least 45 s or cervical dilatation of 5 cm with any contraction pattern. Hyperstimulation was defined as a single contraction lasting 2 min or longer or a contraction frequency of greater than 5 in 10 min with a contraction duration of 45 sec or greater. Nonreassuring fetal heart tracings were defined as those with fetal bradycardia, variable decelerations, or late decelerations.

Analysis was performed for both the total population and the subgroups of nulliparas and multiparas. Spontaneous and induced abortions were not included in parity calculations.

Statistical analysis was done utilizing Fisher's exact test, Wilcoxon's two-sample rank-sum test, and Student's *t*-test where appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

Two hundred six patients entered the study: 102 received active agent and 104 received placebo. Of the original patient group, 13 (10 active agent and 3 placebo) patients were disqualified from the efficacy analysis because of early removal (7 active agent and 1 placebo) or protocol violations (3 active agent and 2 placebo). Reasons for early removals included hyperstimulation (5 active agent), labor (1 active agent), patient request due to uterine irritability without hyperstimulation (1 active agent), and nonreassuring fetal heart rate tracing (1 placebo). Protocol violations in-

TABLE 3. Primary Indication for Induction of Patients Enrolled*

	Placebo	Active agent
Decreased amniotic fluid	19	25
Postdates	48	44
Diabetes	9	6
Hypertension	11	9
Intrauterine growth retardation	7	8
Maternal pituitary tumor	0	1
Fetal macrosomia	4	2
Preeclampsia	3	5
Previous poor obstetrical history	1	0
Isoimmunization	0	2
Thrombocytopenia	1	0
Elective	1	0
Total	104	102

*$P = 0.732$ by Fisher's exact test.

TABLE 4. Measures of Successful Cervical Ripening for All Evaluable Patients

	Placebo	Active agent	P*
Treatment outcome			<0.004
Success	44	60	
No success	57	32	
Change in Bishop score ≥3			<0.002
Yes	40	57	
No	61	35	
Bishop score ≥6 at 12 h			0.105
Yes	34	42	
No	67	50	
Vaginal delivery within 12 h			0.055
Yes	1	6	
No	100	86	

*P value from Fisher's exact test.

cluded multiple gestation (1 active agent), parity >3 (1 active agent), and baseline Bishop score >4 (1 active agent and 2 placebo).

Demographic data are presented in Table 2. When these data were stratified by parity, there was an imbalance in the multiparous group in which the placebo group was older than the active agent group (28.2 ± 5.1 vs. 25.6 ± 5.3; $P = 0.03$). Parity did not differ between the two groups ($P = 0.34$). Mean gestational age and Bishop score did not differ at trial entry between the groups (Table 2). This was not altered by stratifying into multiparous and primiparous groups. the primary indications for induction were similar in the placebo and active agent groups (Table 3).

The results for the measures of successful cervical ripening for all evaluable patients are presented in Table 4. When the patients were stratified by parity, it was apparent that the response in nulliparous patients was seen primarily in cervical change, while in the multiparous patients, it was seen primarily in increased delivery in 12 h (Table 5). If patients who were excluded for hyperstimulation were included these results were not altered.

The time to vaginal delivery was decreased by use of the active agent (Table 6). The incidence of cesarean section (24%) did not differ between active and placebo insert groups. Neither of these results was altered by stratification for parity, exclusion of patients who were discharged and readmitted for repeat induction, or inclusion of patients excluded for early insert removal.

Five patients receiving active agent experienced hyperstimulation. These episodes occurred between 1.5 and 9.5 h after insert placement and resolved within 2–13 min after insert removal. Only 3 patients were associated with evidence of nonreassuring fetal heart rate tracings. Only 1 patient required tocolysis to assist in resolving the hyperstimulation. Hyperstimulation resolved 13 min after removal of the insert with administration of a single subcutaneous dose of terbutaline. Parity did not influence the occurrence of hyperstimulation as 3 patients were nulliparous and 2 patients were multiparous. All patients experiencing hyperstimulation delivered healthy infants vaginally with Apgar scores of 8 or above at 1 and 9 at 5 min.

DISCUSSION

The sustained release (0.3 mg/h) of PGE_2 insert with its retrieval system is effective in producing cervical ripening when compared to placebo. Insertion is simply performed digitally obviating the need for speculum examination. The PGE_2 insert has a distinct advantage over other forms of PGE_2 for intravaginal or intracervical administration 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 cervical ripening in nulliparous patients and more multiparous patients delivering within 12 h of insert application. For all patients, the time to vaginal delivery is shortened by the active agent. Cesarean section rates were unaffected by use of the active agent. The high rate of Bishop score change with placebo seen in this study has been previously reported in studies of cervical ripening at term [6,10].

Monitoring requirements differ between this prepa-

TABLE 5. Measures of Successful Cervical Ripening

	All evaluable patients					
	Nulliparous			Multiparous		
	Placebo	Active agent	*P*	Placebo	Active agent	P*
Treatment outcome			0.014			0.117
Success	27	37		17	23	
No success	33	17		24	15	
Change in Bishop score ≥3			0.005			0.179
Yes	24	36		16	21	
No	36	18		25	17	
Bishop score ≥6 at 12 h			0.038			1.000
Yes	21	30		13	12	
No	39	24		28	26	
Vaginal delivery within 12 h			1.000			0.051
Yes	0	0		1	6	
No	60	54		40	32	

*P value from Fisher's exact test.

TABLE 6. Summary of Time to Delivery Data

	Time from insertion of pessary to vaginal delivery (h)		
	Placebo	Active agent	P*
All patients	29.4 (10.8–347.7)[a]	21.2 (5.6–437.0)	<0.001
Nulliparous patients	38.2 (19.3–347.7)	24.5 (12.9–77.5)	<0.001
Multiparous patients	25.3 (10.8–213.2)	17.2 (5.6–437.0)	0.001

[a]Median (range).
*P value from Wilcoxon's two-sample rank-sum test.

ration and gel preparations of PGE_2. Because PGE_2 is rapidly metabolized, the only systemic measure available for its absorption is its stable metabolite 13,14-dihydro-14-keto PGE_2 (PGEM). With gel preparations, this stable metabolite has peaked by 2 h in most patients [11]. This reflects rapid absorption of PGE_2 from gel preparations. Therefore, if there is no uterine activity at 2 h, monitoring may be discontinued in patients receiving gel. However, because PGE_2 is released at a rate of 0.3 mg/h from the active insert, monitoring should continue for the entire duration of the insert use.

Uterine contractions were frequently produced by the active insert. The most common pattern was irregular frequent mild contractions comparable with the diagnosis of uterine irritability. Uterine irritability was well tolerated by the fetuses in this study. The incidence of hyperstimulation was 4.9% (5 patients). In 3 of the patients experiencing hyperstimulation, nonreassuring fetal heart rate tracings were diagnosed. Only 1 of these patients required tocolysis in addition to insert removal to resolve the hyperstimulation and the nonreassuring fetal heart rate tracing. No fetuses experienced adverse perinatal outcome as a result of hyperstimulation from this agent. All were delivered vaginally with normal Apgar scores. The incidence of hyperstimulation in this study is well within the range reported in the literature for the use of PGE_2 in cervical ripening of 0.6–6% [9].

The unique net of the retrieval system greatly enhanced the ease of insert removal. The insert with its retrieval system offers a significant advantage with regard to reversibility to other methods of intravaginal or intracervical PGE_2 administration.

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