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Vaginal Misoprostol vs. Concentrated Oxytocin Plus Low-Dose Prostaglandin E_2 for Second Trimester Pregnancy Termination

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Objective: To examine the efficacy of vaginal misoprostol for mid-trimester pregnancy termination.
Methods: This randomized trial compared misoprostol, 200 μg per vaginum q 12 h to a protocol of concentrated oxytocin plus low-dose vaginal prostaglandin E_2 suppositories (10 mg q 6 h). Success was defined as an induction-to-delivery interval ≤24 h.
Results: Interim analysis of the first 30 (15-misoprostol, 15-concentrated oxytocin) women demonstrated that the 2 groups were similar with regard to indication for delivery, gestational age, and demographic characteristics. Misoprostol was associated with a lower success rate (67 vs. 87%, $P = .2$), a longer induction-delivery interval (22 h vs. 18 h, $P = .09$), a higher rate of retained placenta requiring curettage (27 vs. 13%, $P = .65$), and a higher live birth rate (50 vs. 0%, $P = .006$).
Conclusions: Compared to a regimen of concentrated oxytocin plus low-dose prostaglandin E_2, misoprostol administered as vaginal tablets in a dose of 200 μg q 12 h is not satisfactory for mid-trimester pregnancy termination in an unselected population. *J. Matern.-Fetal Med. 1999;8:48–50.*

Key words: pregnancy termination; oxytocin; misoprostol

INTRODUCTION

Misoprostol, a thermally stable tablet form of prostaglandin E_1 (PGE_1) has been reported to reliably effect delivery in the mid-trimester [1]. Most of the published clinical outcomes data involving the use of PGE_1 have resulted predominantly from populations with fetal death as the indication for induction. Our intent was to study vaginal PGE_1 in an unselected population of women undergoing an indicated pregnancy termination in the mid-trimester.

SUBJECTS AND METHODS

This clinical trial was approved by the Institutional Review Board at the University of Alabama Hospital. Women at 16–24 weeks' gestation admitted for an indicated pregnancy termination and those with a fetal death and a fundal height ≤24 cm were eligible. Gestational age was calculated for all gravidas using a combination of a reliable last menstrual period and sonographic data. At ≤20 weeks' gestation, if the biometric parameters confirmed the last menstrual period within 7 days, we used the menstrual estimate, otherwise we used the sonographic estimate. Similarly, if the sonographic parameters indicated a gestational age >20 weeks' but ≤24 weeks' gestation, more than a 10-day discrepancy would reject the menstrual estimate. In cases of fetal death, the biometric parameters on admission were utilized.

Exclusion criteria included severe preeclampsia, known sensitivity to prostaglandins, or a cervical dilatation ≥2 cm. Consenting women were randomly assigned to receive either two, 100 mg PGE_1 tablets per vaginum q 12 h [1], or a previously validated regimen of concentrated oxytocin plus low-dose vaginal prostaglandin E_2 (PGE_2), suppositories (10 mg q 6 h) [2]. Briefly, each 4-h course of concentrated oxytocin consisted of 50X units of oxytocin in 500 ml of normal saline, where X ranged from 1 to 6. The mixture was administered over a 3-h period (minimum rate = 278 milliunits per min; maximum rate = 1,440 milliunits per min) with a 1-h rest period prior to the next course. All

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women routinely received laminaria for cervical ripening approximately 3 h prior to beginning the uterotonic agent. The managing physicians (Obstetrics and Gynecologic residents and Maternal-Fetal Medicine supervising faculty) were instructed to place as many laminaria as would comfortably fit through the internal os. Patients were routinely premedicated with acetaminophen 650 mg, promethazine 25 mg, and diphenoxylate hydrochloride plus atropine (Lomotil®; G.D. Searle, Inc., Chicago, IL).

Full treatment was defined as 24 h of therapy: either 6 courses of concentrated oxytocin plus 40 mg of vaginal PGE_2 vs. 2 vaginal applications of PGE_1, 200 μg, 12 h apart. Treatment success was defined as delivery (or imminent delivery) within the first 24 h of treatment. Following delivery of the fetus, all patients received oxytocin 50 units in 500 ccs of normal saline over 3 h. Failure to complete the third stage in this time period prompted a physical examination and attempts at manual placental removal. Only cases in which manual removal could not be accomplished were taken for curettage. Other outcomes of interest included the incidence of maternal side effects, the total time interval from induction to delivery, and the live birth rate (defined as a nonzero Apgar score at 1 min). Sealed opaque envelopes contained the computer generated, randomized block assignments, and directed the mode of induction to either PGE_1 or concentrated oxytocin plus low-dose PGE_2.

The null hypothesis was that the success rates in the 2 groups were similar. Original sample size estimates were based on an intergroup success rate difference of 15% (as from 95 to 80%, $\alpha = .05$) and considering a beta error of 0.2. Under these assumptions, 150 women would have to be studied. Statistical analyses were performed using the SAS Software for the personal computers (SAS Institute, Cary, NC). Chi-square and Fisher's exact test were used to compare proportional data. The Student *t*-test and Wilcoxon rank-sum test were used to compare continuous data as determined by a test for normal distribution. A *P*-value $\leq .05$ was chosen to represent statistical significance. The technique of stochastic curtailment was utilized to predict the likelihood of observing a statistically significant difference in the intergroup success rates for an interim analysis.

RESULTS

We performed an interim analysis on the first 30 patients (15, PGE_1; 15, concentrated oxytocin plus low-dose PGE_2). Patient characteristics of the 2 groups were similar with regard to maternal age, race, parity, gestational age at induction, and initial cervical dilation (Table 1). Indications for pregnancy termination were also similarly distributed between the 2 groups (Table 1), and most (77%) were performed for fetal anomalies, while the remainder included fetal death and maternal disease.

The 24-h success rate was 87% for concentrated oxytocin plus low-dose PGE_2 vs. 67% in the PGE_1 group ($P = .2$). All 7 patients who failed their assigned treatment received PGE_2 vaginal suppositories (20 mg q 4 h) and were delivered within the subsequent 24 h. The mean induction to delivery times also favored the concentrated oxytocin plus low-dose PGE_2 group (18 ± 6.6 vs. 22 ± 7.3 h, $P = .09$). The rate of retained placenta requiring curettage was 27% in the PGE_1 group vs. 13% using concentrated oxytocin and low-dose PGE_2 ($P = .65$). Considering the 26 patients who were delivered for indications other than fetal death, the live birth rate was 50% in the PGE_1 group vs. 0% using concentrated oxytocin and low-dose PGE_2 ($P = .006$). The incidence of nausea (47%) was identical in both groups, while vomiting, diarrhea, and fever $\geq$100.4°F were more common with concentrated oxytocin plus low-dose PGE_2 ($P = .07$–$.14$).

TABLE 1. Patient Characteristics

	Misoprostol N = 15	Concentrated oxytocin N = 15	*P*
Age[a] (years)	27.2 (8.0)	27.3 (7.3)	.74
Caucasion race (%)	67	67	1.0
Nulliparity (%)	53	53	1.0
Indication for termination (N)			.21
Fetal anomalies	11	12	
Fetal death	1	3	
Maternal disease	3	0	
Gestational age[a] (weeks)	20.4 (1.4)	20.4 (1.7)	.95
Initial cervical dilation[b] (cm)	0 (0–0.5)	0 (0–0.5)	1.0
Laminaria placed[b] (N)	4 (3–6)	4 (2–4)	1.0

[a]Mean, standard deviation.
[b]Median, range.

Stochastic curtailment was used to estimate the likelihood of observing a significant difference in the intergroup success rates, considering plausible assumptions about future trends in the success rates, had the trial been completed. Assuming that the observed intergroup success rates continued, there would be a 99.99% chance that the null hypothesis would be rejected at the $\alpha = .05$ level.

DISCUSSION

This interim analysis was conducted because of concerns on the part of our managing physicians that PGE_1 was associated with a higher failure rate and live birth rate than our standard regimen of concentrated oxytocin and low-dose PGE_2 [2]. Mid-trimester pregnancy loss for any reason is a very distressing occurrence for most women, and many times these are requested for fetal anomalies. These decisions are very difficult, and may further heighten the psychological discomfort. Moreover, medical terminations are usually performed in an inpatient setting, often in the labor suite, which has an atmosphere even less conducive to the psychological needs of the patient. Thus, the efficacy and timeliness of the uterotonic regimen is of real concern.

We chose a misoprostol dose of 200 μg q 12 h per vaginum because it had been previously validated and shown to be effective in a recent report [1]. While other dosing schedules (e.g., higher doses or more frequent doses of PGE_1) may increase efficacy, this will require further investigation.

As with essentially any uterotonic regimen, the possibility of live birth must be considered, especially for cases beyond 20 weeks' gestation. The occurrence of a live birth, while neither desirable nor predictable in this clinical setting, can further aggravate the psychological stress which these women have already encountered. Although various adjunctive strategies are available to prevent live birth, these procedures add additional complexity (e.g., fetal intercardiac KCL) and may increase the risk of the procedure (e.g., hypertonic saline); either might be unacceptable to the patient. By state law, all live births in Alabama, regardless of gestational age or birth weight, generate a birth certificate requiring parental validation. Neonatal issues also arise in cases of live birth, and can occasionally result in resuscitative efforts, particularly if a nonlethal anomaly is present. A mechanism by which concentrated oxytocin appears to lower the live birth rate is unclear, but it makes PGE_1 a less desirable alternative.

Although the possibility of intergroup selection bias in the delivery indications might have influenced our observed live birth rates, we were unable to determine this on review of the delivery indications. Specifically, of the 14 fetuses in the misoprostol group who began the procedure alive, 11 were anomalous and included 5 cases of aneuploidy (trisomy 21—4; trisomy 18—1), and 6 structural defects (holoprosencephaly—1; sacral teratoma—1; ventral wall defect—1; neural tube defect—2; bilateral multicystic kidney disease—1). Similarly, 12 fetuses in the concentrated oxytocin group were initially viable and these included four aneuploidies (trisomy 21—3; trisomy 18—1), and 8 structural anomalies (neural tube defects—5; megacystis—1, holoprosencephaly—1; ventral wall defect—1). Six of the 7 live births observed in the misoprostol group occurred in anomalous fetuses (holoprosencephaly—1; teratoma—1; trisomy 21—2; neural tube defect—1; bilateral multicystic kidney disease—1). Thus, although the delivery indications for anomalous fetuses were not identical, they appeared to be similar. A larger trial with group assignment stratification by presence and type of fetal anomaly could better address this issue.

Stochastic curtailment depends on plausible assumptions about the intergroup success rates anticipated in the remaining patients. The validity of our assumptions is supported by a recent report [3] in which the 24-h success rate with the same PGE_1 dosing regimen was 69%, quite similar to our observed rate. We determined that even if the 24-h success rate of PGE_1 were as high as 80%, there is still greater than an 80% likelihood (power) that a significant intergroup success rate would have been observed if the trial had continued to completion.

Although PGE_1 was associated with fewer gastrointestinal side effects than concentrated oxytocin plus low-dose PGE_2, we feel that this is outweighed by its other apparent disadvantages. In summary, this interim analysis does not support the utility of vaginal misoprostol administered in a dose of 200 μg q 12 h for mid-trimester pregnancy termination in an unselected population.

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