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Misoprostol for treatment of early pregnancy failure in women with prior uterine surgery

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Abstract

INTRODUCTION—Misoprostol use in early pregnancy may incur a risk of uterine rupture in women with prior uterine surgery.

STUDY DESIGN—We analyzed 488 women who received misoprostol 800 mcg vaginally in a study evaluating medical and surgical management of early pregnancy failure (EPF). Subjects received a repeat misoprostol dose if expulsion was not confirmed 2 days after treatment. We compared efficacy, acceptability, and safety in subjects with history (n=78) or absence (n=410) of uterine surgery, defined as cesarean section or myomectomy.

RESULTS—Expulsion rates following a single misoprostol dose (69% vs 72%, p=0.64) and overall success at 30 days (82% vs. 85%, p=0.50) were comparable. Pain, bleeding, complications, and acceptability did not differ. No uterine ruptures occurred (95% CI 0.0, 3.8%).

CONCLUSION—Misoprostol treatment for EPF had similar success, acceptability, and complications in women with and without prior uterine surgery.

CONDENSATION—Misoprostol treatment for EPF has similar success, acceptability, and adverse events in women with and without prior uterine surgery.

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Keywords

cesarean section; early pregnancy failure; miscarriage; misoprostol; myomectomy

INTRODUCTION

The number of women who have undergone cesarean section is increasing. The number of these procedures performed annually in the United States has risen from 4.5% of all births in 1965 to 29.1% in 2004.[1, 2] The rate of vaginal birth after cesarean (VBAC) has decreased from a high of 28.3% in 1996 to 9.2% in 2004.[2] Other uterine surgery is common as well, with nearly 17,000 myomectomies performed each year.[3] Since early pregnancy failure (EPF) is a common pregnancy complication, with 15 to 20% of clinically recognized pregnancies ending in miscarriage,[4] more and more women who have experienced prior uterine surgery, including cesarean sections and myomectomies, will present with EPF.

Options for treatment of early pregnancy failure include expectant management, surgical management (D&C), or medical management with medications such as misoprostol. Misoprostol (Cytotec, Pfizer Inc., New York, NY) is a prostaglandin E_1 analogue that is approved by the Food and Drug Administration for the prevention of gastric ulcers and has been used off-label for a variety of obstetric and gynecologic indications. Misoprostol alone appears to be an acceptable and effective treatment for women with EPF.[5] However, use of misoprostol in late pregnancy is associated with uterine rupture, albeit rarely; still, misoprostol is not recommended for induction of labor after prior cesarean section due to this increased risk.[6] By inference, use of misoprostol in the first trimester of pregnancy also may cause disruption of a previous uterine scar and extrusion of the products of conception into the abdominal cavity, causing pain and hemorrhage.

The magnitude of the risk of uterine rupture with use of misoprostol in comparison to risks of D&C, including perforation and organ injury, is unknown. It is also unknown whether the presence of a uterine scar influences response to misoprostol treatment. The limited information available complicates the counseling of women who present with EPF and a history of prior uterine surgery. For these reasons, we report on the outcome of women with prior uterine surgery who were enrolled in a randomized study evaluating the efficacy and safety of misoprostol treatment versus D&C for EPF.

MATERIALS AND METHODS

The institutional review boards of the National Institute of Child Health and Human Development, Columbia University, the University of Miami, the University of Pennsylvania, the University of Pittsburgh, and Clinical Trials and Surveys Corporation approved this multicenter study. This trial was designed to compare the efficacy and safety of misoprostol and vacuum aspiration for treatment of EPF.

The study protocol, demographics, and treatment outcomes were previously described.[5] Briefly, a medical history, hemoglobin level, and Rh-antigen status were obtained at enrollment and a physical examination was performed. The medical history included history of prior uterine surgery including cesarean section and myomectomy. Using a centralized computer-automated telephone response system, eligible subjects were randomized in a 3:1 ratio to receive either misoprostol or vacuum aspiration respectively. Randomization was stratified by study site and by type of pregnancy failure using random permuted blocks. The day of randomization was considered study day one.

Subjects assigned to the medical arm received four 200 mcg tablets (800 mcg) of misoprostol inserted in the posterior vaginal fornix through a speculum. They received 30 tablets of ibuprofen (200 mg) and 20 tablets of codeine (30 mg) for pain as needed and recorded side effects, medications, and emergency calls or hospital visits in a diary. These subjects returned on day 3 (range 2–5) and underwent examination by pelvic ultrasonography to assess treatment success. A second dose of misoprostol was given if a gestational sac was still present or if the endometrial lining was greater than 30mm. These subjects returned on day 8 (range 6–10) to evaluate expulsion of products of conception. If expulsion was not complete, subjects were offered vacuum aspiration. Women were asked to return on day 15 for a follow-up visit, including assessment of quality of life. Subjects were contacted at 30 days by phone to determine whether they underwent additional treatment.

For this planned secondary analysis, we included only subjects in the misoprostol group stratified by history or absence of prior uterine surgery. We defined overall success as avoidance of vacuum aspiration during the 30 days after treatment, but also examined the risk of D&C at time points after 30 days. All statistical analyses were performed with Stata 9 (College Station, TX). Student's t-tests and Mann-Whitney U tests were used for normally distributed and nonparametric continuous variables, respectively. Chi-square or Fisher's exact tests were used for categorical variables as appropriate.

RESULTS

Of the 652 women enrolled in the study, 488 received misoprostol treatment. Seventy-eight (16.0%) women had prior uterine surgery consisting of one cesarean section in 54 women, two or more cesarean sections in 20 women, and myomectomy in four women. Women with prior uterine surgery were older and more parous, but otherwise similar to the women without prior uterine surgery (Table 1).

Of the subjects randomized to treatment with misoprostol, 411 (84.6%) of 486 women successfully evacuated the gestational sac after treatment with misoprostol at 30 days. Outcomes stratified by history of prior uterine surgery are presented in Table 2. Four subjects underwent D&C after day 30 for heavy or persistent bleeding, including 1 woman with prior uterine surgery (1.3%) and 3 women without prior uterine surgery (0.7%). The overall risk of D&C and the risk of D&C by indication did not differ between groups (Table 2).

Side effects and complications are reported in Table 3. There were no differences in reported side effects within two days of treatment with misoprostol between the two groups based on diary data. The number of days of bleeding reported by diary did not differ in women with and without prior uterine surgery (11.1 days vs 11.0 days, respectively, p=0.67). None of the women with prior uterine surgery experienced uterine rupture or injury (95% CI 0.0, 3.8%). In women with and without prior uterine surgery, there were no differences in hemorrhage requiring blood transfusion.

Misoprostol treatment was equally acceptable among women who received misoprostol, with 81% and 78% of women with and without prior uterine surgery, respectively, willing to use misoprostol again if needed (p=0.17). There was no difference in the acceptability of side effects, with 57% and 59% of women with and without prior uterine surgery finding the side effects somewhat or totally acceptable (p=0.52).

COMMENT

We found that in women with prior uterine surgery, vaginal misoprostol treatment for early pregnancy failure resulted in similar rates of success, acceptability, and adverse events compared to women without prior uterine surgery. There were no cases of uterine rupture. This

multicenter randomized trial, which included 78 women with prior cesarean section or myomectomy, is one of the largest case series involving use of misoprostol in women with prior uterine surgery, and the only case series involving medical management of early pregnancy failure. This population included 20 women with two or more prior cesarean sections. Our sample size allows calculation of a 95% confidence interval of uterine rupture that ranges from 0 to 3.8%.

The demographic variables were comparable between our subjects with and without a history of prior uterine surgery with the exception of age and parity. We would expect women with prior uterine surgery to have a greater age and parity given that most of the uterine surgeries were cesarean sections. Side effects were also similar between the groups, though interestingly, there was a trend towards decreased telephone calls to the doctor or nurse in women with prior uterine surgery. We believe this finding may potentially also be related to parity as women with prior pregnancy experience may have been more tolerant of anticipated side effects.

One of the major concerns about use of misoprostol in pregnancy is uterine rupture. There are several case reports of uterine rupture in the first trimester. These case reports generally involve a predisposing factor such as uterine anomalies, prior uterine surgery, placenta percreta, or cesarean scar ectopic.[7–12] Two case reports describe spontaneous uterine rupture in the first trimester without an underlying predisposing factor, though in one case, trophoblastic tissue was found to invade the myometrium on pathology.[13, 14] There are two case reports of uterine rupture following misoprostol administration, both in women with prior cesarean sections, though one uterine rupture occurred in a uterine horn and not the uterine scar.[15, 16]

Three prior case series of women with prior cesarean sections who received medical abortion using mifepristone and oral misoprostol[17, 18] or methotrexate and vaginal misoprostol[19] include a total of 314 women with no reports of uterine rupture. The largest series included 213 women with prior cesarean sections who desired medical abortion at less than 69 days gestation.[17] The authors had no comparison group but stated that safety and efficacy were similar to what is reported in the general population. In this case series, 63 of the women underwent two medical abortions and 70 women underwent medical abortion within 6 months of their cesarean section. A smaller study compared the outcomes in 35 women with prior cesarean section to 157 women without a uterine scar who underwent medical abortion at less than 49 days of pregnancy with mifepristone and oral misoprostol.[18] The authors reported no significant difference in success rates, duration of bleeding, or side effects. A third study included 66 women with history of one or two prior cesarean sections who received methotrexate and misoprostol for medical abortion at less than 60 days gestation. The authors reported a success rate of 94% and gastrointestinal side effects as “uncommon and mild.”[19] When the 78 subjects from our study are included with the 314 women in the prior case series, the calculated 95% confidence interval for uterine rupture ranges from 0 to 0.8%.

One of the limitations of this study is that given the rarity of serious adverse events such as uterine rupture, we cannot achieve adequate power to see a difference in such adverse events. However, it is reassuring that there was no difference in other more common outcomes such as pain, bleeding, or need for D&C in this prospective trial. The presence of a uterine scar does not appear to influence uterine response to misoprostol or success of treatment. Only four women had undergone prior myomectomy, so conclusions about the effect of myomectomy on misoprostol treatment for early pregnancy failure are limited. Given that nearly 30% of deliveries in the United States result in cesarean sections, and 15–20% of clinically recognized pregnancies end in miscarriage, many health care providers will encounter women with early pregnancy failure who have a history of uterine surgery. In light of prior reports of misoprostol use in first-trimester elective abortion, the data presented here are reassuring that medical

management of early pregnancy failure is an acceptable option in women with prior uterine surgery.

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Table 1

Demographics and pregnancy history of women receiving medical management

	Previous uterine surgery n= 78	No uterine surgery n=410	p-value
Age*	32.7±5.8	29.3±7.4	<0.01
Race/Ethnicity†			
Black	24 (30.8)	125 (30.5)	0.62
Hispanic	36 (46.2)	164 (40.0)	
White	14 (17.9)	100 (24.4)	
Other	4 (5.1)	21 (5.1)	
Education†			
Less than High School	11 (14.1)	104 (25.4)	0.06
High School	29 (37.2)	114 (27.8)	
College or higher	38 (48.7)	192 (46.8)	
Insurance type†			
Medicaid/Medicare	33 (42.3)	145 (35.4)	0.36
Private	26 (33.3)	144 (35.1)	
Uninsured	18 (23.1)	119 (29.0)	
Unsure	1 (1.3)	2 (0.5)	
Number of prior pregnancies†			
None	0 (0)	115 (28.1)	<0.01
One	22 (28.2)	105 (25.6)	
Two	17 (21.8)	73 (17.8)	
Three or more	39 (50.0)	117 (28.5)	
Smoking status†			
Non-smoker	68 (87.2)	332 (81.0)	0.19
Smoker	10 (12.8)	78 (19.0)	
Pregnancy type†			
Embryonic/fetal demise	44 (56.4)	236 (57.6)	0.73
Anembryonic gestation	28 (35.9)	151 (36.8)	
Inevitable/incomplete abortion	6 (7.7)	23 (5.6)	
Gestational Age*	7.8±1.6	7.6±1.4	0.31

*Data are presented as mean ± standard deviation

†Data are presented as number of subjects and percentage

Table 2

Outcomes of misoprostol treatment at 30 days for early pregnancy failure stratified by history or absence of prior uterine surgery*

	Previous uterine surgery	No uterine surgery	p-value
Success with single dose of misoprostol	54/78 (69.2%)	293/408 (71.8%)	0.64
Received 2 doses of misoprostol	19/78 (24.4%)	88/410 (21.5%)	0.57
Success with 2nd dose of misoprostol	10/19 (52.6%)	54/88 (61.4%)	0.48
Overall success at 30 days	64/78 (82.1%)	347/408 (85.1%)	0.50
Overall D&C	14/78 (18.0%)	63/410 (15.4%)	0.57
D&C for persistent gestational sac	8/78 (10.3%)	43/410 (10.5%)	0.95
D&C for other reasons†	6/78 (7.7%)	20/410 (4.9%)	0.28

*Data missing for 2 subjects at 30 days

†Other reasons include bleeding, pain, infection, or patient choice

Table 3

Side effects or complications*

	Previous uterine incision n= 78	No uterine incision n=410	P value
Abdominal pain†	76 (98.7)	396 (99.5)	0.41
Heavy vaginal bleeding†	49 (63.6)	262 (66.0)	0.69
Fever†	15 (19.5)	70 (17.8)	0.72
Diarrhea†	16 (20.8)	99 (24.9)	0.44
Chills†	37 (48.7)	177 (44.6)	0.51
Nausea†	37 (48.1)	217 (54.8)	0.28
Use of codeine†	59 (75.6)	291 (71.0)	0.40
Called doctor or nurse†	9 (11.7)	82 (20.6)	0.07
Emergency visit to doctor or nurse†	5 (6.5)	25 (6.3)	1.0
Blood transfusion	1 (1.3)	3 (0.7)	0.50
Hospitalization	1 (1.3)	7 (1.7)	1.0

* Data are presented as number of subjects and percentage

† Within two days of treatment with misoprostol