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Endometrial thickness after misoprostol use for early pregnancy failure

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Abstract

Objectives: To assess if there was any potential relationship between endometrial thickness and final treatment outcome in women successfully treated with misoprostol for a first trimester anembryonic gestation, embryonic demise or fetal demise. *Methods:* Eighty women were treated with up to two doses of misoprostol 800 μg vaginally for early pregnancy failure. Subjects were scheduled to return 2 (range 1-4), 7 (range 5-9) and 14 (range 12-17) days after treatment. Transvaginal ultrasonography was performed at each follow-up visit. *Results:* The median endometrial thickness at each of the follow-up visits for women who had expelled the gestational sac was 14 mm, 10 mm, and 7 mm, respectively. The endometrial thickness at the first follow-up visit exceeded 15 mm in 20 subjects (36%) and 30 mm in four subjects (7%). Only three women had a suction aspiration for bleeding after documented expulsion. The endometrial thickness for these women was 11, 13, and 14 mm at the first follow-up visit. *Conclusions:* There is no obvious relationship between increasing endometrial thickness and the need for surgical intervention in women treated with misoprostol for early pregnancy failure.

Keywords

Misoprostol; Early pregnancy failure; Miscarriage; Transvaginal ultrasound; endometrial thickness

1. Introduction

For more than 50 years, the standard management of early pregnancy failure (EPF) has been surgical evacuation of the uterus [1]. Over the last decade, investigators have questioned both the need for urgent treatment as well as the need for any treatment in women with EPF [2-5]. As an alternative to surgical evacuation, vaginal misoprostol has been investigated, often resulting in complete expulsion of the gestational sac in more than 80% of women [6-10]. However, previously published studies have included small numbers of women, ranging from 8 to 42, treated with this regimen.

These small studies do not provide any clear evidence of what to expect sonographically following expulsion of the pregnancy tissue. Moreover, no clear understanding exists as to whether or not women who are sonographically diagnosed with an ‘incomplete abortion’ or ‘retained products of conception’ truly need any treatment. The best evidence to date comes from the medical abortion literature. Harwood et al. [11] reported that the average endometrial

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thickness in 36 women who experienced a complete abortion was 17.5 mm when evaluated 24 h after using misoprostol in a medical abortion regimen. Interestingly, the thickness ranged from 7.6 to 29.0 mm. The authors indicated that if 16 mm had been used as a cut-off point as suggested by other investigators [12-14], 61% of women with a complete abortion would have received unnecessary intervention.

We evaluated the ultrasound findings in 80 women treated with misoprostol for an EPF to assess if the endometrial thickness measurement after expulsion of the gestational sac is correlated with the need for further treatment. The aims of this study are to evaluate endometrial thickness over a 2-week period in women who are successfully treated with misoprostol for early pregnancy failure, to investigate if there is any correlation of endometrial thickness with a need for surgical intervention after expulsion, and to examine if there is an association between endometrial thickness and bleeding patterns.

2. Materials and methods

This multicenter study was performed at Columbia University, the University of Miami, the University of Pennsylvania, and the University of Pittsburgh. This trial was designed to compare the efficacy and safety of misoprostol, administered with or without saline, as a treatment for EPF. The study design included the prospective collection of data to allow a planned analysis of the ultrasound findings after misoprostol treatment. The study was approved by the Institutional Review Boards of the respective institutions and the National Institutes of Health (NIH).

The study protocol and treatment outcomes have been previously described [15]. Briefly, the study randomized 80 women to wet or dry misoprostol 800 μg as the treatment regimen, and the day of treatment was considered study day 1. Follow-up visits were scheduled to occur on study day 3 (range 2-5), day 8 (range 6-10), and day 15 (range 13-18). Transvaginal ultrasonography was performed at each follow-up visit to determine if the gestational sac was still present. If the gestational sac was still present at the first follow-up visit, a second dose of misoprostol 800 μg was administered. If the gestational sac had not been expelled by the second follow-up visit, a D&C was performed. A telephone interview was arranged to occur around study day 30 for all subjects to identify any health problems or further treatment since the final follow-up visit. After misoprostol-induced expulsion, a suction aspiration was performed only when clinically indicated based on heavy bleeding, prolonged bleeding or significant pain requiring intervention. Treatment success was defined a priori as expulsion of the pregnancy tissue without the need for surgical intervention at any time by study day 30. However, three women who had a suction aspiration after this time for prolonged or heavy bleeding (on study days 31, 43, and 50) were also considered treatment failures.

When ultrasonography confirmed that the gestational sac was expelled, the maximal anterior-posterior endometrial thickness in the longitudinal plane of the uterus was measured. If the sac was not expelled then the endometrial thickness was not measured as such a finding was irrelevant given the presence of the gestational sac. Prior to initiating the trial, the investigators met to review sonography techniques and agreed to measure the endometrial thickness as the hyperechoic region (including any blood and clots) between the anterior and posterior edges of the myometrium. The endometrial thickness data were obtained solely for research purposes and were not used to define whether or not treatment was successful or further treatment was indicated.

A total of 80 subjects were enrolled based on sample size estimates for the primary outcome evaluations [15]. For this evaluation, the 69 women who expelled the gestational sac after one or two doses of misoprostol and had sonographic measurements of the endometrial thickness

performed were included. The other 11 women included 9 women who had a D&C with the gestational sac still present (treatment failure or subject request) and two subjects who were lost to follow-up and had no post-treatment ultrasound data available. Of the 69 women in this analysis, 46 had three post-expulsion endometrial thickness measurements, 17 women had two measurements, and six women had one measurement.

There were no significant differences in baseline characteristics, success rates, or side effects between the wet and dry misoprostol groups [15]. Additionally, there were no differences in treatment outcome by study site [15]. Therefore, we combined all subjects enrolled in the study into one cohort for this evaluation of endometrial thickness measurements.

Medians, standard means, and geometric means were calculated for endometrial thickness. Statistical comparisons comparing expulsion rates and endometrial thickness were performed using Chisquare analysis, and those related to endometrial thickness and bleeding patterns were performed using a Wilcoxon rank-sum test. A $P<0.05$ was considered statistically significant.

3. Results

Maximal endometrial thickness measurements after complete expulsion are described in Table 1. Medians and geometric means were identical at each follow-up visit and varied by no more than 2 mm from the standard mean. Only three women had a suction aspiration (all performed for clinically significant bleeding) after documented expulsion. The endometrial thickness for these women was 11, 13, and 14 mm at the first follow-up visit. A fourth subject, who was without any clinical complaints, had a suction aspiration at the third follow-up visit because the ultrasound examination was misinterpreted as demonstrating a retained collapsed sac; the pathology evaluation revealed no gestational tissue. The endometrial thickness at her first follow-up visit was 15 mm. Using the endometrial thickness measurement at the first follow-up visit at which expulsion was documented, 4 of 35 women (11%, 95% CI 3, 27%) with a thickness of 15 mm or less needed future surgical intervention as compared to 0 of 20 women (0%, 95% CI 0, 17%) with a thickness exceeding 15 mm ($P=0.3$).

There was no relationship between endometrial thickness and presence of active bleeding at follow-up visits #1 and #3 (Table 2). However, the median endometrial thickness was statistically significantly greater at follow-up #2 in women who were bleeding than those who had no bleeding or only spotting.

4. Discussion

In this study of misoprostol treatment for EPF, a wide range of endometrial thickness was observed after expulsion of the gestational sac. All studies published prior to this study have included very small numbers of subjects. As larger trials are published, an understanding of the relationship between endometrial thickness and need for future surgical intervention is important. Our findings suggest that such a relationship unlikely exists, and that endometrial thickness measurements are not likely to be predictive of incomplete abortion or the need for further treatment.

The results presented in Table 1 demonstrate that a wide variation in endometrial thickness is seen after expulsion of the gestational sac, and that the thickness generally decreases with time. We chose to include all measurements regardless of whether the expulsion occurred with the first or second dose, realizing that those women who expelled the gestational sac with the first dose of misoprostol had a few more days for the lining to be thinner. Importantly, no cut-off value from this small trial appears to be predictive of incomplete abortion.

No prior studies have established an ultrasound measured 'amount' of intrauterine tissue that is considered significant after expulsion of uterine gestational contents and would require further treatment. Chung et al. [16] use 5 cm^2 as their criteria for a 'significant' amount of tissue based on a study by Haines et al. [17] in which women with an EPF had transvaginal ultrasonography 24 h after a suction aspiration. The authors found that the uterine contents after suction aspiration did not vary by gestational age (range 6-17 weeks) and selected two standard deviations above either the mean transverse width (5 cm) or the area (6 cm^2) to represent an 'empty' uterus. Haines et al. [18] then performed a prospective cohort study of 50 women who had a spontaneous abortion within 24 hours of enrollment. Women were managed conservatively if the sagittal and transverse measurements of the uterine cavity area were less than 6 cm^2. Thirty-two (64%) women met the criteria for conservative management and none required a curettage in the following 2 weeks. Although this study suggests that women who have a spontaneous abortion and have an ultrasound examination demonstrating intrauterine tissue with an area less than 6 cm^2 have a successful outcome with expectant management, the results still do not demonstrate that women with more intrauterine tissue do not have successful outcomes.

Nielsen and colleagues [12-14] have repeatedly performed trials in women experiencing miscarriage in which an anterior-posterior endometrial thickness of 15 mm or greater is required for study enrollment. These investigators considered this measurement as the defining amount of tissue for complete abortion because 'pregnancy tissue with a diameter of less than 15 mm would not have been considered for D&C as a routine procedure in our department' [12]. Luise et al. [19] used the same criteria to define complete miscarriage in their recent report of expectant management of 1096 women with EPF also without any evidence for using such criteria. In follow-up, Luise et al. [20] attempted to evaluate if endometrial thickness predicts the outcome of expectant management. The authors concluded that the endometrial thickness was not predictive of the likelihood of expectant management failure. However, because they defined failure using the '15 mm' criteria, their results are difficult to interpret.

In our study, women who were successfully treated with misoprostol for EPF had a wide range of endometrial thickness measurements, calling into question the use of any cut-off values for universally defining incomplete abortion. A thickened endometrial lining after miscarriage is a normal finding. Therefore, based on the available evidence, clinical signs and symptoms rather than endometrial thickness should guide treatment decisions. None of our subjects with an endometrial thickness greater than 15 mm required surgical evacuation. In future trials using misoprostol for evacuation of early pregnancy failure, women who are clinically stable with a thickened endometrium following expulsion of the gestational sac likely do not need any further treatment. Confirmation of these findings with larger trials would be beneficial.

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Table 1

Endometrial thickness as measured by transvaginal ultrasonography in women successfully treated with misoprostol for early pregnancy failure

Follow-up visit[a]	Subjects *n*	Endometrial thickness			
		Median (mm)	Range (mm)	> 30 mm *n* (%)	> 15 mm *n* (%)
1	55	14	4–52	4 (7%)	20 (36%)
2	60[b]	10	3–31	1 (2%)	15 (25%)
3	63	7	1–31	1 (2%)	7 (11%)

[a] Follow-up visits #1, #2, and #3 occurred on study day 3 (range 2—5), day 8 (range 6—10), and day 15 (range 13—18), respectively.

[b] Measurements from two subjects with complete expulsion were not performed.

Table 2

Endometrial thickness (median) and presence of active bleeding in women who were successfully treated with misoprostol for early pregnancy failure

Follow-up visit[a]	Number[b]	Endometrial thickness (mm)		*P*-value
		Active bleeding	No bleeding	
1	55	14.5 (*n* = 30)	13 (*n* = 25)	0.33
2	60	12.5 (*n* = 28)	7.5 (*n* = 32)	0.007
3	62	6 (*n* = 9)	7 (*n* = 53)	0.90

[a] Follow-up visits #1, #2 and #3 occurred on study day 3 (range 2—5), day 8 (range 6—10), and day 15 (range 13—18), respectively.

[b] Number of women with physical examination and ultrasound measurements available.