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Predictors of uterine evacuation following early medical abortion with mifepristone and misoprostol☆

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Abstract

Objectives: We sought to determine predictors of uterine evacuation for women undergoing medical abortion using mifepristone and vaginal misoprostol through 63 days' gestation.

Study Design: We pooled data from two prospective multicenter medical abortion trials. In one study, women received mifepristone 200 mg followed either 6–8 or 23–25 h later by misoprostol 800 mcg vaginally. In the second study, women received mifepristone 200 mg followed either <15 min or 23–25 h later by misoprostol 800 mcg vaginally. We examined the absolute risk (AR) of uterine evacuation using Fisher's Exact Tests for categorical variables and Student *t* test and Wilcoxon rank-sum tests for continuous variables. We used logistic regression to calculate odds ratios (ORs) of uterine evacuation.

Results: Uterine evacuation was performed for 75 (3.5%) of 2160 women. In multivariable analysis, 5 or more prior deliveries (AR 11.9%, OR 4.6) and gestational age of 8 weeks or more (AR 4.1%, OR 2.1) were significantly associated with uterine evacuation, while age of 20 years or younger (AR 1.4%, OR 0.4) was significantly and inversely associated with uterine evacuation. Prior cesarean delivery, multiple gestations, smoking, weight, body surface area and body mass index were not predictive of uterine evacuation in univariate or multivariable analysis.

Conclusion: Uterine evacuation is an uncommon outcome in medical abortion with mifepristone and vaginal misoprostol. Five or more deliveries are the only significant predictor that identifies a group with an AR of uterine evacuation of more than 6%.

Implications: Uterine evacuation is uncommon in medical abortion with mifepristone and vaginal misoprostol. Parity of five or more is the only significant predictor of uterine evacuation exceeding 6%. Until additional research is completed, medical abortion should not be withheld from women with five or more deliveries.

Keywords: Medical abortion; Mifepristone; Misoprostol; Uterine evacuation

1. Introduction

Medical abortion with mifepristone and misoprostol is highly effective. With a regimen of mifepristone and vaginal misoprostol, approximately 3% to 5% of women will subsequently undergo uterine evacuation [1–3]. Regimens using mifepristone and buccal misoprostol have a similar (3.3%) risk of requiring uterine evacuation [4,5]. In approximately 2%–3% of women, uterine evacuations are performed after expulsion of the pregnancy due to pain or bleeding [1–3,5].

Predictors of uterine evacuation following medical abortion have been examined previously using regimens of mifepristone followed by oral misoprostol. These regimens are less effective than regimens with vaginal misoprostol and thus less relevant to current clinical practice [6–9]. Three of these studies included from 271 to 879 women, with 7% to 36% undergoing uterine evacuation [6–8]. These three studies identified increasing parity, prior cesarean delivery, obesity [body mass index (BMI)], initial human chorionic gonadotropin (hCG), older age and prior spontaneous abortion as predictors of uterine evacuation. A prior pooled

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Table 1
Summary of pooled study populations from two studies including women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg vaginally.

Study group	MOD study[a]		MAST study[b]		Pooled	
Total subjects enrolled	1080		1128		2208	
Excluded[c]	22	(2.0%)	26	(2.3%)	48	(2.2%)
Included in analysis	1058	(98.0%)	1102	(97.7%)	2160	(97.8%)
Uterine evacuation performed	31	(2.9%)	44	(4.0%)	75	(3.5%)
Days from mifepristone to uterine evacuation						
6 or fewer	8	(25.8%)	6	(13.6%)	14	(18.7%)
7–13	2	(6.5%)	2	(4.5%)	4	(5.3%)
14–27	13	(41.9%)	27	(61.4%)	40	(53.3%)
28 or more	8	(25.8%)	9	(20.5%)	17	(22.7%)
Indication for uterine evacuation						
Bleeding or pain	18	(58.1%)	18	(40.9%)	36	(48.0%)
Viable pregnancy	2	(6.5%)	6	(13.6%)	8	(10.7%)
Persistent gestational sac	4	(12.9%)	13	(29.5%)	17	(22.7%)
Other	5	(16.1%)	7	(15.9%)	12	(16.0%)
Repeat dose of misoprostol[d]	17	(1.6%)	57	(5.2%)	74	(3.4%)

[a] Medical abortion in 1 day [1].
[b] Medical abortion at the same time [2].
[c] Reasons for exclusion: lack of follow-up data (n=45) and withdrawal from study prior to use of misoprostol (n=1).
[d] Subjects in both studies were offered a repeat dose of misoprostol if the pregnancy was not expelled based on transvaginal ultrasonography at the follow-up visit.

analysis of four trials who received mifepristone 600 mg with oral misoprostol, with uterine evacuation performed in 3.9% to 14.6%, reported that women younger than 23 years, at less than 50 days' gestation and with no prior abortions were more likely to have a successful medical abortion [9].

We sought to identify predictors of uterine evacuation in a sample with a risk of uterine evacuation similar to that seen in typical clinical practice today. We specifically sought predictors which would be available prior to starting the medical abortion process to help clinicians and the patients that they are counseling. Based on prior research, we hypothesized that increasing gestational age, increasing obesity, increasing parity, prior cesarean delivery and increasing age might be associated with an increased risk of uterine evacuation.

2. Materials and methods

This study is a pooled secondary analysis of data from two multicenter randomized trials of medical abortion. In the first study, 1080 women received an oral dose of mifepristone 200 mg after which they were randomly assigned to self-administer misoprostol 800 mcg vaginally within the next 6 to 8 h or in 23 to 25 h [1]. Women were enrolled at the University of Pittsburgh, Columbia University, Boston University and the University of Rochester. In the second study, 1128 women received mifepristone 200 mg after which they were randomized to self-administer misoprostol 800 mcg vaginally within the next 15 min or in 23 to 25 h [2]. Women were enrolled at the University of Pittsburgh, Oregon Health Science University, Northwestern University and the University of Southern California. Population demographics and treatment outcomes have been previously described [1,2]. Both studies were approved by the institutional review boards of participating institutions. All data were collected prospectively.

The follow-up and outcome assessment were similar for the two study protocols. In both studies, participants were scheduled to return for a follow-up visit including sonographic examination approximately 6–8 days after taking mifepristone. Women who had not expelled the gestational sac were given a repeat dose of misoprostol 800 mcg vaginally. In both protocols, subjects who missed the first follow-up visit but were seen within 11 days after receiving the mifepristone could receive a second dose of misoprostol for a persistent sac. Subjects who received a second dose of misoprostol had another follow-up visit scheduled 12–16 days after receiving mifepristone. Transvaginal ultrasonography was performed at each visit with successful expulsion defined as absence of the gestational sac. The research staff attempted to contact all subjects by telephone 5 weeks after initiating the study to review if there had been any problems during or after the medical abortion process. We only included women who used both agents (mifepristone and misoprostol) and had at least one follow-up visit during the study.

The primary outcome for this analysis was uterine evacuation, regardless of the indication. In both clinical trials, uterine evacuation was performed following pregnancy expulsion if clinically necessary because of subject request or symptoms consistent with incomplete abortion such as prolonged or heavy bleeding or cramping. In both studies, uterine evacuation was recommended for women with a persistent sac with gestational cardiac activity at the second follow-up visit. Women with a non-viable persistent gestation at the second follow-up were offered uterine evacuation or expectant management. In neither trial was the decision for uterine evacuation based on endometrial thickness as assessed

Table 2
Association between participant factors and uterine evacuation in women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg vaginally.

	Uterine evacuation				p
	No		Yes		
	n	(%)	n	(%)	
All women	2085	(96.5)	75	(3.5)	
Study					.2
MOD[a]	1027	(97.1)	31	(2.9)	
MAST[b]	1058	(96.0)	44	(4.0)	
Interval from mifepristone to misoprostol					.04
23–25 h	1052	(97.5)	27	(2.5)	
6–8 h	504	(95.8)	22	(4.2)	
<15 min	529	(95.3)	26	(4.7)	
Age (y)					.02
20 or younger	417	(98.6)	6	(1.4)	
21–29	1249	(96.2)	50	(3.8)	
31–34	223	(97.0)	7	(3.0)	
35 or older	196	(94.2)	12	(5.8)	
Gestational age					.2
6 weeks or less	867	(97.5)	22	(2.5)	
7 weeks	654	(95.8)	29	(4.2)	
8–9 weeks	564	(95.9)	24	(4.1)	
Twin pregnancy					.2
No	2064	(96.6)	73	(3.4)	
Yes	21	(91.3)	2	(8.7)	
Prior deliveries					.008
0	806	(97.6)	20	(2.4)	
1	572	(96.8)	19	(3.2)	
2-4	670	(95.6)	31	(4.4)	
5 or more	37	(88.1)	5	(11.9)	
Prior cesarean delivery					.2
0	1858	(96.7)	63	(3.3)	
1 or more	226	(95.0)	12	(5.0)	
Prior elective abortion					.6
0	1116	(96.8)	37	(3.2)	
1	587	(96.4)	22	(3.6)	
2 or more	371	(95.9)	16	(4.1)	
Race and ethnicity					.3
White (non-Hispanic)	954	(97.0)	29	(3.0)	
African American (non-Hispanic)	625	(96.7)	21	(3.3)	
Hispanic	394	(95.4)	19	(4.6)	
Other	112	(94.9)	6	(5.1)	
Smoking					.15
Nonsmokers	1214	(96.0)	50	(4.0)	
Smokers	849	(97.3)	24	(2.7)	
Weight (kg)					.3
50 or less	115	(95.8)	5	(4.2)	
51–75	1345	(96.9)	43	(3.1)	
76–100	494	(95.4)	24	(4.6)	
101 or more	130	(97.7)	3	(2.3)	
BMI category (kg/m^2)					.7
Underweight (<18.5)	176	(96.7)	6	(3.3)	
Normal (18.5–24.99)	899	(97.0)	28	(3.0)	
Overweight (25.00–29.99)	543	(95.8)	24	(4.2)	
Obese I (30.00–34.99)	275	(96.5)	10	(3.5)	
Obese II (35.00–39.99)	123	(95.3)	6	(4.7)	
Obese III (≥40.00)	68	(98.6)	1	(1.4)	
BSA percentile					.5
<25%ile	535	(97.1)	16	(2.9)	
25–75%ile	1034	(96.6)	36	(3.4)	
>75%ile	515	(95.7)	23	(4.3)	

[a] Medical abortion in 1 day [1].
[b] Medical abortion at the same time [2].

Table 3
ORs for uterine evacuation in women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg vaginally.

Predictor	Unadjusted		Adjusted[a]	
	OR	95% CI (%)	OR	95% CI (%)
Study				
MOD[b]	1	Referent	1	Referent
MAST[c]	1.4	0.9–2.2	2.2	0.9–4.9
Interval from mifepristone to misoprostol				
23–25 h	1	Referent	1	Referent
6–8 h	1.7	1.0–3.0	2.4	1.1–5.2
<15 min	1.9	1.1–3.3	1.6	0.8–3.0
Age (y)				
20 or younger	0.4	0.2–0.8	0.4	0.2–0.9
21–29	1	Referent	1	Referent
31–34	0.8	0.4–1.8	0.6	0.3–1.5
35 or older	1.5	0.8–2.9	1.1	0.5–2.2
Gestational age				
6 weeks or less	1	Referent	1	Referent
7 weeks	1.7	1.0–3.1	2.0	1.1–3.5
8–9 weeks	1.7	0.9–3.0	2.1	1.1–3.9
Twin pregnancy				
No	1	Referent	1	Referent
Yes	2.7	0.6–11.7	3.6	0.8–16.4
Prior deliveries				
0	1	Referent	1	Referent
1	1.3	0.7–2.5	1.2	0.6–2.4
2–4	1.9	1.1–3.3	1.4	0.7–2.8
5 or more	5.4	1.9–15.3	4.6	1.5–14.9
Prior cesarean delivery				
0	1	Referent	1	Referent
1 or more	1.6	0.8–2.9	1.4	0.7–2.8
Prior elective abortion				
0	1	Referent	1	Referent
1	1.1	0.7–1.9	1.1	0.6–1.9
2 or more	1.3	0.7–2.4	1.2	0.6–2.2
Race and ethnicity				
White (non-Hispanic)	1	Referent	1	Referent
African American (non-Hispanic)	1.1	0.6–2.0	0.8	0.4–1.5
Hispanic	1.6	0.9–2.9	1.7	0.9–3.3
Other	1.8	0.7–4.3	1.9	0.8–5.0
Smoking				
Nonsmokers	1	Referent	1	Referent
Smokers	0.7	0.4–1.1	0.6	0.4–1.1
Weight (kg)				
50 or less	1.4	0.5–3.5	1.8	0.5–6.3
51–75	1	Referent	1	Referent
76–100	1.5	0.9–2.5	1.0	0.3–3.3
101 or more	0.7	0.2–2.4	0.7	0.1–5.0
BMI category (kg/m^2)				
Underweight (<18.5)	1.1	0.4–2.7	0.9	0.3–3.0
Normal (18.5–24.99)	1	Referent	1	Referent
Overweight (25.00–29.99)	1.4	0.8–2.5	1.0	0.5–1.9
Obese I (30.00–34.99)	1.2	0.6–2.4	0.7	0.2–1.9
Obese II (35.00–39.99)	1.6	0.6–3.9	0.8	0.2–3.4
Obese III (≥40.00)	0.5	0.1–3.5	0.2	0.0–2.9
BSA percentile				
<25%ile	0.9	0.5–1.6	0.7	0.3–1.5
25–75%ile	1	Referent	1	Referent
>75%ile	1.3	0.8–2.2	1.6	0.5–4.8

[a] Adjusted for all other variables in the table and for study site.
[b] Medical abortion in 1 day [1].
[c] Medical abortion at the same time [2].

by ultrasonography. The relevant outcomes for each study are summarized in Table 1. Serum hCG levels were not assessed in either study.

In examining predictors of uterine evacuation, BMI was calculated using the Quetelet formula [10,11]. Body surface area (BSA) was calculated using the formula developed by Gehan and George [12] which was found in our data to be strongly correlated (r=0.9996) with the simpler but less accurate Mosteller formula [13,14]. BMI and BSA were both examined as continuous and ordinal variables. Obesity was classified by BMI according to the World Health Organization system [15]. BSA was categorized as quartiles, and the upper and lower quartiles were compared to the interquartile range.

We compared continuous variables using both the Student t test and Wilcoxon rank-sum test and categorical variables using Fisher's Exact Test. Lowess splines were used to examine graphically the linearity assumption of continuous variables with the outcome of uterine aspiration. For all variable types, we compared the odds of the outcome by each variable using logistic regression. We then performed a multivariable linear regression using all variables and then using a stepwise elimination protocol with an "entry" significance of ""0.2 and a "remain" significance of 0.1. Randomization group was forced to remain in the stepwise model regardless of level of significance. A stepwise modeling technique was used to maximize power while examining a large number of predictors in this large sample with a relatively small number of outcome events. Study site was included in both regressions.

In an effort to distinguish sociologic vs. biologic origin for predictors of uterine aspiration, we compared women who chose a repeat dose of misoprostol to those who had a uterine aspiration. For this portion of the analysis, women who had a repeat dose of misoprostol comprised one group, whether or not those women subsequently had a uterine aspiration using Fisher's Exact Test. We examined whether the proportion who chose repeat misoprostol or uterine aspiration varied by each of the significant predictors of uterine aspiration. We used Lowess plots to identify thresholds in continuous variable. We performed a logistic regression to examine the relationship between predictors of uterine aspiration and the choice between repeat misoprostol and uterine aspiration.

Results are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). All statistical analyses were performed using Stata 11 (StataCorp, College Station, TX, USA).

3. Results

Of the 2208 women enrolled in the two studies, 2160 (97.8%) used a regimen mifepristone 200 mg and misoprostol 800 mcg vaginally and had follow-up data available. Seventy-five (3.5%) women underwent uterine evacuations, all of which were performed using suction aspiration. The overall proportion undergoing uterine evacuation was similar between the two studies (p=.2). The reasons for uterine evacuation are shown in Table 1. The median time to uterine evacuation was 16 days with a range of 1 to 67 days. Twelve women (16.0%) returned prior to the follow-up visit for uterine evacuation; 5 (6.7%) had a uterine evacuation on the day of the first follow-up visit, and 58 (77.3%) returned after the first follow-up visit for uterine evacuation. Table 2 presents the proportion of women undergoing uterine evacuation based on study and participant characteristics.

Predictors of uterine evacuation using multivariable logistic regression are shown in Table 3. When examined as a continuous variable, parity was found to be predictive of uterine evacuation, with an OR of 1.30 (95% CI 1.11–1.52) for each additional birth. However, the increase in risk was nonlinear, with grand mulitparity (five or more deliveries) having a much greater risk of uterine evacuation. Like the results for cesarean delivery as a dichotomous variable, the number of cesarean deliveries was not predictive of uterine evacuation as a continuous variable, either independently (OR 1.49, 95% CI 0.97–2.3) or after adjustment for parity (OR 1.26, 95% CI 0.80–1.97). When examined as continuous variables, weight, BMI and BSA were not significant predictors of uterine evacuation (all p>.2), as was found when examining these variables categorically.

In a stepwise logistic regression model, the results were similar to the full logistic regression model. The following factors were predictive of uterine evacuation in the stepwise model: 6- to 8-h interval between mifepristone and misoprostol (OR 2.5, 95% CI 1.1–5.5); women age 20 years or younger (OR 0.3, 95% CI 0.1–0.8), gestational age (OR 1.3 per additional week, 95% CI 1.02–1.6), grand multiparty (OR 3.2, 95% CI 1.2–8.8) and Hispanic ethnicity (OR 2.9, 95% CI 1.5–5.6). All of the other variables in Table 3 were included in the model and were either dropped or not significant in the final model.

The proportion of women undergoing uterine evacuation varied from 1.2% to 8.8% among the seven sites. The number of uterine evacuations for each indication was too small to determine predictors of the indication for the uterine evacuation procedure.

In total, 123 women had interventions for unsuccessful abortions. Of these women, 48 women had repeat doses of misoprostol only, 26 had repeat misoprostol then a uterine aspiration and 49 chose uterine aspiration initially. Thus, 74 (60%) women opted for a repeat dose of misoprostol rather than proceeding directly to uterine aspiration. When faced with an unsuccessful abortion, women under 20 years of age were much more likely to choose repeat misoprostol (85%) than uterine aspiration as compared to women over 20 years of age (55%, p=.01). The choice between misoprostol and aspiration did not vary significantly by race, parity or prior cesarean delivery. However, we observed a linear trend toward decreasing choice of repeat misoprostol as parity increased from 68% for nulliparous women to 40% for women with five or more deliveries (p=.06). The choice of

repeat misoprostol differed between the MOD and MAST studies: (40% vs. 70%, respectively; p=.02). In the women assigned the 6- to 8-h interval between mifepristone and misoprostol, only 36% chose repeat misoprostol, compared to 58% in the 24-h group and 77% in the same-time group (p=.002). We observed a trend toward more women at 6 weeks or less choosing repeat misoprostol (p=.07). We observed a nonsignificant trend toward increased of repeat misoprostol among women with very high weight, body surface area or body mass index. In multivariable regression analysis, only age less than 20 years and gestational age less than 6 weeks were significantly correlated with using repeat misoprostol rather than choosing uterine aspiration.

4. Discussion

As medical abortion regimens have improved and as experience with medical abortion has increased, the proportion of women undergoing uterine evacuation has decreased [16]. Because the proportion of women undergoing uterine evacuation in most prior studies of predictors was more than double what is commonly seen in clinical practice [9], we sought to examine the validity of these predictors in a sample using an evidence-based regimen and with a low risk of uterine evacuation. The limitation of this approach is that a lower risk of uterine evacuation results in fewer outcome events (uterine evacuation), which translates into less power to examine predictors. The indications for uterine evacuation are often subjective. Consequently, the proportion of women undergoing uterine evacuation varies greatly between studies and between clinics. In these pooled data, relatively few women underwent uterine evacuation compared to prior studies, suggesting that a higher threshold was used before proceeding with uterine evacuation. However, this study benefits from being representative of uterine evacuation percentages seen in current practice.

Even in the sub-group with the highest risk of uterine evacuation (women with five deliveries or more), 88.1% of women did not need a uterine evacuation. However, this subgroup was composed of just 42 women, and the basis for this observation is unclear. It is likely that none of the significant predictors identified here or in other studies are solely biologically based. Our finding that younger women and women with lower parity are more likely to choose repeat misoprostol supports the idea that some component of these predictors represents markers of personal or social situations. For example, it is plausible that the observed association between young age and decreased risk of uterine aspiration is driven by fear of an invasive procedure. Similarly, it is plausible that the reverse is true of women with five or more deliveries, many of whom may not have time or patience for expectant management. However, in this analysis, we are able only to report the observed associations and are unable to determine the driving factors. Thus, clinicians should use caution when using the findings presented here to guide patient selection.

In multivariable regression, we found that women who used misoprostol 6–8 h after mifepristone had an increased risk of uterine evacuation while women who used mifepristone and misoprostol at the same time did not. This somewhat contradictory finding may reflect differences in the populations or a hidden bias in the nonblinded trial with the 6- to 8-h interval. We believe that lower incidence of uterine aspiration in the simultaneous use of mifepristone and misoprostol compared to the 6- to 8-h interval may be explained by the increased use of repeat doses of misoprostol in the study that compared simultaneous use to a 24-h interval.

Two prior studies of predictors of uterine evacuation were retrospective chart reviews [6,8], raising the possibility of diagnostic, selection and follow-up biases. One of these retrospective studies identified prior cesarean delivery as a predictor of uterine evacuation [8]. We did not find that prior cesarean delivery is a predictor of uterine evacuation. This difference may be attributable to the higher proportion of women undergoing uterine evacuation in that cohort (9%), differences in the population or an increased propensity among providers to perform uterine aspiration in women with prior cesarean deliveries.

In one study, BMI and initial hCG level were identified as predictors [7]. Although well conducted and with good follow-up, that study was limited by the fact that multiple regimens were used (most of which are no longer used) and that 36% of women underwent uterine evacuations. In our pooled data, we found that BMI, BSA and weight were not associated with uterine evacuation with a trend toward a decreased risk of uterine evacuation in the highest BMI category. This finding may reflect decreased willingness by providers to perform a uterine evacuation on severely obese women. Regardless, these data are reassuring that mifepristone and misoprostol are effective for medical abortion in obese women.

Like the data presented here, an investigation of adolescents receiving medical abortions in Finland found that they were less likely to experience surgical evacuation compared to adults [17]. Similarly, a retrospective cohort study found that medical abortions in adolescents under the age of 18 years were significantly more likely to be successful compared to those in other age groups [18]. While we had similar findings, we also observed that younger women were more likely to choose repeat misoprostol suggesting a sociologic rather than a biologic origin to this observation.

Most importantly, we found that the mifepristone and vaginal misoprostol are very effective in most women. Further research is needed to examine the relationship between parity and uterine evacuation after medical abortion, particularly with the use of buccal misoprostol. Although some women may have slightly higher risk of ultimately needing or requesting a uterine aspiration, all women should be offered medical abortion.

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