

Endometrial thickness following medical abortion is not predictive of subsequent surgical intervention

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ABSTRACT

Objectives To evaluate the ability of endometrial thickness after medical abortion to predict the need for subsequent dilatation and curettage (D&C).

Methods We pooled data from two multicenter medical abortion trials involving 2208 women who received mifepristone orally followed by misoprostol vaginally. Women returned for transvaginal ultrasonography approximately 7 days later. The endometrial thickness was measured if no gestational sac was present. Final status was confirmed by a phone interview at 5 weeks. The area under the receiver–operating characteristics (ROC) curve was calculated to assess the overall ability of endometrial thickness to predict the need for subsequent D&C. Endometrial thickness was dichotomized using threshold values at 5-mm increments from 10 to 30 mm. The sensitivity, specificity, negative predictive value and positive predictive value were calculated to evaluate the ability of each endometrial thickness threshold value to predict subsequent D&C. Multivariable regression analysis was performed to adjust endometrial thickness values for study, treatment group, and study site.

Results At 7 days after misoprostol treatment, 1870 women (84.7%) had endometrial thickness assessed. Thirty of these women (1.6%) subsequently underwent D&C. The mean endometrial thickness was 14.5 mm for women who underwent D&C and 10.9 mm for those who did not (difference 3.5 mm (95% CI, 1.8–5.3 mm)). Endometrial thickness was poorly predictive of the need for D&C, with an area under the ROC curve of 0.65. All endometrial thickness thresholds had positive predictive values of 25% or less. The results were

unchanged by adjustment of endometrial thickness values by multivariable modeling.

Conclusions Although endometrial thickness following successful expulsion of the gestational sac is thicker in women who will eventually require surgical intervention after medical abortion, endometrial thickness is not a clinically useful predictor of the subsequent need for D&C. Copyright © 2009 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Medical abortion with mifepristone and misoprostol is highly effective but complete abortion rates vary significantly by regimen. Approximately 3–5% of women will subsequently undergo dilatation and curettage (D&C) with a regimen of mifepristone and vaginal misoprostol^{1–3}. In approximately 2–3% of women, D&C procedures are performed after expulsion of the pregnancy due to pain or bleeding^{1–3}.

Ultrasonography is commonly used to evaluate the success of medical abortion. The primary purpose is to confirm that the gestational sac has been expelled. The endometrial thickness is also commonly measured to quantify the amount of tissue and debris remaining within the uterus after expulsion of the pregnancy. A variety of endometrial thickness values have been proposed as thresholds to indicate the need for surgical intervention after medical abortion, spontaneous abortion, and vaginal delivery^{4–6}. An endometrial thickness of less than 15 mm has been used to define a completely evacuated uterus after spontaneous abortion and after medical abortion^{7,8}. In a large prospective study, however, endometrial thickness

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was not found to be a useful predictor of the subsequent need for D&C following medical management of early pregnancy failure⁹.

Studies on the utility of endometrial thickness after medical abortion have produced conflicting results^{10,11}. One retrospective study suggests that endometrial thickness is not a useful clinical predictor of subsequent D&C after medical abortion using mifepristone and misoprostol¹⁰. Another retrospective study found that endometrial thickness was greater in women ultimately needing D&C⁶. However, it is unclear if clinical management in this study was influenced by the sonographic findings. Two prospective studies found that human chorionic gonadotropin assays performed better than endometrial thickness in predicting the success of medical abortion^{12,13}. Several studies of ultrasonography after medical abortion have reported descriptive results^{8,14}. However, the ability of these qualitative descriptions to predict subsequent D&C is difficult to assess. A quantitative measure such as endometrial thickness allows assessment of its predictive ability.

Prospectively collected data regarding the clinical utility of endometrial thickness in predicting the need for subsequent D&C in women having elective medical abortion with mifepristone and misoprostol is lacking. We sought to evaluate the predictive value of endometrial thickness for subsequent D&C after elective abortion with mifepristone and misoprostol.

METHODS

This study was a pooled secondary analysis of data from two multicenter randomized trials of medical abortion. Owing to the low incidence of surgical intervention after medical abortion, the studies were combined to obtain an adequate sample. In the first study 1080 women were enrolled at the University of Pittsburgh, Columbia University, Boston University, and the University of Rochester. They received an oral dose of 200 mg of mifepristone, after which they were randomly assigned to use 800 µg misoprostol vaginally 6 to 8 hours or 23 to 25 hours later¹. In the second study 1128 women were enrolled at the University of Pittsburgh, Oregon Health and Science University, and Northwestern University. They received 200 mg oral mifepristone, after which they were randomized to self-administer 800 µg misoprostol vaginally within the next 15 min or 24 h later². Population demographics and treatment outcomes have been previously described^{1,2}. Both studies were approved by the Institutional Review Boards of each participating institution. 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 sonographic examination approximately 7 days after taking mifepristone. A trained, experienced physician or advanced-care clinician performed the sonographic examination, and

images from all examinations were reviewed by a physician investigator. Endometrial thickness was assessed by transvaginal ultrasound examination if the gestational sac was absent. In both studies, endometrial thickness was defined as the maximal dimension of the endometrial cavity in the anteroposterior plane of the uterus, including all contents of the endometrial cavity¹⁵. Doppler imaging was not used in assessing the endometrium. In both protocols, endometrial thickness was collected only for research purposes and was not used for determination of success or failure. Serum human chorionic gonadotropin levels were not assessed in either study.

For this analysis, we excluded women who had a gestational sac identified on the day of the sonographic examination and women who underwent a D&C before sonography. We also excluded women if the interval between treatment and the sonogram was less than 5 days or more than 11 days.

The outcome for this analysis was D&C. The decision for D&C was based solely on clinical indications. D&C was performed by vacuum aspiration if clinically necessary, because of subject request, or for symptoms consistent with incomplete abortion such as prolonged or heavy bleeding and/or cramping. All subjects were contacted by telephone 5 weeks after initiating the study to see if there had been any problems since the abortion.

We examined the predictive value of endometrial thickness for the need for subsequent D&C, using both Student's *t*-test and the Mann–Whitney *U*-test. We constructed a receiver–operating characteristics (ROC) curve for the utility of endometrial thickness in predicting the need for subsequent D&C. We then fitted a maximum-likelihood ROC model using a binormal distribution¹⁶. Additionally, endometrial thickness was dichotomized using threshold values at each 5-mm increment from 10 to 30 mm. We calculated the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for each endometrial thickness threshold value as a predictor of subsequent D&C¹⁷.

We adjusted endometrial thickness values for study site, randomization group (time between mifepristone and misoprostol) and the time interval between administration of misoprostol and the ultrasound examination at which endometrial thickness was assessed. The adjustment was performed using multivariable linear regression analysis with categorical independent variables. We then repeated the analyses described above using the adjusted endometrial thickness values. All statistical analyses were performed using Stata 9 (StataCorp, College Station, TX, USA).

RESULTS

Of the 2208 women enrolled in the two studies, 1870 (84.7%) were eligible for inclusion. The exclusion criteria are summarized in Table 1, and demographic characteristics of the included subjects are summarized in Table 2. Thirty (1.6% (95% CI, 1.1–2.2%)) of the

Table 1 Summary of analysis population, excluded patients and indications for dilatation and curettage (D&C) according to study

Parameter	MOD study ¹ (n = 1080)	MAST study ² (n = 1128)	Pooled (n = 2208)
Number included in analysis	903 (83.6)	967 (85.7)	1870 (84.7)
Reason for exclusion			
Gestational sac present	16 (1.5)	66 (5.9)	82 (3.7)
D&C before ultrasound scan	7 (0.6)	5 (0.4)	12 (0.5)
Outside day range*	125 (11.6)	75 (6.6)	200 (9.1)
Other†	29 (2.7)	15 (1.3)	44 (2.0)
D&C after sonogram‡	13 (1.4)	17 (1.8)	30 (1.6)
Indication for D&C‡			
Incomplete abortion	10 (1.1)	13 (1.3)	23 (1.2)
Subject's preference	3 (0.3)	3 (0.3)	6 (0.3)
Gestational sac identified at follow-up ultrasound scan	0 (0)	1 (0.1)	1 (0.05)

Data are given as *n* (%). *The day range is the time between misoprostol administration and the ultrasound examination. Interval between mifepristone and sonogram < 5 or > 11 days was excluded. †Lost to follow-up or missing data. ‡Percentages calculated as proportion of women included in the analysis. MOD, Medical abortion in One Day; MAST, Medical Abortion at the Same Time.

Table 2 Demographic characteristics of included subjects

Parameter	MOD study ¹ (n = 903)	MAST study ² (n = 967)	Pooled (n = 1870)
Age (years, mean ± SD)	25.3 ± 5.7	26.0 ± 5.7	25.7 ± 5.7
Gestational age estimate			
5 weeks or less	146 (16.2)	150 (15.5)	296 (15.8)
6 weeks	262 (29.0)	224 (23.2)	486 (26.0)
7 weeks	272 (30.1)	322 (33.3)	594 (31.8)
8–9 weeks	223 (24.7)	271 (28.0)	494 (26.4)
Race/ethnicity			
White	343 (38.0)	530 (54.8)	873 (46.7)
Hispanic	250 (27.7)	105 (10.9)	355 (19.0)
African-American	264 (29.2)	279 (28.9)	543 (29.0)
Other	46 (5.1)	53 (5.5)	99 (5.3)
Prior deliveries			
0	330 (36.5)	420 (43.4)	750 (40.1)
1	260 (28.8)	249 (25.7)	509 (27.2)
2	198 (21.9)	186 (19.2)	384 (20.5)
3 or more	115 (12.7)	112 (11.6)	227 (12.1)
Prior elective abortion			
0	458 (50.7)	564 (58.3)	1022 (54.7)
1	262 (29.0)	260 (26.9)	522 (27.9)
2 or more	183 (20.3)	143 (14.8)	326 (17.4)

Data are expressed as *n* (%) except for age. MOD, Medical abortion in One Day; MAST, Medical Abortion at the Same Time.

1870 women subsequently underwent D&C after the initial ultrasound examination confirmed expulsion of the gestational sac. The median time between mifepristone administration and the D&C was 24 days, with a range of 6 to 67 days. The mean endometrial thickness was 14.5 mm for women who required a D&C and 10.9 mm for those who did not (difference 3.5 mm (95% CI, 1.8–5.3 mm)). The distribution of endometrial thickness values is summarized in Figure 1a. The area under the ROC curve for endometrial thickness as a test to predict the need for subsequent D&C is 0.65 (95% CI, 0.54–0.76) (Figure 1b). The test characteristics of endometrial thickness threshold values at 5-mm intervals from 10 to 30 mm are shown in Table 3. All endometrial thickness thresholds had a PPV of

25% or less, and the balanced accuracy (equivalent to the area under the ROC curve for a dichotomous threshold; (sensitivity + specificity)/2) was below 0.6 for all thresholds.

Endometrial thickness was found to differ slightly by study site, randomization group, and time interval between administration of misoprostol and assessment of endometrial thickness. The mean endometrial thickness varied by up to 4 mm by site and by less than 1 mm by randomization group. The mean endometrial thickness varied by less than 3 mm by time interval, and did not show a trend toward increasing or decreasing over the range 5 to 11 days between administration of misoprostol and assessment of endometrial thickness. Endometrial thickness values were adjusted for these factors. Using

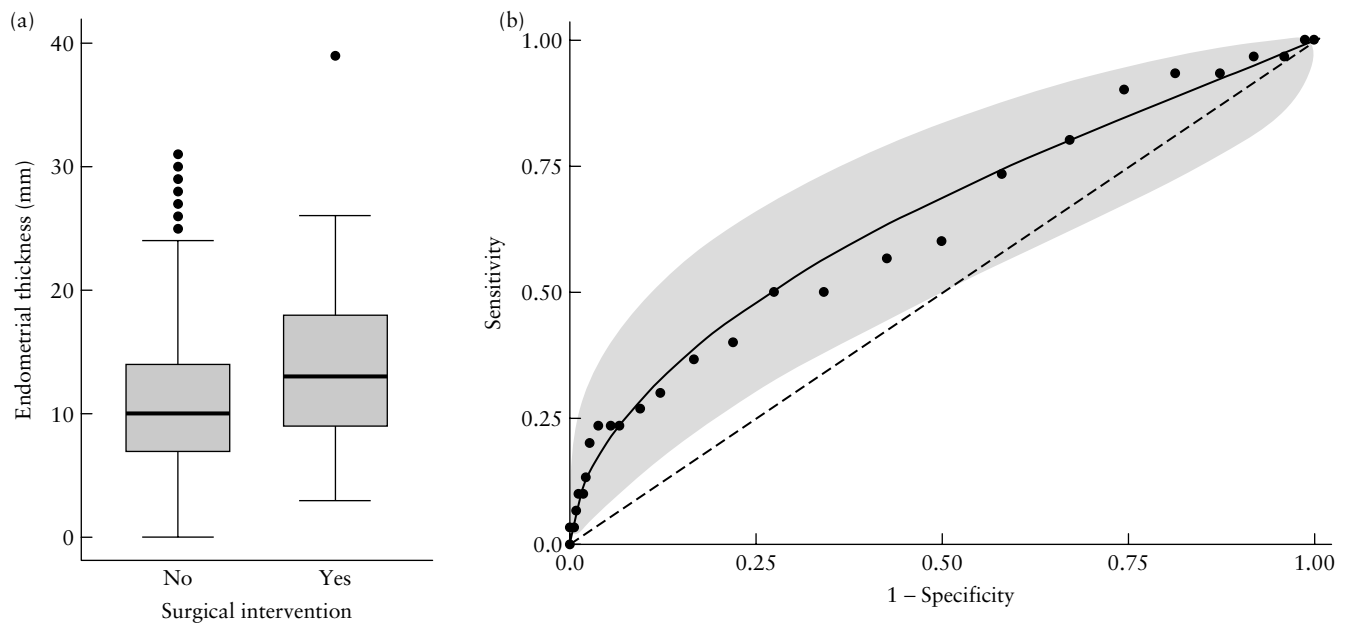


Figure 1 Endometrial thickness at approximately 7 days following medical abortion. (a) Box plot of the distribution of endometrial thickness for women at 5–11 days after misoprostol who did and did not subsequently have surgical intervention (dilatation and curettage (D&C)). The lower and upper limits of the boxes show the 25th and 75th percentiles, respectively, and the lines within the boxes show the medians. The whiskers show the range of values, with the points outside of the whiskers showing values more than 1.5 times the interquartile range. (b) Receiver–operating characteristics (ROC) curve of endometrial thickness as a predictor of subsequent D&C, generated using the data shown in (a). The region in gray defines the 95% CI around the fitted ROC curve (—) and ● represents observed points. The x-axis (1 – Specificity) represents the false-positive rate.

Table 3 Test characteristics of dichotomous thresholds of endometrial thickness (EMT), assessed approximately 7 days after medical abortion, in the prediction of subsequent dilatation and curettage (D&C)

EMT threshold (mm)	D&C performed (n)		Sensitivity (% (95% CI))	Specificity (% (95% CI))	PPV (% (95% CI))	NPV (% (95% CI))	Balanced accuracy (95% CI)
	Yes	No					
≥ 10	22	1066	73.3 (54.1–87.7)	42.1 (39.8–44.4)	2.0 (1.3–3.1)	99.0 (98.0–100)	0.58 (0.50–0.66)
< 10	8	774					
≥ 15	12	402	40.0 (22.7–59.4)	78.2 (76.2–80.0)	2.9 (1.5–5.0)	98.8 (98.1–99.3)	0.59 (0.50–0.68)
< 15	18	1438					
≥ 20	7	98	23.3 (9.9–42.3)	94.7 (93.5–95.7)	6.7 (2.7–13.3)	98.7 (98.1–99.2)	0.59 (0.51–0.67)
< 20	23	1742					
≥ 25	3	23	10.0 (2.1–26.5)	98.8 (98.1–99.2)	11.5 (2.5–30.2)	98.5 (97.9–99.0)	0.54 (0.49–0.60)
< 25	27	1817					
≥ 30	1	3	3.3 (0.1–17.2)	99.8 (99.5–100)	25.0 (0.63–80.6)	98.4 (97.8–99.0)	0.52 (0.48–0.55)
< 30	29	1837					

EMT was assessed 5–11 days after (n) medical abortion. The balanced accuracy is the same as the area under the receiver–operating characteristics curve for a dichotomous threshold and is equal to ((sensitivity + specificity)/2). NPV, negative predictive value; PPV, positive predictive value.

the adjusted endometrial thickness values, the area under the ROC curve was 0.65 (95% CI, 0.55–0.76). The area under the ROC curve using the adjusted endometrial thickness did not differ from that for the unadjusted endometrial thickness ($P > 0.2$).

Four women received a second dose of misoprostol after the ultrasound examination on study day 7 had shown absence of the gestational sac. The endometrial thickness

values for these subjects were 11, 15, 17 and 21 mm. Nine days later, one subject (endometrial thickness = 21 mm) subsequently required D&C. We performed a sensitivity analysis to assess the potential impact on the primary analysis results: all women who received a second dose of misoprostol were assumed to have needed a D&C. The results were unchanged, with an area under the ROC curve of 0.65.

One subject was erroneously diagnosed with complete expulsion at her initial ultrasound examination 7 days after treatment, at which time her endometrial thickness was 11 mm. A subsequent ultrasound scan demonstrated the presence of a gestational sac and she underwent D&C.

DISCUSSION

Ultrasonography is commonly performed after medical abortion to confirm expulsion of the gestational sac. As part of the sonographic assessment, endometrial thickness is also often measured and has been described as a tool to guide decision-making regarding the need for surgical intervention^{6,8}. Although we found endometrial thickness to be greater in women who subsequently required D&C, our data show that endometrial thickness is not a clinically useful test for predicting this unwanted outcome. Regardless of the endometrial thickness threshold used, the PPV did not exceed 25%. Additionally, the sensitivity and specificity values obtained confirm that endometrial thickness is a poor test for predicting the subsequent need for D&C.

ROC curves are a useful tool for quantitatively summarizing the usefulness of a test with a continuous result such as endometrial thickness, for a specific outcome¹⁸. The ROC curve compares the sensitivity to the false positive rate (1 – specificity) over all possible threshold values. A perfect test would have an area under the ROC curve of 1.0 while a test equivalent to random chance would have an area of 0.5. The average area under the ROC curve for endometrial thickness as a predictor of future D&C in our study was 0.65. Although endometrial thickness is slightly better than chance at predicting the need for D&C, it poorly discriminates between those women who will and will not require D&C. Importantly, endometrial thickness remains a poor predictor of subsequent surgical intervention, even with high threshold values.

The findings presented here corroborate the results of previous studies showing that endometrial thickness is not clinically useful for predicting the need for D&C after medical abortion^{10,12,13}. Using ultrasound criteria to define a successful outcome results in a lower overall success¹². Not surprisingly, medical abortion studies that use ultrasound criteria to define failure have higher failure rates¹⁹. The endometrial thickness results were known to the study staff, but they were not used to guide care. It seems most likely that knowledge of endometrial thickness results would bias towards more interventions with increased endometrial thickness. Owing to this ascertainment bias, it is conceivable that the estimated area under the ROC curve is greater than the true value. Thus the true area under the ROC curve may be closer to 0.5 than estimated by our results.

As might be expected with 1870 cases, a few unusual occurrences were identified. Most notably, one subject was erroneously diagnosed with complete expulsion at her initial ultrasound scan. She underwent D&C after a subsequent scan demonstrated a gestational sac. The

data for this woman were included in this analysis since future events were unknown at the time of the initial evaluation. This case shows that sonography soon after medical abortion can falsely confirm expulsion of the gestational sac, albeit rarely. Four women received misoprostol after the initial ultrasound examination confirmed expulsion of the gestational sac. Unfortunately, the rationale for giving the second dose is unclear. The sensitivity analysis shows that even if all four women would have required a D&C if not for the misoprostol, the results would not be altered.

Many studies of medical abortion, both with and without use of ultrasonography, do not follow women routinely for more than 2 weeks. Most studies have passive follow-up for situations in which a woman would later present with incomplete abortion, hoping she would contact the researchers for treatment or inform them of treatment received elsewhere. The two studies pooled for this analysis present the data on women who were contacted through the prolonged follow-up period. Our finding that only 1.6% of women underwent D&C following the sonographic diagnosis of sac expulsion demonstrates the high predictive value of sonography as a follow-up tool at 1 week following medical abortion treatment. Consequently, we believe that ultrasonography is a clinically useful means of confirming expulsion of the gestational sac. However, endometrial thickness is not a useful predictor of the need for surgical intervention once expulsion of the gestational sac has been confirmed. Therefore, in the management of medical abortion, clinical presentation and not endometrial thickness should be used to determine the need for D&C.

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Conflict of Interest: Dr Creinin receives compensation from Danco Laboratories, LLC, the distributor of mifepristone in the United States, for providing third-party telephone consults to clinicians who call for expert advice on mifepristone. The other authors do not have any conflicts of interest.

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