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A Comparison of Medical Management with Misoprostol and Surgical Management for Early Pregnancy Failure

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and Human Development (NICHD) Management of Early Pregnancy Failure Trial*

ABSTRACT

BACKGROUND

Misoprostol is increasingly used to treat women who have a failed pregnancy in the first trimester. We assessed the efficacy, safety, and acceptability of this treatment in a large, randomized trial.

METHODS

A total of 652 women with a first-trimester pregnancy failure (anembryonic gestation, embryonic or fetal death, or incomplete or inevitable spontaneous abortion) were randomly assigned to receive 800 μ g of misoprostol vaginally or to undergo vacuum aspiration (standard of care) in a 3:1 ratio. The misoprostol group received treatment on day 1, a second dose on day 3 if expulsion was incomplete, and vacuum aspiration on day 8 if expulsion was still incomplete. Surgical treatment (for the misoprostol group) or repeated aspiration (for the vacuum-aspiration group) within 30 days after the initial treatment constituted treatment failure.

RESULTS

Of the 491 women assigned to receive misoprostol, 71 percent had complete expulsion by day 3 and 84 percent by day 8 (95 percent confidence interval, 81 to 87 percent). Treatment failed in 16 percent of the misoprostol group and 3 percent of the surgical group (absolute difference, 12 percent; 95 percent confidence interval, 9 to 16 percent) by day 30. Hemorrhage or endometritis requiring hospitalization was rare (1 percent or less in each group), with no significant differences between the groups. In the misoprostol group, 78 percent of the women stated that they would use misoprostol again if the need arose and 83 percent stated that they would recommend it to others.

CONCLUSIONS

Treatment of early pregnancy failure with 800 μ g of misoprostol vaginally is a safe and acceptable approach, with a success rate of approximately 84 percent.

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*Participants in the NICHD Management of Early Pregnancy Failure Trial are listed in the Appendix.

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EARLY PREGNANCY FAILURE OCCURS IN 15 percent of clinically recognized pregnancies.¹ The most common types of early pregnancy failure include spontaneous abortion, anembryonic gestation, and embryonic or fetal death. Approximately one in four women will have an early pregnancy failure during her lifetime.¹ For most of the 20th century, dilatation and curettage was the commonly accepted approach to early pregnancy failure. This practice can be traced back to the late 19th and early 20th centuries, when illegally induced abortions commonly resulted in hemorrhage and sepsis.² With the legalization of abortion and the availability of antibiotics, these problems have become rare. In more recent years, the medical community began to question whether immediate evacuation by surgical intervention was necessary for uncomplicated cases of early pregnancy failure.^{3,4}

Expectant management is clearly an option for incomplete spontaneous abortion, but the success rate with the use of this approach for embryonic or fetal death or anembryonic gestation is suboptimal (ranging from 25 to 76 percent).^{5,6} The interval to spontaneous expulsion is unpredictable, and it may take a month. The uncertainty and anxiety, along with the sadness resulting from pregnancy loss, often make expectant management less appealing to patients.

Medical management with misoprostol for early pregnancy failure appears to offer more prompt evacuation of the uterus and has become an increasingly popular alternative.⁷ However, the efficacy, safety, and acceptability of this approach have yet to be established in a large, randomized trial. We conducted a multicenter randomized trial comparing misoprostol treatment with vacuum aspiration, the current standard of care, for early pregnancy failure.

METHODS

This randomized trial was approved by 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. Patients who sought medical care for possible early pregnancy failure at the four university settings from March 2002 to March 2004 were screened. Women who had an anembryonic gestation or embryonic or fetal death were eligible for inclusion if they had

an ultrasound examination demonstrating an embryonic pole or crown-rump length between 5 and 40 mm without cardiac activity,⁸ an anembryonic gestational sac with a mean diameter between 16 and 45 mm,⁹ growth of the gestational sac by less than 2 mm over a five-day period or less than 3 mm over a seven-day period,¹⁰ or an increase in human chorionic gonadotropin levels of less than 15 percent over a two-day period, with a yolk sac visualized by ultrasound examination. Women who had an incomplete or inevitable abortion were also included. Incomplete spontaneous abortion was defined as the passage of some products of conception, with the residual anteroposterior endometrial lining exceeding 30 mm on transvaginal ultrasonography and a uterine size indicating less than 13 weeks of gestation. This cut-off was based on evidence from prior studies of women treated with misoprostol for medical abortion¹¹ or early pregnancy failure.¹² Inevitable abortion was defined as an intrauterine gestational sac of less than 45 mm or embryonic pole of less than 40 mm and an internal cervical os that was open to digital examination with active vaginal bleeding. Women were excluded if they had anemia (hemoglobin level below 9.5 g per deciliter), had hemodynamic instability, had a history of a clotting disorder or were using anticoagulants (not including aspirin), were allergic to prostaglandins or nonsteroidal antiinflammatory drugs, or had previously undergone a surgical or medical abortion that was either self-induced or induced by other physicians during the current pregnancy. All subjects provided written informed consent.

At enrollment, the medical history, hemoglobin level, and Rh-antigen status were assessed and a physical examination was performed. Using a centralized, computer-automated telephone response system, we randomly assigned eligible subjects to either medical or surgical management in a 3:1 ratio (i.e., approximately 75 percent of the subjects were assigned to receive medical management and 25 percent to receive surgical treatment). Randomization was stratified according to the study site and the type of pregnancy failure (anembryonic gestation or fetal death vs. incomplete or inevitable spontaneous abortion) and used randomly permuted blocks. The day of randomization was considered study day 1.

Surgical management typically consisted of manual vacuum aspiration in an outpatient setting at Columbia University and the University of Pittsburgh and electric vacuum aspiration in an operating room at the University of Miami and the

University of Pennsylvania. The aspiration was performed by a study investigator or by a resident physician who was supervised by an investigator. All women were contacted by telephone on day 8 to inquire about any symptoms, medications, or emergency visits to the hospital after the treatment. Women returned for a follow-up visit on day 15 (range, day 13 to day 18).

Although randomized trials have not identified the optimal dose of misoprostol, 800 μg given vaginally was the most commonly tested regimen.⁷ Thus, for the women assigned to medical treatment in our study, four 200- μg tablets (800 μg) of misoprostol (Cytotec, Searle) were inserted into the posterior fornix through a speculum. These women returned on day 3 (range, day 2 to day 5). If expulsion of the products of conception was not complete (that is, a gestational sac was still visualized or the endometrial lining was greater than 30 mm on transvaginal ultrasonography), a second 800- μg dose of misoprostol was administered vaginally. On day 8 (range, day 6 to day 10), if the expulsion of products of conception was still not complete, vacuum aspiration was offered. The women returned for a follow-up visit on day 15.

The women were given 30 tablets of ibuprofen (200 mg) and 20 tablets of codeine (30 mg) for pain and were instructed to use ibuprofen primarily and the narcotic as needed. They also received a structured diary in which to record side effects, medications, and emergency calls or visits to the hospital, and they were instructed to take their temperature daily for two weeks. Pain intensity was recorded on a 10-cm visual-analogue scale, with higher numbers indicating greater pain.¹³ At each follow-up visit, transvaginal ultrasonography was performed, and the clinical investigator performed a physical examination, conducted an interview, and collected the diary pages. In addition, at the day 15 visit, hemoglobin was measured and each woman completed a questionnaire assessing the acceptability of the treatment and the quality of life. A telephone interview was conducted on day 30 (range, day 25 to day 35) to determine whether any woman underwent additional treatment. Women with symptoms potentially related to the study treatment were followed until the symptoms resolved.

STATISTICAL ANALYSIS

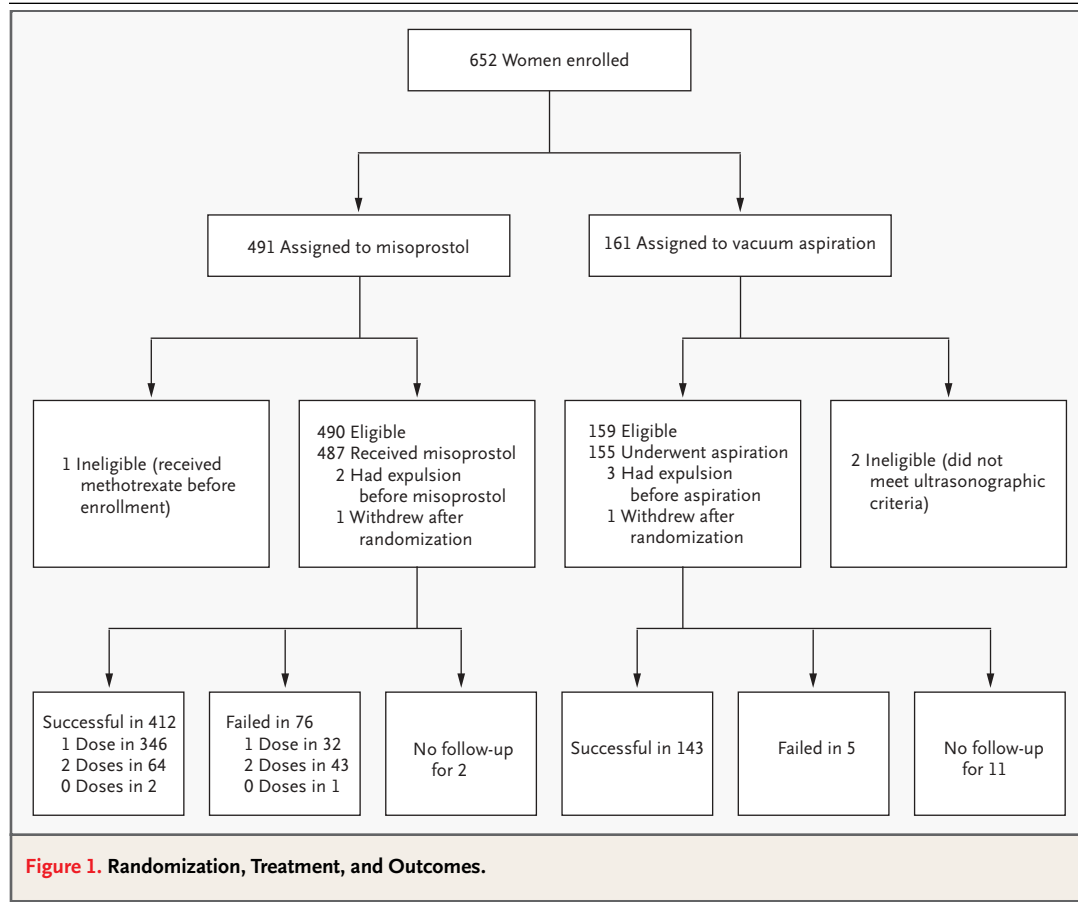
Recognizing that the success rate of medical treatment was unlikely to exceed that of surgical treatment for early pregnancy failure,⁷ we designed the

study as a noninferiority trial. Success was defined a priori as complete uterine evacuation without the need for vacuum aspiration in the medical-management group or a repeated aspiration in the surgical-management group within 30 days after initial treatment. On the basis of clinical judgment, we decided that, for medical treatment to be considered a reasonable alternative to surgery, it should be successful in at least 80 percent of the women; since prior data suggested a success rate of 98 percent for surgical intervention,¹⁴ we selected an absolute difference of 18 percent as the maximal acceptable difference between the two treatment groups to indicate noninferiority. We used a one-sided test of equivalence with a significance level of 0.05. A total of 620 subjects were needed for the study to achieve a statistical power of 80 percent.¹⁵

We first compared the baseline characteristics and the success rate according to clinical site in the two groups, using the chi-square test (or Fisher's exact test) and Student's t-test for categorical and continuous variables, respectively. All these analyses were done with the use of SAS software. In addition, we calculated 95 percent confidence intervals for differences in success rates with the use of StatXact software.¹⁶ According to the protocol, the data and safety monitoring committee conducted one interim analysis after half the subjects had been recruited. No early termination occurred.

RESULTS

A total of 652 women were enrolled: 491 were randomly assigned to receive misoprostol, and 161 to undergo vacuum aspiration (Fig. 1). Overall, embryonic or fetal death was diagnosed in 58 percent of the women, an anembryonic gestation was diagnosed in 36 percent, and an incomplete or inevitable abortion was diagnosed in 6 percent. The average gestational age was 7.6 weeks. There were no significant differences in demographic characteristics at enrollment between the two groups (Table 1). Almost all the women who were assigned to medical management received misoprostol immediately after randomization. In contrast, 63 percent of the women who were assigned to surgical management received the treatment on the day of randomization, 28 percent did so one day after randomization, and 9 percent did so two or more days after randomization, owing to the need to wait for an operating room. Surgical treatment was manual vacuum aspiration in 57 percent of the women and electric aspi-



ration in 43 percent. The efficacy of these treatments did not vary significantly among the four clinical centers (Table 2).

The success rates of the treatments are presented in Table 3. Of the women who completed the trial according to the protocol, 84 percent (95 percent confidence interval, 81 to 87 percent) were successfully treated with misoprostol and 97 percent (95 percent confidence interval, 94 to 100 percent) were successfully treated with vacuum aspiration. The absolute difference in success rates between the two treatments was 12 percentage points (95 percent confidence interval, 9 to 16 percent).

To assess the potential effect of losses to follow-up, we performed secondary analyses assessing success rates on the basis of various assumptions. Assuming that women who did not return for follow-up had all been successfully treated yielded an absolute difference in success rates between treatments of 12 percentage points. Assuming that treatment had failed in all women who did not complete follow-up resulted in an absolute difference be-

tween groups of 6 percentage points. Our study defined success a priori as the absence of the need for vacuum aspiration for any reason within 30 days after the initial treatment with misoprostol. Four women (all from the misoprostol group), however, underwent vacuum aspiration after day 30 for heavy bleeding or persistent bleeding.

In the misoprostol group, the expulsion of products of conception was complete after one dose in 71 percent of the women (346 of 490). Among those who received a second dose, this approach was successful by day 8 in 60 percent (64 of 107), for an overall success rate of 84 percent by day 8. The success rate varied among the subtypes of early pregnancy failure; women with an anembryonic gestation had a lower rate of success by day 8 than did the other groups combined (P=0.02). There was no significant relationship in either treatment group between the gestational age at the time of the treatment and the success rate (P=0.67 for the misoprostol group and P=0.30 for the surgical group) (Table 3).

Table 1. Characteristics of the Study Population at Enrollment.*

Characteristic	Misoprostol (N=491)	Vacuum Aspiration (N=161)
Age — yr	29.8±7.2	30.9±7.3
Race or ethnic group — no. (%)†		
Non-Hispanic white	114 (23)	32 (20)
Non-Hispanic black	149 (30)	48 (30)
Hispanic	202 (41)	69 (43)
Asian or other	26 (5)	12 (7)
Education — no. (%)		
Less than high-school graduate	116 (24)	33 (20)
High-school graduate	143 (29)	43 (27)
Attended college	232 (47)	85 (53)
No. of previous pregnancies — no. (%)		
0	116 (24)	31 (19)
1	128 (26)	49 (30)
≥2	247 (50)	81 (50)
Planned pregnancy — no. (%)	165 (34)	56 (35)
Best estimate of gestational age — wk	7.6±1.5	7.6±1.4
Low abdominal pain in previous 24 hr — no. (%)	298 (61)	86 (53)
Vaginal bleeding in previous 24 hr — no. (%)	318 (65)	101 (63)
Type of pregnancy failure — no. (%)		
Embryonic or fetal death	282 (57)	96 (60)
Anembryonic gestation	179 (36)	56 (35)
Incomplete spontaneous abortion	19 (4)	3 (2)
Inevitable abortion	11 (2)	6 (4)
Hemoglobin — g/dl	12.8±1.0	12.8±1.0

* Plus-minus values are means ±SD. There were no significant differences between groups.

† Race or ethnic group was self-reported.

Hemorrhage and pelvic infection were rare after either treatment (1 percent or less); the rates of these complications did not differ significantly between groups (Table 4). The incidence of fever (temperature, 38.0°C [100.4°F] or greater) was also similar in the two groups. Among 13 women in the misoprostol group who had fever, 2 visited the hospital and 1 received antibiotic therapy. Among six women in the surgical group who had fever, three visited the hospital and two received antibiotic therapy. No maternal sepsis occurred. The frequency of emergency visits to the hospital during the first 24 hours after treatment was similar in the medical and surgical groups (3 percent and 2 percent, respectively; $P=0.59$).

The percentage of women who made unscheduled visits to the hospital was slightly but not significantly higher in the misoprostol group than in the vacuum-aspiration group (23 percent vs. 17 per-

cent, $P=0.09$). A decrease in hemoglobin of at least 3 g per deciliter occurred more frequently in the misoprostol group than in the vacuum-aspiration group (5 percent vs. 1 percent, $P=0.04$). Women who received misoprostol were also more likely to report nausea, vomiting, abdominal pain, and more severe pain. Nonetheless, 83 percent of women stated that they would probably or absolutely recommend misoprostol treatment to their family and friends, and 78 percent stated that they would probably or absolutely use it again should similar circumstances occur in the future. The acceptability of treatment did not differ significantly between groups. Furthermore, among 190 women who had undergone vacuum aspiration in previous pregnancies but who received misoprostol during the current pregnancy, 80 percent stated that they would recommend misoprostol treatment and 73 percent stated that they would use misoprostol again if needed.

Table 2. Results According to Clinical Site.

Site	Misoprostol					Vacuum Aspiration				
	No. of Women*	Success (N=412)	Failure (N=76)	No Follow-up (N=2)	P Value†	No. of Women‡	Success (N=143)	Failure (N=5)	No Follow-up (N=11)	P Value†
	<i>no. of women (%)</i>					<i>no. of women (%)</i>				
Columbia University	101	82 (81)	17 (17)	2 (2)	0.17	33	29 (88)	1 (3)	3 (9)	0.79
University of Miami	166	143 (86)	23 (14)	0		53	49 (92)	2 (4)	2 (4)	
University of Pennsylvania	113	97 (86)	16 (14)	0		37	34 (92)	0	3 (8)	
University of Pittsburgh	110	90 (82)	20 (18)	0		36	31 (86)	2 (6)	3 (8)	

* One patient was ineligible.

† P values are for the comparison among the four groups.

‡ Two patients were ineligible.

Table 3. Efficacy of the Treatments.

Variable	Misoprostol	Vacuum Aspiration	Absolute Difference
	% (no./total no.)		%
Success by day 30			
Data on women lost to follow-up treated as missing	84 (412/488)	97 (143/148)	12
Outcome among women lost to follow-up considered a success	84 (414/490)	97 (154/159)	12
Outcome among women lost to follow-up considered a failure	84 (412/490)	90 (143/159)	6
Success after 0 or 1 dose of misoprostol by day 30	71 (348/488)	—	
Success by day 3	71 (347/490)	—	
Success by day 8	84 (414/490)	—	
Success by day 15	85 (417/490)	90 (143/159)	5
Embryonic or fetal death	88 (244/278)	—	
Anembryonic gestation	81 (142/176)	—	
Incomplete or inevitable abortion	93 (28/30)	—	
Success rate according to timing of treatment			
5 Wk of gestation	67 (6/9)	100 (2/2)	
6 Wk of gestation	82 (93/114)	91 (31/34)	
7 Wk of gestation	84 (115/137)	100 (41/41)	
8 Wk of gestation	85 (90/106)	100 (36/36)	
9 Wk of gestation	88 (67/76)	91 (20/22)	
10 Wk of gestation	88 (21/24)	100 (8/8)	
11 Wk of gestation	94 (15/16)	100 (1/1)	
12 Wk of gestation	83 (5/6)	100 (3/3)	

DISCUSSION

Our study indicates that treatment of early pregnancy failure with 800 µg of misoprostol vaginally, with the dose repeated after 48 hours when necessary, is efficacious. The success rate by day 30 was 84 percent (95 percent confidence interval, 81 to 87 per-

cent). The risks of hemorrhage and pelvic infection were very low, and the side effects were tolerable. Misoprostol treatment was acceptable to most women.

The efficacy of misoprostol treatment for early pregnancy failure has varied greatly (ranging from 13 to 100 percent) in previous retrospective and

Table 4. Adverse Events and Acceptability of Medical and Surgical Treatment of Early Pregnancy Failure.*

Variable	Misoprostol	Vacuum Aspiration	P Value†
Adverse event			
Hemorrhage requiring hospitalization with or without blood transfusion — % (no./total no.)	1 (5/488)	1 (1/148)	1.0
Hospitalization for endometritis — % (no./total no.)	<1 (2/488)	0 (0/148)	1.0
Fever (temperature $\geq 38.0^{\circ}\text{C}$ [100.4°F]) — % (no./total no.)	3 (13/477)	4 (6/148)	0.41
Emergency visit to hospital within 24 hr after treatment — % (no./total no.)	3 (15/488)	2 (3/148)	0.59
Unscheduled hospital visits — % (no. of visits/total no. of patients)‡	23 (114/488)	17 (25/148)	0.09
Change in hemoglobin between day 1 and day 15 — g/dl§	-0.65 ± 1.10	-0.18 ± 0.89	<0.001
Decrease in hemoglobin ≥ 2 g/dl — % (no./total no.)§	9 (38/421)	4 (5/134)	0.05
Decrease in hemoglobin ≥ 3 g/dl — % (no./total no.)§	5 (19/421)	1 (1/134)	0.04
Nausea — % (no./total no.)¶	53 (250/472)	29 (41/141)	<0.001
Vomiting — % (no./total no.)¶	20 (96/475)	7 (10/142)	<0.001
Diarrhea — % (no./total no.)¶	24 (113/473)	10 (14/142)	<0.001
Abdominal pain — % (no./total no.)¶	99 (473/476)	95 (134/141)	<0.001
Pain-severity score¶	5.7 ± 2.4	3.2 ± 2.4	<0.001
Acceptability — % (no./total no.)			
Would probably or absolutely recommend this procedure	83 (379/456)	83 (125/150)	0.95
Would probably or absolutely use this treatment again	78 (357/456)	75 (112/150)	0.36

* Plus-minus values are means \pm SD.

† The chi-square test (or Fisher's exact test) was used for categorical variables, and Student's t-test was used for continuous variables.

‡ A woman could have had multiple unscheduled visits.

§ Hemoglobin analyses included four women who received a blood transfusion. Values were available for 421 women in the misoprostol group and 134 women in the vacuum-aspiration group.

¶ This symptom was reported in a woman's diary within 48 hours after the treatment.

|| A 10-cm visual-analogue scale was used to record the severity of pain. Scores could range from 0 (no pain) to 10 (worst pain ever). Scores were available for 476 women in the misoprostol group and 141 women in the vacuum-aspiration group.

prospective studies.⁷ This variation may be attributable to small sample sizes, the type of pregnancy failure (anembryonic gestation and embryonic or fetal death vs. incomplete abortion), the dose of misoprostol, and the criteria used to define success.

Studies of misoprostol to date have used a single dose (ranging from 400 to 800 μg), two or three consecutive doses given 2 to 4 hours apart (with a total dose of 600 to 1800 μg within 24 hours), or an initial dose (ranging from 400 to 800 μg) that could be repeated 24 to 48 hours later if needed.⁷ We found that an 800- μg dose of misoprostol administered vaginally was sufficient in the majority of women, with side effects that were tolerable to most women. We also found that women with an incomplete or inevitable spontaneous abortion were more likely to have complete expulsion after one dose of misoprostol than were women with embryonic or fetal death or women with an anembryonic gesta-

tion. However, by using a second dose if expulsion is incomplete, a similarly high success rate can be achieved in the latter group of women. We waited 48 hours between doses in an attempt to allow sufficient time for the initial dose to be effective while acknowledging the desire for prompt uterine evacuation; the majority of the women in our study reported satisfaction with this approach.

Some previous studies have used an endometrial thickness of 15 mm as assessed by transvaginal ultrasonography as a cut-off for success.¹⁷ However, increasing evidence from women who have had a spontaneous abortion¹⁸ or a medical abortion^{11,12} or received medical treatment for early pregnancy failure¹⁹ suggested that such a cut-off may be too stringent. In our study, almost all women with an endometrial thickness of greater than 15 mm but less than 30 mm after misoprostol treatment completed expulsion spontaneously and uneventfully.

In findings consistent with those of previous studies, our trial demonstrated that complications with misoprostol treatment occur at a rate of less than 1 in 70 treated patients. In the misoprostol group, 3 percent of women reported an emergency visit within 24 hours after treatment (a rate not significantly different from that in the surgical group), and one woman (0.2 percent) required emergency vacuum aspiration within 24 hours. Our experience, in accordance with that in other literature on medical abortion,²⁰ suggests that hospitalizing patients for the misoprostol treatment is unnecessary. As long as clear instructions for monitoring bleeding and infection are given to women and emergency service is readily accessible, self-administration of misoprostol at home could increase the convenience and privacy and further reduce the cost. Previous data have clearly demonstrated that women can comfortably insert pills into the vagina at home.²⁰

Our trial was large and involved a 30-day follow-up period. The vast majority of patients recovered satisfactorily in two weeks, but a small number required surgical evacuation even after one month. In addition, tissue was often seen in the cervical os of women who came for an emergency visit and sometimes at the follow-up visit; it was removed in many cases with ring forceps without further treatment. It is uncertain whether tissue in the os simply reflects the normal process of expulsion or whether its presence intensifies and prolongs bleeding.

Our study included relatively few women with an incomplete or inevitable abortion. This is attrib-

utable to our use of a relatively stringent definition of incomplete abortion (an endometrial thickness of 30 mm, as compared with one of 15 mm in previous studies). In addition, women who were having active, heavy bleeding when they presented to the hospital were ineligible, since they had a medical indication for emergency vacuum aspiration. Thus, women who had an anembryonic gestation or embryonic or fetal death were overrepresented in our study population. Furthermore, we studied only vaginal administration of misoprostol. Previous randomized trials have indicated that the efficacy of misoprostol is similar whether it is administered vaginally or orally, whereas the incidence of nausea, vomiting, and diarrhea was higher when the agent was administered orally.²¹⁻²³ It is not known whether 800 µg of misoprostol represents the lowest effective dose for all subtypes of early pregnancy failure.

In summary, our study shows that treatment of early pregnancy failure with 800 µg of misoprostol vaginally, with the dose repeated after 48 hours when necessary, is efficacious and safe. The risks of hemorrhage and pelvic infection are similar to those with vacuum aspiration, and the side effects are tolerable. Misoprostol treatment is an acceptable alternative to surgical management for most women.

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Drs. Creinin and Westhoff report having served as consultants to Pfizer, which now owns Searle. Dr. Westhoff reports having received grant support from Pfizer.

APPENDIX

The following persons and institutions participated in the NICHD Management of Early Pregnancy Failure Trial: *NICHD* — J. Zhang, T. Nansel; *Columbia University* — C. Westhoff, A. Davis, C. Robilotto; *University of Miami* — J. Gilles, M. Diro, F. Doyle, N. Vazquez; *University of Pennsylvania* — K. Barnhart, J. Hollander, T. Bader, K. Timbers, A. Hummel, L. Martino; *University of Pittsburgh* — M. Creinin, B. Harwood, R. Guido, L. Reid; *Clinical Trials and Surveys Corporation* — M. Frederick, X.K. Huang; *Data and Safety Monitoring Committee* — P. Coney (chair), J.M. Alvir, P.D. Blumenthal, B. Littman, T. MacKay.

REFERENCES

- Alberman E. Spontaneous abortions: epidemiology. In: Stabile I, Grudzinskas G, Chard T, eds. *Spontaneous abortion: diagnosis and treatment*. London: Springer-Verlag, 1992:19-20.
- Hertig AT, Livingstone RG. Spontaneous, threatened, and habitual abortion: their pathogenesis and treatment. *N Engl J Med* 1944;230:797-806.
- Macrow P, Elstein M. Managing miscarriage medically. *BMJ* 1993;306:876.
- Ballagh SA, Harris HA, Demasio K. Is curettage needed for uncomplicated incomplete spontaneous abortion? *Am J Obstet Gynecol* 1998;179:1279-82.
- Jurkovic D, Ross JA, Nicolaidis KH. Expectant management of missed miscarriage. *Br J Obstet Gynaecol* 1998;105:670-1.
- Luise C, Jermy K, May C, Costello G, Collins WP, Bourne TH. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. *BMJ* 2002;324:873-5.
- Creinin MD, Schwartz JL, Guido RS, Pymar HC. Early pregnancy failure — current management concepts. *Obstet Gynecol Surv* 2001;56:105-13.
- Goldstein SR. Significance of cardiac activity on endovaginal ultrasound in very early embryos. *Obstet Gynecol* 1992;80:670-2.
- Rowling SE, Coleman BG, Langer JE, Arger PH, Nisenbaum HL, Horii SC. First trimester US parameters of failed pregnancy. *Radiology* 1997;203:211-7.
- Nyberg DA, Mack LA, Laing FC, Patten RM. Distinguishing normal from abnormal gestational sac growth in early pregnancy. *J Ultrasound Med* 1987;6:23-7.

11. Harwood B, Meckstroth KR, Mishell DR, Jain JK. Serum beta-human chorionic gonadotropin levels and endometrial thickness after medical abortion. *Contraception* 2001;63:255-6.
12. Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J. Endometrial thickness after misoprostol use for early pregnancy failure. *Int J Gynaecol Obstet* 2004;86:22-6.
13. Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976;31:1191-8.
14. Grimes DA, Cates WC Jr. Complications from legally-induced abortion: a review. *Obstet Gynecol Surv* 1979;34:177-91.
15. Makuch R, Simon R. Sample size requirements for evaluating a conservative therapy. *Cancer Treat Rep* 1978;62:1037-40.
16. StatXact 4 for Windows: user's manual. Cambridge, Mass.: Cytel Software Corporation, 2000:428-35.
17. Graziosi GCM, Mol BWJ, Reuwer PJH, Drogdrop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. *Hum Reprod* 2004;19:1894-9.
18. Fox MC, Creinin MD, Meyn LA, Murthy AS, Harwood B. Ultrasound appearance of the endometrium after medical abortion. *Contraception* 2004;70:261. abstract.
19. Luise C, Kermy K, Collons WP, Bourne TH. Expectant management of incomplete, spontaneous first-trimester miscarriage: outcome according to initial ultrasound criteria and value of follow-up visits. *Ultrasound Obstet Gynecol* 2002;19:580-2.
20. Newhall EP, Winikoff B. Abortion with mifepristone and misoprostol: regimens, efficacy, acceptability and future directions. *Am J Obstet Gynecol* 2000;183:Suppl 2:S44-S53.
21. Pang MW, Lee TS, Chung TKH. Incomplete miscarriage: a randomized controlled trial comparing oral with vaginal misoprostol for medical evacuation. *Hum Reprod* 2001;16:2283-7.
22. Tang OS, Lau WNT, Ng EHY, Lee SWH, Ho PC. A prospective randomized study to compare the use of repeated doses of vaginal with sublingual misoprostol in the management of first trimester silent miscarriages. *Hum Reprod* 2003;18:176-81.
23. Honkanen H, Piaggio G, Herten H, et al. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. *BJOG* 2004;111:715-25.

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