Published in final edited form as:
Am J Obstet Gynecol. 2004 February ; 190(2): 389–394. doi:10.1016/j.ajog.2003.08.024.

A randomized trial of saline solution–moistened misoprostol versus dry misoprostol for first-trimester pregnancy failure

Jerry M. Gilles, MD[a], **Mitchell D. Creinin, MD**[b], **Kurt Barnhart, MD, MSCE**[c], **Carolyn Westhoff, MD**[d], **Margaret M. Frederick, PhD**[e], and **Jun Zhang, MD, PhD**[f] **for the National Institute of Child Health and Human Development Management of Early Pregnancy Failure Trial**

[a] University of Miami, Miami, Fla

[b] University of Pittsburgh, Pittsburgh and Philadelphia, Pa

[c] University of Pennsylvania

[d] Columbia University, New York, NY

[e] Clinical Trials and Survey Corporation, Baltimore and Bethesda, Md

[f] National Institute of Child Health and Human Development, Baltimore and Bethesda, Md

Abstract

Objective—The purpose of this study was to estimate whether the efficacy of treatment with intravaginal misoprostol for first-trimester pregnancy failure is enhanced by the addition of saline solution.

Study design—Eighty women with embryonic/fetal death or anembryonic pregnancy were assigned randomly to receive either 800 μg of misoprostol with saline solution (group I, 41 women) or without (group II, 39 women). Treatment was repeated on day 3 if the gestational sac remained. Curettage was performed if the gestational sac remained on day 8 or as necessary during at least 30 days of follow-up. Data were analyzed with the Student *t* test and the χ^2 or Fisher exact test.

Results—By the first follow-up visit, 73% (group I) and 64% (group II) of women passed the gestational sac ($P = .38$). By the second follow-up visit, expulsion rates were 83% and 87%, respectively ($P = .59$). Five subjects in each group underwent curettage.

Conclusion—Misoprostol is effective for the treatment of failed first-trimester pregnancy. The expulsion rate is not improved by adding saline solution.

Keywords

Missed abortion; Misoprostol; Anembryonic pregnancy; Fetal death; Spontaneous abortion

Approximately 15% of clinically evident pregnancies result in first-trimester loss.[1] Curettage, commonly performed for this condition, is comparatively costly when performed in the operating room.[2] Although curettage is relatively safe, it can be associated with intrauterine infection, adhesion, perforation, and cervical stenosis.[3] An alternative may be expectant or medical treatment. Expectant treatment usually results in the complete expulsion of the products of conception[4]; however, the interval after diagnosis and expulsion varies. Luise et al[5] reported that most women passed products within 2 weeks of diagnosis. Jurkovic et al[6] found only a 25% success rate in women whose cases were followed for >6 weeks. Medical

treatment may provide prompt expulsion and avoid costs and complications that are associated with surgery and the uncertainties of expectant treatment.

A uterotonic drug that is proposed for medical treatment is misoprostol, an inexpensive widely available prostaglandin E_1 analog that is stable at room temperature.[7,8] The drug is absorbed through mucous membranes and can be administered sublingually, orally, vaginally, and rectally.[9,10] Misoprostol used alone for nonviable first-trimester pregnancy resulted in uterine expulsion in 13% to 96% of women.[11,12] Explanations for this wide range include different indications for treatment, dosing regimen, routes of administration, and measures of success. Vaginal administration appears to be more effective than oral administration for the inducement of uterine contractions and cervical effacement,[10] while minimizing systemic side effects (such as diarrhea, fever, nausea, and vomiting).[13]

Drug absorption after vaginal administration varies widely.[9,14] In an observational study, Zalanyi[15] moistened the tablets with saline solution and reported expulsion in 88% of women with anembryonic or embryonic/fetal death pregnancies. Perhaps the addition of saline solution to the tablets enhanced the drug's effectiveness.

In planning a large multicenter trial comparing misoprostol with curettage, we faced a decision about how to apply the drug. This randomized trial was conducted to compare the efficacy, frequency, and severity of side effects after misoprostol administration with or without saline solution for the expulsion of nonviable first-trimester pregnancies.

Material and methods

Approval was obtained from the Food and Drug Administration, the Investigational Review Board of the National Institute of Child Health and Development, and the investigational review board of each clinical center. Women with intrauterine pregnancies were recruited if they had a closed cervix and one of the following transvaginal ultrasound findings: embryonic pole or crown-rump length between 5 and 40 mm without cardiac activity,[16] mean anembryonic gestational sac diameter between 16 and 45 mm or no growth over at least 1 week,[17,18] or an increase in human chorionic gonadotropin of <15% over 2 days with a yolk sac.[13] Women were excluded if they were anemic (hemoglobin level, <9.5 mg/dL), if their condition was hemodynamically unstable, or if they had a contraindication to treatment with prostaglandins or nonsteroidal anti-inflammatory drugs.

At enrollment, medical history, hemoglobin level, and Rh-antigen status were obtained, and a physical examination was performed. Eligible subjects were assigned randomly to receive four 200-μg tablets (800 μg) of misoprostol that was inserted into the posterior fornix through a speculum followed by either adding 2 mL of saline solution to the tablets (group I) or not adding saline solution (group II). The day of misoprostol insertion was considered study day 1.

Subjects were given 30 tablets of ibuprofen (200 mg) and 20 tablets of codeine (30 mg) and were instructed to use ibuprofen primarily and the narcotic as needed. Side effects, medication usage, and the use of medical facilities were recorded on a diary. Pain intensity was recorded on a visual analog scale.[19] Subjects were instructed to contact study personnel if their temperature was ≥38°C or if they soaked >4 maxipads in 2 hours.

Follow-up visits were scheduled for day 3 (range, 2–5 days), day 8 (range, 6–10 days), and day 15 (range, 13–18 days). The allowable range of ±2 days was to adjust for weekends. At each visit, the presence of a gestational sac was assessed by transvaginal ultrasonography, and the clinical investigator performed a physical examination and an interview and collected the diary pages.

If the gestational sac remained on day 3, a second dose of misoprostol was administered in the same manner as the first. Curettage was performed on the day 8 visit if the sac persisted. At the day 15 visit, an acceptability questionnaire was completed. A telephone interview was conducted on day 30 (range, 25–35 days) to determine whether any subject underwent additional treatment. Symptomatic women received additional follow-up.

Randomization was performed with a computer-automated telephone response system. The subjects were stratified by pregnancy type with the use of random permuted blocks of size 4 or 8. The Data Coordinating Center developed the process for randomization, and the enrollment sequence was concealed from investigators. The Data and Safety Monitoring Committee monitored the study for adverse events. Neither the investigators nor the subjects were masked because the addition of saline solution made the interventions visibly different.

Success was defined as expulsion of the gestational sac without the need for curettage during a period of at least 30 days. Losses to follow-up were counted as failures. We aimed to enroll 80 subjects. Assuming that dry misoprostol has a success rate of 80% and moistened misoprostol has a success rate of 94%, we had 80% power to detect a statistically significant difference between the groups. Additionally, with baseline estimates of 36%, 22%, and 36% for vomiting, diarrhea, and fever/chills, respectively, the sample size was powered to detect an increase in these side effects to 57%, 41%, and 57%, respectively. The data were analyzed with the Student *t* test for continuous variables and χ^2 or Fisher exact test for categoric variables. A probability value of <.05 was considered significant.

Results

Eighty subjects were recruited from four clinical centers between September 2001 and February 2002. In group I, 41 were randomized to receive 800 μg of saline solution–moistened misoprostol (Table I). In group II, 39 subjects were assigned randomly to receive 800 μg of dry misoprostol. All subjects received their treatment allocation on day 1. Both groups were similar demographically (Table II).

The success rates for groups I and II were 83% and 87%, respectively (*P* = .59). The combined rate of success at day 30 was 85% (95% CI, 77%–93%). In group I, nine subjects required a second dose; the treatment failed for four of these subjects, who then underwent curettage. One subject expelled the gestational sac by day 3 and had curettage for excessive bleeding on day 43. Two subjects were lost to follow-up.

In group II, after having received one dose, 12 subjects did not pass the sac. One subject opted for curettage on day 2. Eleven subjects received a second dose, among whom 8 subjects passed the sac and 3 subjects underwent curettage. All subjects who missed the day 3 or day 8 visit were determined to have passed the sac on subsequent follow-up visits. Two subjects passed the sac by day 3 and underwent curettage for excessive bleeding on study day 31 or 50.

Outcome did not vary by clinical center. There was no association between the day of the first follow-up visit and the need for a second dose. For subjects who received a second dose, the interval to the next follow-up visit was 2, 4, 5, and 7 days for two, five, seven, and one subjects, respectively. Similarly, there was no association between the expulsion rate and the interval to the follow-up visit (*P* = .61).

The rate of side effects was similar for groups I and II (Table III). Although most subjects characterized their pain as mild, nearly all of them used ibuprofen, and 71% of them also used codeine, regardless of whether saline solution was added to the misoprostol tablets. In group I, 8 of 40 subjects (20%) and in group II, 12 of 37 subjects (32%) contacted study personnel outside the study visits (*P* = .21), which often resulted in emergency visits. By day 15, the

change in hemoglobin level in group I was −0.4±1.2 g (n = 31 subjects); the change in group II was 0.5±1.3 g (n = 34 subjects; *P* = .67). The only adverse events were four curettage procedures for excessive bleeding.

At the day 15 interview, 33 of 36 subjects in group I and 30 of 36 in group II reported that they would probably or absolutely be willing to recommend treatment with misoprostol. A similar number of subjects in group I and II reported that they would probably or absolutely want the same procedure for another failed pregnancy (31/36 subjects and 27/37, respectively; *P* = .16). Among 31 subjects with and 41 subjects with no history of a previous curettage, there was no difference in willingness to recommend (*P* = .49) or to repeat the treatment (*P* = .15).

We pooled and analyzed the data for outcome on the basis of pregnancy type. We found no significant difference in gestational age between pregnancy type as determined by last menstrual period, ultrasonography, and uterine size. Subjects with embryonic/fetal demise were significantly more likely to evacuate successfully (48/51 subjects [94%]; 95% CI, 88%–100%) than those with anembryonic pregnancies (20/29 subjects [69%]; 95% CI, 52%–86%; *P*<.01). By day 30, two women with an embryonic/fetal death and eight women with an anembryonic pregnancy underwent curettage. Pelvic pain at enrollment was more common among subjects with embryonic/fetal demise (33/51 subjects [65%]) than with anembryonic gestations (11/29 subjects [38%], *P* = .02).

Comment

This is the first multicenter randomized controlled trial to evaluate the efficacy and side effects that are associated with saline solution–moistened misoprostol versus dry misoprostol for the treatment of first-trimester pregnancy failure. Regardless of the method used, 800 μg of misoprostol is effective for the expulsion of the gestational sac. In this study, the investigators were the care providers and were not masked to the treatment allocation. It is unlikely that this influenced the results. Success or failure was based primarily on the dichotomous finding of the presence or absence of a gestational sac.

Treatment outcomes, side effects, and acceptability were comparable whether or not the misoprostol was administered with or without saline solution. This similarity suggests that systemic activity for both methods is comparable. The expulsion rate of 83% with saline solution was similar to that reported by Zalanyi.[15] However, that study had no control subjects and could not determine whether adding saline solution was necessary. Other investigators attempted to increase the efficacy of treatment by adding water or acetic acid. The addition of water did not increase the bioavailability[9] of the drug nor did acetic acid decrease the labor induction time.[20]

A study of this size cannot detect a minor difference in efficacy between saline solution–moistened and dry misoprostol. On the basis of the success rate that we observed (83% vs 87%), we would need a total of 2068 subjects to be able to detect a statistically significant difference that would be of limited clinical value. Misoprostol that is administered dry is effective, less cumbersome, more economic, and more suitable for home application. Self-administration in itself is an area worthy of additional study, if only for allowing patients to avoid pain while traveling from the site of medical care.

Most subjects passed the gestational sac after the first dose (64%–73%). A second dose increased the success rate (83%–87%). Additional doses might raise the success rate, but prolonging treatment could affect patient satisfaction adversely. It is possible that women respond differently to treatment with misoprostol because of differences in their serum levels of the active metabolite and in their levels of chemical modulators of prostaglandin E_1 activity

(such as progesterone and cytokines).[21] Such differences may account for those subjects who required an additional dose or curettage.

The follow-up intervals were designed to minimize loss to follow-up. The resulting variance in the number of days that elapsed between doses does not appear to affect the success rate. This finding may be an artifact from the fragmentation of the 80 subjects into multiple samples. Additional studies are needed to evaluate whether the interval between doses can be reduced on an outpatient basis while maintaining efficacy.

Women who were treated with misoprostol needed continued access to medical care. All subjects had follow-up to at least day 30. This is a more encompassing time frame than is used by other investigators, who commonly define outcome within 1 week of treatment.[22,23] Despite this, three subjects had curettage on extended follow-up. Overall, 26% of the subjects called study personnel for reassurance. Whether this poses a burden is dependent on the woman and her health care provider. We do not have data to compare this to those women who underwent expectant or surgical treatment.

Previous studies have reported a lower rate of drug-related side effects.[22,24] Our high incidence of side effects is likely due to a more meticulous collection of subjects' complaints through diaries and interviews. Despite the frequency of reported side effects, most women find the treatment acceptable and would recommend it to others.

Varying methods of pain control can be used with misoprostol treatment. Wood and Brain[25] used acetaminophen and codeine for pain and reported success in 20 of 25 subjects. We provided ibuprofen and codeine and had a comparable success rate (83%–87%). Ibuprofen, an inhibitor of prostaglandin synthesis, does not appear to decrease treatment success. Most of our subjects used ibuprofen and codeine, despite describing their pain as mild to moderate. Wood and Brain[25] also reported the frequent use of pain medication when drugs are provided rather than prescribed.

More studies are needed to confirm that the conditions of women with embryonic/fetal death respond more favorably than the conditions of those with anembryonic pregnancies. Luise et al[5] also noted that complete expulsion was more likely during 1 month in expectantly treated subjects with embryonic/fetal death (76%) than with anembryonic pregnancy (66%). Specific diagnosis may be one factor that influences success rate and is often overlooked when anembryonic pregnancy and embryonic/fetal death are lumped as missed abortions. The development of fetal tissue may influence uterine response to prostaglandins that result in a more frequent occurrence of pain and uterine evacuation.

Expectant treatment as an alternative has been reported to be successful in up to 79% of subjects within 3 days of follow-up.[26] This high success rate appears to be a result of the inclusion of subjects with incomplete abortions. Contrastingly, Waard et al[27] reported that only 30 of 64 subjects (47%) who were treated expectantly evacuated successfully within 6 weeks. Sixty of these 64 subjects were diagnosed with embryonic/fetal death. In our study, 48 of 51 subjects (94%) with embryonic/fetal death had successful expulsion. This argues favorably for misoprostol treatment as a promising alternative to surgery and expectant treatment.

Similar to our findings, Muffley et al[22] reported no serious adverse events in 25 women who were treated with misoprostol. However, of 25 subjects who were assigned randomly to curettage, one subject underwent laparotomy for uterine perforation. More study is needed to confirm that, by reducing the need for curettage with misoprostol treatment, fewer women have severe complications from miscarriage.

To decide between treatment options, information is needed about the risks, acceptability, and likelihood of success. In this study, apart from emergency curettage procedures, there were no serious adverse events, and women reported outpatient treatment to be acceptable. Treatment with misoprostol is efficacious in women with first-trimester pregnancy failure, and the success rate is not improved by the addition of saline solution. The drug is effective and well tolerated as manufactured.

Acknowledgments

The following persons and institutions participated in the National Institute for Child Health and Human Development Management of Early Pregnancy Failure Trial (principal investigators are indicated by asterisks): J. Zhang* and T. Nansel (National Institute of Child Health and Human Development); C. Westhoff,* A. Davis, and C. Robilotto (Columbia University); J. Gilles,* J. Kang, F. Doyle, and N. Vazquez (University of Miami); K. Barnhart,* T. Bader, and K. Timbers (University of Pennsylvania); M. Creinin,* B. Harwood, R. Guido, M. Fox, L. Reid (University of Pittsburgh); and M. Frederick,* S. Forman, and X. K. Huang (Clinical Trials and Surveys Corporation).

Supported by National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services under contracts No. N01-HD-1-3321 through 3325.

References

1. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. N Engl J Med 1988;319:189–94. [PubMed: 3393170]
2. Hughes J, Ryan M, Hinshaw K, Henshaw R, Rispin R, Templeton A. The costs of treating miscarriage: a comparison of medical and surgical management. BJOG 1996;103:1217–21.
3. Hakim-Elahi E, Tovell HMM, Burnhill MS. Complications of first-trimester abortion: a report of 170,000 cases. Obstet Gynecol 1990;76:29–135.
4. Nielsen S, Hahlin M, Platz-Christensen J. Randomized trial comparing expectant with medical management for first trimester miscarriages. BJOG 1999;106:804–7.
5. Luise C, Jeremy 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. [PubMed: 11950733]
6. Jurkovic D, Ross JA, Nicolaides KH. Expectant management of missed miscarriage. BJOG 1998;105:670–1.
7. Collins PW, Pappo R, Dajani EZ. Chemistry and synthetic development of misoprostol. Dig Dis Sci 1985;30:114–7S. [PubMed: 3967559]
8. Blanchard K, Clark S, Winikoff B, Gaines G, Ka G. Misoprostol for women's health. Obstet Gynecol 2002;99:316–32. [PubMed: 11814515]
9. Tang OS, Schweer H, Seyberth HW, Lee SWH, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. Hum Reprod 2002:332–6. [PubMed: 11821273]
10. Goldberg AG, Greenberg MB, Darney PD. Misoprostol and pregnancy. N Engl J Med 2001;344:38–47. [PubMed: 11136959]
11. El-Refaey H, Hinshaw K, Henshaw R, Smith N, Templeton A. Medical management of missed abortion and anembryonic pregnancy. BMJ 1992;305:1399–405. [PubMed: 1486304]
12. De Jonge EM, Makin JD, Manefeldt E, De Wet GH, Pattinson RC. Randomised clinical trial of medical expulsion and surgical curettage for incomplete miscarriage. BMJ 1995;311:662–8. [PubMed: 7549636]
13. Creinin MD, Moyer R, Guido R. Misoprostol for medical evacuation of early pregnancy failure. Obstet Gynecol 1997;89:768–72. [PubMed: 9166318]
14. Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997;90:88–92. [PubMed: 9207820]
15. Zalanyi S. Vaginal misoprostol alone is effective in the treatment of missed abortion. BJOG 1998;105:1026–35.
16. Goldstein SR. Significance of cardiac activity on endovaginal ultrasound in very early embryos. Obstet Gynecol 1992;80:670–2. [PubMed: 1407892]

17. Rowling SE, Coleman BG, Langer JE, Arger PH, Nisenbaum HL, Horiii SC. First-trimester US parameters of failed pregnancy. Radiology 1997;203:211–7. [PubMed: 9122395]

18. Nyberg DA, Mack LA, Laing FC, Patten RM. Distinguishing normal form abnormal gestational sac growth in early pregnancy. J Ultrasound Med 1987;6:2–7.

19. Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. Anaesthesia 1976;31:1191–8. [PubMed: 1015603]

20. Sanchez-Ramos L, Danner CJ, Delke I, Kaunitz A. The effect of tablet moistening on labor induction with intravaginal misoprostol: a randomized trial. Obstet Gynecol 2002;99:1080–4. [PubMed: 12052603]

21. Kelly RW, King AE, Critchley OD. Cytokine control in human endometrium. Reproduction 2001;121:3–19. [PubMed: 11226025]

22. Muffley PE, Stitely MI, Gherman RB. Early intrauterine pregnancy failure: a randomized trial of medical versus surgical treatment. Am J Obstet Gynecol 2002;187:321–6. [PubMed: 12193919]

23. Ayre-de-Campos D, Teixeira-da-Silva J, Campos I, Patricio B. Vaginal misoprostol in the management of first-trimester missed abortions. Int J Gynecol Obstet 2000;71:53–7.

24. Demetroulis C, Saridogan E, Kunde D, Naftalin AA. A prospective randomized control trial comparing medical and surgical treatment for early pregnancy failure. Hum Reprod 2001;16:365–9. [PubMed: 11157836]

25. Wood SL, Brain PH. Medical management of missed abortion: a randomized clinical trial. Obstet Gynecol 2002;99:563–6. [PubMed: 12039111]

26. Nielsen S, Hahlin M. Expectant management of first-trimester spontaneous abortion. Lancet 1995;345:84–6. [PubMed: 7815886]

27. Waard MW, Vos J, Bonsel JG, Bindels PJE, Ankum WM. Management of miscarriage: a randomized controlled trial of expectant management versus surgical evacuation. Hum Reprod 2002;17:2445–50. [PubMed: 12202439]

Table I

Enrollment and cumulative outcome by visit day

	Group I (n = 41)*	Group II (n = 39)†
Day 3		
Expelled sac	30	25
Retained sac	9	12
Missed visit	2	2
Day 8		
Expelled sac	34	31
Curettage	5	4
Missed visit	2	4
Day 15		
Expelled sac	34	35
Curettage	5	4
Missed visit	2	0
Day 30		
No curettage	34	34
Curettage	5	5
No contact	2	0

*Group I, misoprostol 800 μg vaginally plus 2 mL of saline solution.

†Group II, misoprostol 800 μg vaginally.

Table II

Baseline characteristics

Characteristic	Group I: saline solution moistened (n = 41)	Group II: dry (n = 39)	*P* value
Race (n)			.73
Hispanic	18 (44%)	14 (36%)	
Non-Hispanic black	12 (29%)	10 (26%)	
Non-Hispanic white	10 (24%)	14 (36%)	
Asian	1 (2%)	1 (3%)	
Maternal age (y)*	29.4±7.0	30.2±8.0	.66
Age of menarche (y)*	12.6±1.6 (n = 40)	13.0±1.5 (n = 38)	.21
Estimated gestational age (wk)*	7.7±1.6	7.2±1.2	.09
Uterine size (wk)*	7.6±1.6 (n = 39)	7.9±1.9 (n = 36)	.54
Pain in this pregnancy (cm)*	2.4±3.0	2.3±2.6 (n = 37)	.86
Hemoglobin (gm/dL)*	13.0±1.4	12.6±1.0	.11
Diagnosis			.69
Embryonic/fetal death	27 (66%)	24 (62%)	
Anembryonic gestation	14 (34%)	15 (38%)	

*Data are given as mean±SD.

Table III

Symptoms reported on subject's diary within 48 hours after the first or second misoprostol insertion

Symptom	Group I: saline solution moistened (n = 40)	Group II: dry (n = 37)	*P* value
Diarrhea	17 (42%)	9 (24%)	.09
Headaches	20 (50%)	17 (46%)	.72
Heavy vaginal bleeding	23 (58%)	19 (51%)	.60
Chills	28 (70%)	19 (51%)	.09
Fever	10 (25%)	12 (32%)	.47
Nausea	18 (45%)	20 (54%)	.43
Vomiting	6 (15%)	6 (16%)	.88
Abdominal pain	39 (95%)	36 (97%)	.96
Pain severity score (cm)*	6.4±2.5	6.4±2.9	.94

* Data are given as mean±SD; maximum pain intensity reported on a 10-cm visual analog scale.