

Bleeding patterns after vaginal misoprostol for treatment of early pregnancy failure

A.R.Davis^{1,4}, C.M.Robilotto¹, C.L.Westhoff¹, S.Forman², J.Zhang³ and for the NICHD Management of Early Pregnancy Failure Trial group

¹Department of Obstetrics and Gynecology, Columbia University, 630 West 168th Street, New York, NY 10032, ²Clinical Trials and Surveys Corporation, 2 Hamill Road, Suite 350 West Quadrangle, Baltimore, MD 21210-1874 and ³Epidemiology Branch, National Institute of Child Health and Human Development, National Institute of Health, 6100 Executive Blvd, Room 7B03, Rockville, MD 20852, USA

⁴To whom correspondence should be addressed. E-mail: ard4@columbia.edu

BACKGROUND: Dilatation and curettage (D&C) has been the usual treatment for early pregnancy failure (EPF). Medical management with misoprostol may be an effective alternative. Bleeding patterns during and after medical management of EPF are unknown. **METHODS:** A prospective cohort study was conducted at University-based clinics and physician offices. Eighty women <11 weeks estimated gestational age with a diagnosis of missed abortion or fetal demise were enrolled. Treatment consisted of either 800 µg of moistened (2 ml of saline) or dry vaginal misoprostol. Self-reported bleeding and sanitary product usage were recorded in a daily 2 week diary. Haemoglobin was assessed at enrolment and 2 weeks later. **RESULTS:** After misoprostol treatment, patients reported bleeding or spotting every day for the 14 days observed. Self-assessed heavy bleeding days were few (median 3) and usually occurred immediately after treatment. Sanitary pad use was highly variable (mean 30.5, range 2–125 pads over the 2 week period) and not related to changes in haemoglobin. The mean decrease in haemoglobin was 0.5 g/dl (SD 1.2). Complete expulsion without D&C occurred in 85% of subjects. **CONCLUSIONS:** Bleeding for at least 2 weeks after vaginal misoprostol for EPF is common. Heavy bleeding is usually limited to a few days after treatment. Clinically important changes in haemoglobin are rare.

Key words: bleeding/early pregnancy failure/misoprostol

Introduction

Dilatation and curettage (D&C) has been the standard management of early pregnancy failure (EPF). Medical management of EPF using prostaglandin analogues has been proposed as an alternative to surgery. Prostaglandin analogues combined with mifepristone for elective abortion in the first trimester result in success rates of ~95% (complete uterine evacuation without surgery) (Peyron *et al.*, 1993). Published studies using various prostaglandins for EPF report success rates ranging from 13 to 95% (El-Refaey *et al.*, 1992; De Jonge *et al.*, 1995; Chung *et al.*, 1997; Wood and Brain, 2002). The widely varying success rates may reflect inclusion of different types of pregnancy failure (anembryonic versus fetal demise or incomplete abortion) as well as different treatment protocols and approaches to follow-up.

Both women and health care providers will benefit from information regarding bleeding patterns after medical management of EPF. Information about the duration and quantity of bleeding will aid in counselling regarding medical versus surgical options. In a study using 6 weeks of diary data, participants reported more bleeding and spotting days after voluntary medical abortion (mean 24 days) than after voluntary

surgical abortion (mean 19 days) (Davis *et al.*, 2000). Bleeding data from voluntary abortion studies may not be generalizable to EPF. Physiological differences between ongoing pregnancies and early pregnancy failures may result in different bleeding patterns after management with prostaglandins.

Little detailed information regarding bleeding after medical management of miscarriage has been published. For subjective bleeding outcomes, most studies rely on retrospective reporting rather than diary data, and do not distinguish heavy from light bleeding. No study has included data on sanitary product use, which might guide clinical management of bleeding. Most studies include objective outcomes such as haemoglobin changes after treatment. No study, however, has related subjective bleeding reports to changes in haemoglobin.

The objective of the current analysis was to describe bleeding patterns, sanitary product use and changes in haemoglobin following vaginal misoprostol for EPF.

Materials and methods

We used data from a randomized clinical trial comparing the efficacy of moistened versus dry misoprostol for medical management of EPF.

This study was conducted between September 2001 and January 2002 at four medical centres (Columbia University, NY, University of Miami, FL, University of Pennsylvania, PA, and the University of Pittsburgh, PA). Approval for conducting this trial was obtained from the Food and Drug Administration, the Investigational Review Board (IRB) of the National Institute of Child Health and Development and from the IRB at each clinical centre. Women diagnosed with EPF were referred from emergency rooms, residents and clinicians from within the participating institutions. A detailed description of the study methods and results is published separately (Gilles *et al.*, 2004).

Healthy women diagnosed with EPF were offered enrolment when ultrasound documented at least one of the following: (i) crown-rump length between 5 and 40 mm without cardiac activity (fetal demise); (ii) gestational sac between 16 and 45 mm mean diameter without an embryonic pole (anembryonic gestation); (iii) no growth of the gestational sac or embryonic pole over 1 week; or (iv) abnormal rise in serum β HCG level of <15% over 2 days with a yolk sac present. Other inclusion criteria included willingness to accept randomization and comply with the study protocol, access to a telephone, venous access and age \geq 18 years. We excluded women with orthostatic hypotension, recent use of ovulation stimulation drugs, contraindication to non-steroidal anti-inflammatory drugs (NSAIDs), use of medication to induce miscarriage, known or suspected ectopic pregnancy, haemoglobin <9.5 mg/dl, current clotting disorder or use of anticoagulants, cardiovascular disease, current breast feeding, or karyotyping required.

At enrolment, all women underwent a transvaginal ultrasound to confirm non-viability as well as a pelvic exam and medical history. Laboratory tests included a baseline and 14 day haemoglobin level. After obtaining informed consent, participants were randomized to receive 800 μ g of moistened (2 ml of saline) or dry misoprostol (Searle, Chicago, IL). A speculum was inserted and four, 200 μ g tablets of misoprostol were placed into the posterior fornix with or without 2 ml of saline.

Each woman received a daily diary to record bleeding for 2 weeks. For each 24 h period, participants indicated if bleeding was (i) none; (ii) spotting; (iii) light; (iv) moderate; (v) heavy; and (vi) more than two pads/h. Participants selected the category of bleeding without

guidance or definition by study staff. Participants also indicated the number of sanitary pads or tampons used daily. Haemoglobin measurement was repeated at 2 weeks at the local laboratory.

Success was defined as complete expulsion of the gestational sac without D&C for any reason. As per the study protocol, the success rate was calculated at 30 days after misoprostol treatment (Gilles *et al.*, 2004). By day 30, 10 women underwent D&C for a success rate of 85%. Additionally, three D&Cs occurred after day 30. There was no difference in success rates between participants who received dry versus moistened misoprostol. The bleeding patterns were similar in the dry and moistened misoprostol groups (data not shown). Therefore, the groups are combined and results of the bleeding analyses are presented as one cohort.

Results

Eighty women participated in the trial; 39 were randomized to dry misoprostol and 41 were randomized to moistened misoprostol. Baseline characteristics were similar for the two groups. Table I presents demographic characteristics for both groups combined. Thirty-six percent of the pregnancies were anembryonic and the remaining 64% were fetal demises. The mean gestational age was 7.5 weeks (SD 1.4), range 5–12 weeks. Clinicians estimated best gestational age using last menstrual period and sonographic findings.

Most participants completed their diaries. However, some diaries were incomplete especially for days at the end of the 2 weeks. We excluded three women who never returned diaries, leaving 77 participants with diaries for these analyses. For the remaining participants, 12% of diary days were missing; median 2 days and range 1–13 missing days.

At enrolment, 55% of the women reported cramping and 53% reported bleeding during the 24 h prior to treatment. The most common pattern was some bleeding or spotting every day for 14 days. The median number of bleeding or spotting days after treatment was 12. In this analysis, heavy bleeding included the following categories: moderate, heavy or more than two pads/h. Heavy bleeding was much less frequent than light bleeding or spotting. Participants reported a median of 3 days of heavy bleeding (10th percentile 1 day, 90th percentile 9 days).

The pattern of bleeding over time is presented in Figure 1 by the proportion of participants reporting any bleeding or heavy bleeding by study day. In this figure, days with missing diary data are excluded. Since some participants stopped diary entry when bleeding stopped, this may be an overestimate of the true proportion with bleeding. Almost all participants bled throughout the first week, with a modest decline during the second

Table I. Demographic characteristics of participants

Age (years), mean	30 (SD 7)
Parity, mean	1.4 (SD 2)
Race	
White	30%
Hispanic	40%
African-American	27.5%
Asian	2.5%
Education	
High school or less	49%
College	51%

Table II. Clinical course of subjects who underwent D&C for bleeding complaint

Day of D&C	Indication	Baseline haemoglobin (g/dl)	Haemoglobin at time of D&C (g/dl)	Histological examination
2	Heavy bleeding and dizziness	11.2	10.2	Degenerated hydropic immature chorionic villi
17	Prolonged bleeding	12.6	Unknown	Unknown
31	Heavy bleeding with passage of clots	14.1	10.7	Immature placenta and hyalinized decidua
43	Prolonged bleeding	10.9	11.2	Immature placenta and hyalinized decidua
50	Prolonged and heavy bleeding with passage of clots	12.6	13.0	Degenerated products of conception

week. Heavy bleeding usually occurred during the first few days after treatment and declined sharply thereafter. The data were similar after participants undergoing D&C were excluded.

Reported sanitary pad use was highly variable. The median pad use over 2 weeks was 30.5, range 2–125. Pad use was similar between study sites. Because some diaries were incomplete, these numbers underestimate the total pads used. Figure 2 presents the median and 10th and 90th percentiles of pad use by study day. Sanitary pad use during the study was correlated with usual sanitary pad use during menses ($n = 76$, $r = 0.39$, $P < 0.001$). Very few participants used tampons during the study. Ninety-two percent reported using three or fewer tampons during the study. Infrequent use may reflect investigator instructions.

Overall, treatment was associated with small and clinically unimportant changes in haemoglobin. Before treatment the mean haemoglobin was 12.8 g/dl (SD 1, $n = 73$). At 2 weeks, mean haemoglobin was 12.3 (SD 1.5, $n = 65$) for a mean

difference of -0.48 (SD 1.2, $P = 0.002$). Forty-three percent of participants had either no change or a modest increase in haemoglobin (≤ 1.4 g/dl) over the 2 week study period. Among those with a decrease in haemoglobin (57%, $n = 37$), eight had decreases of < 1 g/dl, nine had a decrease between 1 and 2 g/dl, and three had a decrease of at least 3 g/dl, with the largest decrease from 15.4 to 12.0 g/dl. No participant required a blood transfusion during the study.

Neither total days of bleeding nor pad counts was associated with change in haemoglobin (correlation days bleeding and change in haemoglobin $r = 0.003$, correlation total pads and change in haemoglobin $r = -0.184$). Reported days with moderate or greater bleeding was associated with a decrease in haemoglobin ($r = -0.31$, $P = 0.014$). Participants in the highest quartile of heavy bleeding days (> 6 days) had a larger drop in haemoglobin (-0.99 g/dl) than those reporting fewer heavy bleeding days (-0.3 g/dl) ($P = 0.045$).

Thirteen subjects underwent D&C after misoprostol; one subject underwent two D&Cs. Of the 14 D&Cs, eight were performed as per the study protocol for a retained gestational sac after the second dose of misoprostol. One subject decided not to wait for expulsion after misoprostol and opted for a D&C on study day 2. Five D&Cs were performed for bleeding complaints, and Table II summarizes the clinical course for these subjects. Bleeding patterns reported in the 2 week diary were similar for subjects who underwent D&C for bleeding complaints and those who did not (data not shown). Detailed information on bleeding for subjects who underwent D&C after completion of their 2 week diary is unknown.

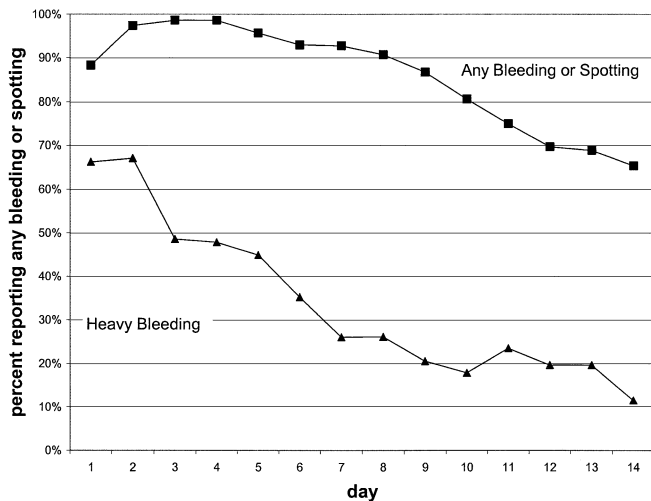


Figure 1. Any versus heavy bleeding after vaginal misoprostol by study day.

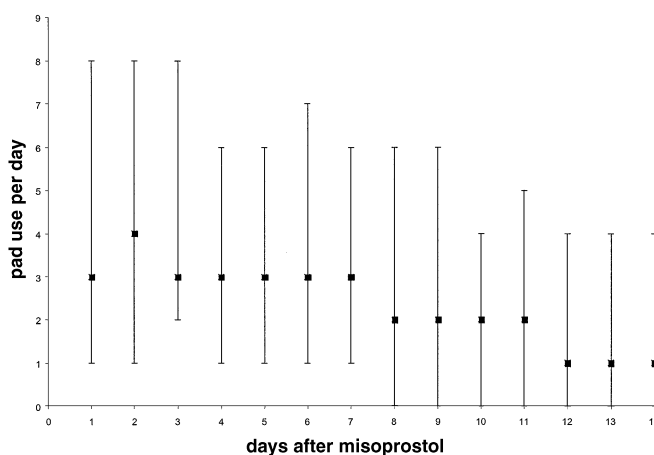


Figure 2. Pad use per day (median, 10th and 90th percentiles).

Discussion

Several studies suggest that management of EPF with misoprostol provides an effective alternative to D&C. Published reports emphasize success rates of medical management but provide little information about associated side effects including bleeding. Expected bleeding patterns are an important part of patient counselling and may influence acceptability and choice of medical versus surgical management.

Overall, misoprostol treatment was safe. Clinically important changes in haemoglobin were very uncommon. Of the five women who underwent D&C for subjective prolonged or heavy bleeding, only one had a large decrease in haemoglobin. No participant required blood transfusion. This agrees with other reports using misoprostol for EPF (Muffley *et al.*, 2002; Wood and Brain, 2002), and large trials using misoprostol after mifepristone for voluntary abortion (Peyron *et al.*, 1993; El-Refaey *et al.*, 1995). A few women, however, will experience important blood loss which can be obscured in analyses of mean changes. This study lacked the power to identify risk factors for uncommon but clinically important decreases in haemoglobin. Since these events are rare, even a large study may fail to identify risk factors.

This study provides the most comprehensive analysis of bleeding after medical management of EPF to date. Daily bleeding for at least 2 weeks was the most often reported pattern. Heavy bleeding days were few and limited to the first

few days after treatment. The duration of bleeding was longer than reported in studies using a similar regimen (El-Refaey *et al.*, 1992; Chung *et al.*, 1999). The use of daily diaries, rather than retrospective recall, and a longer duration of observation could explain this difference. Davis reported a bleeding pattern very similar to our results in a prospective, 6 week diary study of bleeding after mifepristone and misoprostol for voluntary termination of pregnancy. Ninety-five percent of participants reported bleeding at 7 days and 60% reported bleeding at 2 weeks (Davis *et al.*, 2000). Since bleeding after 2 weeks cannot be determined from our data, we underestimate the total days of bleeding after treatment. Davis reported a mean of 24 days of bleeding or spotting during the 6 weeks after mifepristone and misoprostol (Davis *et al.*, 2000). To obtain a more comprehensive description of bleeding patterns, future studies should include a longer duration of follow-up.

Subjective measures of participant experience correlated poorly with objective measures of blood loss. Neither total days of bleeding nor use of sanitary pads was associated with changes in haemoglobin. There was a modest association between heavy bleeding days and decreases in haemoglobin. Clinically important changes were infrequent among participants reporting the most days of heavy bleeding. Ongoing heavy bleeding should alert clinicians to be vigilant, but surgical intervention is rarely necessary. Variable personal habits or insufficient detail could explain the lack of association between pad counts and changes in haemoglobin. Women can choose from many sanitary products with variable capacity. The study diary did not distinguish products designed for light flow from those for heavy flow.

Episodes of prolonged or delayed bleeding may occur following medical management of EPF and occasionally lead to D&C. While uncommon, four participants underwent D&C for bleeding complaints >2 weeks after treatment and apparent successful expulsion of the gestational sac. Our rate of late D&Cs may be an underestimate if subjects sought care from an outside institution after active surveillance had ended. Delayed treatment failures can also occur after medical regimens for voluntary abortion. In two large trials using mifepristone and misoprostol for medical abortion ($n = 4393$), 59 (1.3%) women underwent D&C for bleeding complaints and 41 of these occurred >2 weeks after treatment (Allen *et al.*, 2001). In our study, late bleeding was associated with histological findings of degenerating products of conception at the time of D&C. While suggestive, we cannot determine if these retained tissues contributed to bleeding complaints. Future studies of bleeding which include longer durations of follow-up may identify predictors of late D&C. Such studies would need to be large since late D&C is uncommon.

Conclusion

Bleeding for 2 weeks after vaginal misoprostol for EPF is common. Heavy bleeding is usually limited to a few days after treatment. Clinically important changes in haemoglobin after misoprostol use are rare. Though uncommon, delayed episodes of prolonged or heavy bleeding requiring D&C can occur following medical management of EPF.

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References

- Allen RH, Westhoff C, DeNonno L, Fielding SL and Schaff EA (2001) Curettage after mifepristone-induced abortion: frequency, timing and indications. *Obstet Gynecol* 98,101–106.
- Chung T, Leung P, Cheung LP, Haines C and Chang A (1997) A medical approach to management of spontaneous abortion using misoprostol. *Acta Obstet Gynecol Scand* 76,248–251.
- Chung T, Lee D, Cheung L, Haines C and Chang A (1999) Spontaneous abortion: a randomized trial comparing surgical evacuation with conservative management using misoprostol. *Fertil Steril* 71,1054–1059.
- Davis AR, Westhoff C and De Nonno L (2000) Bleeding patterns after early abortion with mifepristone and misoprostol or manual vacuum aspiration. *J Am Med Women's Assoc* 55,141–144.
- DeJonge EM, Makin JD, Manefeldt E, De Wet GH and Pattinson RC (1995) Randomized clinical trial of medical expulsion and surgical curettage for incomplete miscarriage. *Br Med J* 311,662.
- El-Refaey H, Hinshaw K, Henshaw R, Smith N and Templeton A (1992) Medical management of missed abortion and anembryonic pregnancy. *Br Med J* 305,1399.
- El-Refaey H, Rajasekar D, Abadía M, Calder L and Templeton A (1995) Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. *N Engl J Med* 332,983–988.
- Gilles J, Creinin MD, Barnhart K, Westhoff C, Frederick M and Zhang J (2004) A Randomized trial of saline moistened versus dry misoprostol for first trimester pregnancy failure. *Am J Obstet Gynecol* 190,389–394.
- Muffley PE, Stitely ML and Gherman RB (2002) Early intrauterine pregnancy failure: a randomized trial of medical versus surgical treatment. *Am J Obstet Gynecol* 187,321–326.
- Peyron R, Aubeny E, Targosz V, Silvestre L, Renault M, Elvik F, Lelerc P, Ulmann A and Baulieu EE (1993) Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol. *N Engl J Med* 328,1509–1513.
- Wood SL and Brain PH (2002) Medical management of missed abortion: a randomized clinical trial. *Am Coll Obstet Gynecol* 99,563–566.

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