

Original research article

Two routes of administration for misoprostol in the treatment of incomplete abortion: a randomized clinical trial[☆]

Ayisha Diop^{a,*}, Sheila Raghavan^a, Jean-Pierre Rakotovo^b, Rodica Comendant^c, Paul D. Blumenthal^d, Beverly Winikoff^a

^aGynuity Health Projects, New York, NY 10010, USA

^bBefelatanana Maternity Centre, 101 Antananarivo, Madagascar

^cMunicipal Clinical Hospital No. 1, 2001 Chisinau, Moldova

^dStanford University Medical Center, Palo Alto, CA 94305, USA

Received 13 June 2008; revised 26 November 2008; accepted 27 November 2008

Abstract

Background: This study was conducted to compare the safety, effectiveness and acceptability of 400 mcg sublingual misoprostol and 600 mcg oral misoprostol for treatment of incomplete abortion.

Study Design: We used an open-label randomized controlled trial conducted from July 2005 to August 2006 in a large tertiary level maternity hospital in Antananarivo, Madagascar, and a large tertiary level hospital in Chisinau, Moldova. Three hundred consenting women seeking treatment for clinically diagnosed incomplete abortion with uterine size ≤ 12 weeks since last menstrual period were randomized to misoprostol either 600 mcg orally or 400 mcg sublingually. The primary outcome measure was the complete resolution of clinical signs and symptoms of incomplete abortion without need for surgical intervention. Women were seen for follow-up on Day 7 and, if necessary, on Day 14 to assess abortion status. The study was powered to detect a 7% difference in efficacy with a total of 142 women required in each arm.

Results: Efficacy rates were 94.6% and 94.5%, for the oral and sublingual routes, respectively (RR: 1.00, 95% CI=0.95–1.06, $p=.98$). At 1 week follow-up, more than 80% of women had completed abortions (77.8% oral and 84.8% sublingual, $p=.12$). Mean pain scores were 2.95 and 3.04, respectively, for the oral and sublingual groups. Side effects included abdominal pain, bleeding, headaches and dizziness/weakness with no differences reported between the two groups. Acceptability and satisfaction were high for both routes and women indicated a preference for medical versus surgical treatment if ever needed in the future.

Conclusions: Both treatment regimens were very effective. Four hundred micrograms of sublingual misoprostol and 600 mcg oral misoprostol appear to have similar safety and effectiveness profiles when used for the treatment of incomplete abortion. A lower 400-mcg misoprostol dose may provide an alternative treatment option as well as have potential benefits in terms of cost.

© 2009 Elsevier Inc. All rights reserved.

Keywords: Misoprostol; Sublingual; Incomplete abortion; Postabortion care

1. Introduction

Misoprostol is a proven nonsurgical alternative for treatment of incomplete abortion [1–16]. Numerous studies have established the safety, acceptability and effectiveness of a single 600-mcg oral dose [9–16]. This dose is between 94.5% and 99.0% effective with acceptable side effects and

high patient satisfaction. Effectiveness rates are similar to those for manual vacuum aspiration (MVA) treatment, which range from 91.5% to 100% [13–16].

While oral misoprostol administration works very well, we surmised that a lower sublingual dose may be as effective as a higher oral dose based on pharmacokinetic studies showing that sublingual administration may result in higher, more sustained serum levels [17]. The sublingual route has been explored for treating missed abortion [18–21] but has not been studied for treating symptomatic incomplete abortion. Our study was designed to address this knowledge gap, comparing 600 mcg oral misoprostol to the lower 400-

[☆] This study was made possible by an anonymous donor.

* Corresponding author. Tel.: +1 212 448 1230; fax: +1 212 448 1260.

E-mail address: adiop@gynuity.org (A. Diop).

mcg sublingual dose of misoprostol, which promises an alternative, less expensive regimen.

Because oral administration has been considered more convenient and less uncomfortable than vaginal dosing, numerous studies have focused solely on oral administration [8–12]. Four studies compared a single 600-mcg oral dose of misoprostol to surgery (MVA or dilation and curettage) for the treatment of incomplete abortion, with an efficacy of more than 94% [13–16]. Other studies have examined a lower 400-mcg dose of oral misoprostol with varying results, depending on inclusion criteria and the visit schedule for evaluation of evacuation of the uterus [1,22]. In the largest study using 400 mcg oral misoprostol, Coughlin et al. [12] found that complete abortion was achieved in 77.1% of 131 women after a single 400-mcg oral misoprostol dose, increasing to 92% with a repeat dose. Based on the literature, the 400-mcg oral regimen appears to have a lower efficacy rate than the established 600-mcg oral dose.

A 400-mcg sublingual dose, on the other hand, may maintain the advantages of a 600-mcg oral dose and result in fewer side effects. This dose of sublingual misoprostol has been used to treat missed abortion and studied in early medical abortion [21,23–26]. A range of sublingual misoprostol doses (400 to 800 mcg) after mifepristone has resulted in a success rate of more than 98% for termination of early pregnancy [25,26]. Given its successful use for other indications, the 400-mcg sublingual dose appears to hold considerable promise in the treatment of incomplete abortion, but since no published data exists for this regimen compared to other doses or routes, we undertook this regimen randomized clinical trial to better define the potential utility of this regimen.

2. Materials and methods

Three hundred women presenting with incomplete abortion were enrolled at the Befelatanana Maternity Centre in Antananarivo, Madagascar, and Municipal Clinical Hospital No. 1 in Chisinau, Moldova, from July 2005 to August 2006. Women with a clinical diagnosis of incomplete abortion assessed by an open cervical os with past or present history of vaginal bleeding during the current pregnancy were eligible to participate in the study. Women included in the study also had a uterine size equal to or smaller than 12 weeks since last menstrual period. For women who underwent ultrasound examination, incomplete abortion was confirmed by evidence of retained products in the uterus based on the site's standard practice. Additional eligibility criteria included age over 18 in Moldova; if under 18, parental consent was needed, in Madagascar. Women were required to live or work within 1 h of the study site and provide informed consent, documented by signature or thumbprint. All participants were advised of the alternate option of surgical evacuation, the standard practice at both hospitals. Women were excluded if they presented with signs

of severe infection or ill health or were unwilling to provide contact information for follow-up.

All consenting women were randomized to a dose of 600 mcg misoprostol orally or 400 mcg misoprostol sublingually (GyMiso[®], HRA Pharma, Paris, France) under the supervision of a study nurse. Cards labeled with the assigned dose and route were placed in sealed, opaque envelopes, allocated according to a computer-generated random number scheme. Study staff in New York prepared the randomization scheme, and numbers were assigned using a randomized design in blocks of 10 to ensure equal study group allocation. Following misoprostol administration, women remained under observation for approximately 2 h, during which time side effects were documented. Women were not given antibiotics routinely. They were provided two tablets of 500 mg acetaminophen for pain management.

Each woman was given an appointment to return to the hospital in 1 week to assess the status of her incomplete abortion by clinical examination and/or ultrasound. Success was defined as complete evacuation of the uterus, without recourse to surgical intervention. The providers were encouraged to use clinical judgment alone in their assessment. If signs and symptoms of incomplete abortion had resolved, the woman was discharged from the study. If there was evidence of retained products of conception in the uterus, based on the clinical examination or ultrasound, the woman was given the option of waiting an additional week to see if the products would evacuate or an immediate surgical completion. If the woman chose to wait, a second follow-up visit was scheduled for approximately 1 week later, that is, 2 weeks after enrollment. If there was still evidence of retained products in the uterus at the second follow-up visit, the woman was offered an immediate surgical completion. Data were recorded at each of these visits.

If, for any reason, a woman failed to return to the hospital for follow-up, study staff made attempts to trace her by phone or a home visit. During any attempted contact, confidentiality was maintained, including reasons for contact. Throughout the study, participants were free to return to the hospital or contact study staff by phone at any time for any reason related to their care. Women in both countries were given small monetary compensation for their time and travel for study purposes. The primary outcome measure was complete resolution of signs/symptoms of incomplete abortion without recourse to surgery at any point for any reason. At the follow-up visits, data on secondary outcome measures, including self-reports on acceptability, side effects and pain, were collected. Satisfaction and side effects with the method were measured with 4-point Likert scales [27]. Assessment of satisfaction ranged from *very satisfied* to *very dissatisfied*, and side effects were rated from *easily tolerable* to *very severe*. Pain was also assessed with a visual analog scale, representing a 7-point Likert scale, developed by the study team in which seven circles ranging in size from small (*no pain*) to large (*intense pain*) were used.

Data on side effects, which included documentation of heavy bleeding, fever, chills, nausea, vomiting and abdominal pain, were collected during the 2-h observation period after misoprostol administration. In Moldova, women also recorded on a diary card at home all side effects experienced during the week between the medication and the follow-up visit. Women in Madagascar were not asked to complete a side effects diary. In both sites, women were queried about their experiences at the follow-up visit.

All data were entered in Epi Info (version 3.3.2) and subsequently cleaned and analyzed using the Statistical Package for the Social Sciences, Version 15.0. Chi-square tests were used for comparison of outcome measures, and values $\leq .05$ were considered statistically significant. *t* tests were used to compare mean values. Assuming a 97% efficacy rate for treatment with 600 mcg oral misoprostol, the study was designed as a one-sided test to have an 80% power with an α of .05 to detect whether the 400-mcg sublingual

misoprostol route was no less than 7% as effective. One hundred forty-two women were needed in each arm to achieve the desired sample.

The Ethical Committee of the Ministry of Health and Family Planning of Madagascar approved the protocol and the consent form, which was translated into Malagasy. In Moldova, the hospital ethical committee reviewed and approved the relevant documents, all of which were translated into Romanian and Russian. The protocol was also approved by the United States-based Western Institutional Review Board.

3. Results

Three hundred eligible women, 200 from Madagascar and 100 from Moldova, were randomized for administration of 600 mcg oral misoprostol or 400 mcg sublingual misoprostol

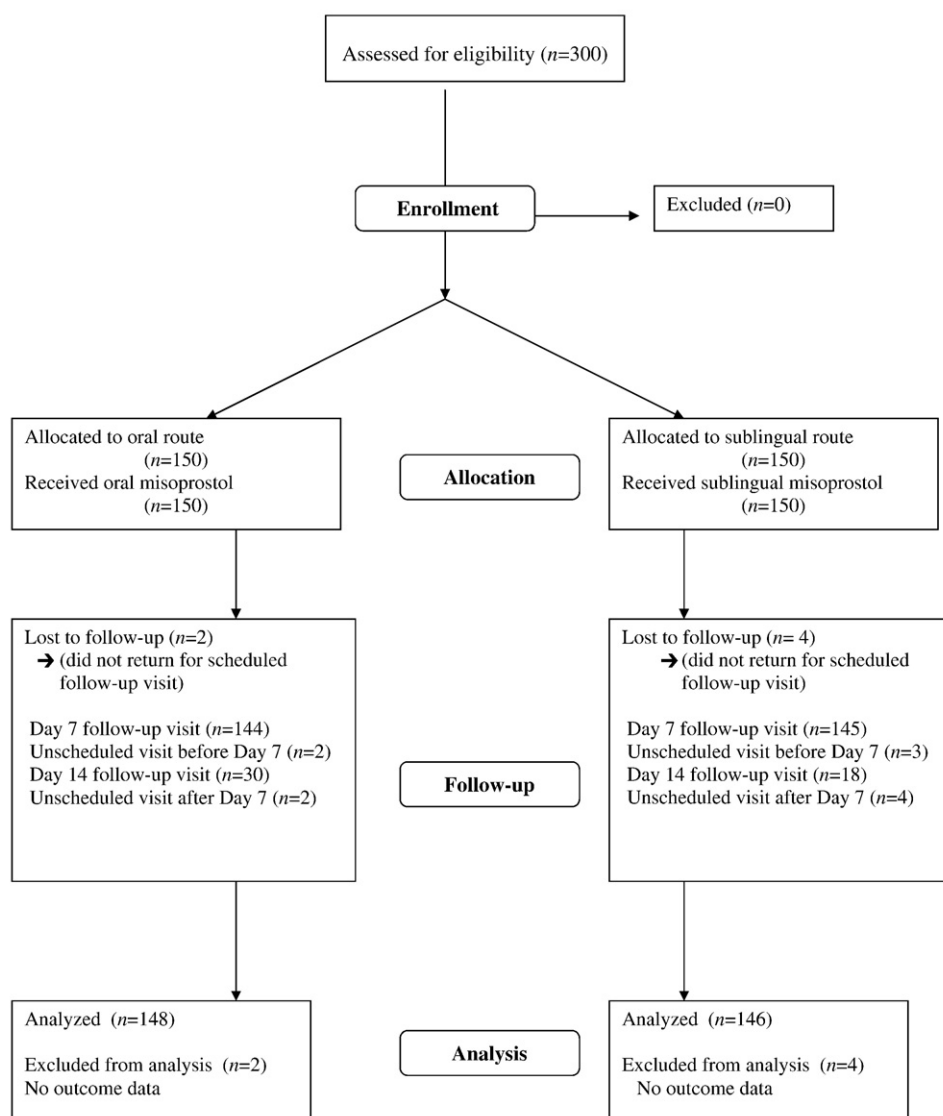


Fig. 1. Consort flow chart.

Table 1
Participant characteristics

	Oral (n=150)	Sublingual (n=150)	p value
Age, in years, mean±SD (range)	29.3±6.24 (16–46)	28.7±6.63 (15–48)	.46
Married women, % (n)	42.0 (63)	49.3 (74)	.20
Years of education, mean±SD	10.1±3.01	10.5±2.84	.22
Parity >1, % (n)	69.3 (104)	74 (111)	.37
Previous induced abortion reported (at least 1), % (n)	35.2 (51/145)	28.9 (42/145)	.26
A previous spontaneous abortion reported, % (n)	35.6 (52/146)	26.7 (40/150)	.09
Women's report that current abortion was induced, % (n)	5.3 (8)	11.3 (17)	.06
Suspected induced abortion, % (n)	29.3 (44)	32.7 (49)	.53

There are no statistically significant differences in the characteristics of women in the two study groups. All available data for the six women lost to follow-up are included in this table.

for treatment of incomplete abortion. Ultrasound was not routinely used for diagnosis (29.3% oral and 26.7% sublingual, $p=.44$). All women received the allocated route of misoprostol; however, two women in the oral arm and four women in the sublingual arm were lost to follow-up. Calls were made to follow up with five of these six women. Incomplete contact information was on file for the sixth woman. They were all last seen at their initial visits. All other women completed the protocol and are included in the analysis (Fig. 1).

3.1. Participant characteristics

The study groups were examined for differences in physical and sociodemographic characteristics (Table 1). No differences were noted between treatment arms, but there were differences between sites. Significantly more women in Moldova were married (76% vs. 31%, $p\leq.001$) with 59% of women reporting having had a previous induced abortion (a question not asked in Madagascar, where induced abortion is highly restricted and usually clandestine). Twelve percent of women in Madagascar reported inducing their abortions, although providers suspected self-induction for nearly half of the women. None of the women in Moldova reported self-

induction, with providers also evaluating that abortion was spontaneous in all cases.

3.2. Efficacy

The method was 94.6% and 94.5% effective (RR=1.00, 95% CI=0.95–1.06) for the oral and sublingual groups, respectively. There were eight failures in each group (Table 2). Of the women returning for their 1-week follow-up visits, 84.8% ($n=123$) in the sublingual group and 77.7% ($n=112$) in the oral group ($p=.124$) had complete abortions according to the clinical staff (nurses in Madagascar and doctors in Moldova). Forty-eight women returned for a second follow-up visit ($n=30$ oral; $n=18$ sublingual), of which 93.3% ($n=28$) in the oral group and 88.8% ($n=16$) in the sublingual group had completed abortions ($p=.59$). A large majority of women correctly assessed their abortions as complete (97.3% oral; 99.2% sublingual); 94.3% of women with an incomplete or uncertain status also correctly assessed their status at the first follow-up visit. The reasons most cited underlying the self-assessment of complete abortion were “no more bleeding” (62.9%) and “expulsion observed” (50.5%). Compliance with the study procedures was high, and nearly all women (96.3%) returned for their scheduled 1-week follow-up visit. Of those given a second appointment, 48 of 49 women returned as scheduled. The six women who were lost to follow-up never returned after the initial visit.

Ultrasound was used to determine abortion status after treatment for 2.5% of women in Madagascar ($n=5$) and 32.6% in Moldova ($n=31$). Of the women for whom ultrasound was used, 11.1% were for women who were treated with oral misoprostol and 13.8% were for women treated with sublingual misoprostol ($p=.49$). The remaining assessments were clinical.

Four hospitalizations were reported, one in each arm at each of the sites. All these women experienced very heavy bleeding and returned to the hospital where they were initially treated. A surgical completion with MVA was performed in each case. No blood transfusion or other treatment was necessary. All four women were released in good condition.

Table 2
Efficacy

	Oral, % (n)	Sublingual, % (n)	Statistical data
Lost to follow-up	1.3 (2/150)	2.7 (4/150)	$p=.41$
Overall success rate ^a	94.6 (140/148)	94.5 (138/146)	$p=.98$
Failure rate ^a	5.4 (8/148)	5.5 (8/146)	$p=.98$
Type of failure			
Incomplete abortion at study end	1.4 (2/148)	2.1 (3/146)	$p=.64$
Medically indicated surgical completion before study end	2.7 (4/148)	1.4 (2/146)	$p=.42$
Surgical completion, provider or woman's choice	1.4 (2/148)	2.1 (3/146)	$p=.64$

^a Does not include women lost to follow-up.

3.3. Side effects and bleeding

Approximately two thirds of the women reported abdominal pain with no difference between groups (62.6% oral; 67.3% sublingual). Similarly, there was no difference in reports of bleeding (24% oral; 26% sublingual), nausea (18.7% oral; 13.3% sublingual) and vomiting (1.3% oral; 1.3% sublingual). Other side effects during the observation period were rare and included headaches (1%) and dizziness/weakness (1%). Women's report of bleeding and side effects following treatment with misoprostol are shown in Table 3A and B.

Though there were no differences in side effects associated with route, several differences were found in reports between the two sites. Significantly more women in Moldova reported experiencing fever/chills, nausea, vomiting and abdominal pain during the observation period. While less than 1% of women in Madagascar reported experiencing nausea or vomiting, 48% of women in Moldova reported experiencing one or both ($p < .001$). Similarly, 3.5% of women in Madagascar reported fever or chills compared to 22% of women in Moldova ($p < .001$). In all cases, these side effects were short-lived, lasting on average less than 2 days.

Eight women (5.4%) in the oral arm returned to the clinic for an unscheduled visit for reasons of abdominal pain ($n=3$), heavy bleeding ($n=2$), anxiety ($n=1$) and feeling faint ($n=1$) and to request a surgical intervention ($n=1$). In the sublingual arm, 10 women (6.8%) returned for an unscheduled visit due to heavy bleeding ($n=4$), fever ($n=3$) and abdominal pain ($n=3$).

3.4. Satisfaction

Women in both groups were equally satisfied with the treatments they received. The large majority of the women reported being either satisfied or very satisfied with their treatments, with no differences between groups (98.0% oral; 97.2% sublingual, $p=.67$). All of the women who reported dissatisfaction experienced method failure and were given a surgical completion. Most women in both groups also reported that, if needed, they would choose the method again (77.6% oral; 71.5% sublingual, $p=.24$) and would recommend the method to a friend (94.6% oral; 95.2% sublingual, $p=.81$). Among women having had a previous surgical evacuation for an incomplete abortion ($n=79$), 75.6% in the

Table 3

Women's reports of bleeding and side effects (A) in the 2 h following treatment with misoprostol and (B) during interval from discharge to follow-up visit

	Oral	Sublingual	p value
A			
% reported (n) ^a			
Heavy bleeding (>period)	24.0 (36/150)	26.0 (39/150)	.69
Nausea	18.7 (28/150)	13.3 (20/150)	.21
Vomiting	1.3 (2/150)	1.3 (2/150)	1.0
Pain/Cramps	62.6 (94/150)	67.3 (101/150)	.39
Fever or chills	8.0 (12/150)	11.3 (17/150)	.33
Adequate pain medication, % (n)			
Yes	73.5 (108/147)	81.9 (118/144)	.08
Would have liked stronger pain medication ^b , % (n)			
No	97.3 (36/37)	100.0 (25/25)	
Mean pain score ^c	2.95	3.04	
Pain compared to previous surgical evacuation			
for incomplete abortion, % (n)			
More painful	15.6 (7/44)	17.6 (6/33)	.80
Same amount of pain	6.7 (3/44)	8.8 (3/33)	.72
Less painful	75.6 (34/44)	64.7 (22/33)	.29
Experience compared to previous surgical evacuation			
for incomplete abortion, % (n)			
Better	95.6 (43/44)	85.3 (29/33)	.11
Same	2.2 (1/44)	8.8 (3/33)	.19
Worse	2.2 (1/44)	2.9 (1/33)	
Not sure	0.0 (0)	2.9 (1/33)	
B			
% reported (n) [mean days] ^d			
Heavy bleeding (>period)	36.0 (18) [1.1]	40.0 (20) [1.2]	.68
Nausea	64.0 (32) [1.2]	48.0 (24) [1.2]	.11
Vomiting	10.0 (5) [1.0]	8.0 (4) [1.3]	.73
Pain/Cramps	92.0 (46) [1.9]	86.0 (43) [2.1]	.33
Fever or chills	36.0 (18) [1.4]	44.0 (22) [1.4]	.41

^a % reported — for women who reported experiencing symptom during the 2-h observation period.

^b Data only from women who reported that they were not given sufficient pain medication.

^c Ranked from 1 to 7 for increasing levels of pain.

^d % data from women using take home study card — reports for women experiencing at least one day of symptom. Moldova data only.

oral and 64.7% in the sublingual group found the misoprostol experience to have been better or less painful than the surgical experience (Table 3A).

Most women, 73.5% and 81.9% in the oral and sublingual groups, respectively, found that the 500 mg of paracetamol they received was sufficient to manage pain (Table 3A). Mean pain scores were 2.95 and 3.04 for the oral and sublingual groups, respectively (Table 3A). Only one woman reported that she would have liked to have stronger medication. A significantly higher percentage of women in Moldova reported experiencing pain (96.0% vs. 49.5% in Madagascar, $p < .001$), although 97.9% ($n = 93$) of Moldovan participants found their pain relief medicine to be adequate.

4. Discussion

Our study suggests that misoprostol is effective and acceptable to women whether administered as a dose of 600 mcg orally or 400 mcg sublingually. Of the 300 participants in this study, fewer than 6% in each group required surgical evacuations; moreover, there were few complications. The reported high levels of satisfaction are in agreement with findings in the published literature [13–16]. In studies with similar eligibility criteria, women who received 600 mcg of oral misoprostol for treatment of incomplete abortion had success rates ranging from 91% to 99% [13–16]. In addition, these studies showed similarly high rates (96.4% to 99%) of women who reported being satisfied or very satisfied with a significantly higher percentage of women reporting being very satisfied when compared to previous experiences with MVA [14–16].

In comparing the two routes, our study documented similar side effect profiles for both routes with no significant differences. There were, however, striking differences in the reports of side effects from the two study sites. Nonetheless, for both sites and both routes, women reported the side effects as tolerable and almost unanimously found the pain medication to be adequate. The acceptability of pain and discomfort levels accords with other published studies comparing the misoprostol treatment with MVA where pain scores were significantly lower in the misoprostol arms [13–16] and women who took misoprostol were more likely to mention “less pain” or the “absence of pain” as a best feature of the method [13,14,16] as compared to women who underwent MVA procedures. Our findings for the 400-mcg sublingual dose are similar to what has been confirmed for the 600-mcg orally administered dose.

Evidence from the study supports the use of misoprostol for treatment of incomplete abortion at lower levels of the health care system. In Madagascar, nurses (who provide the majority of women’s health services) were able to successfully diagnose and manage cases of incomplete abortion, with little to no assistance from a physician. Furthermore, though providers had access to ultrasound, its use was limited. Complete abortion status was determined via history

and clinical exam in most cases. When asked, providers in Madagascar felt that ultrasound may have been useful in 3% ($n = 6$) of the cases, confirming that misoprostol can appropriately and effectively be used in settings where ultrasound is not readily available or is too expensive [14,16]. Even in Moldova, where ultrasound use is fairly common, it was only used at follow-up for 32% of cases. No difference in outcome was found based on the use of ultrasound for assessment.

Although clinical diagnosis of incomplete abortion and determination of treatment success relied largely on provider judgment, thereby leading to potential misclassifications, these cases would have been randomized evenly to both arms. The criteria used to diagnose cases in this study are not any different for women seeking surgical treatment at these sites and, moreover, reflect the reality of services provided in many settings worldwide.

Additionally, the present study provides data supporting the use of misoprostol for this indication in two very different settings. In Moldova, all cases were reported and confirmed as being spontaneous, while in Madagascar, 88% of women reported having had a spontaneous abortion while providers believed that 73.1% of these cases had originally been induced. Nevertheless, regardless of the cause of incomplete abortion, efficacy rates were high in both contexts (93.4% in Madagascar and 96.9% in Moldova) with no significant differences when comparing women suspected of having induced their abortion to women with spontaneous abortions (spontaneous, 96.0%; induced, 91.3%). As noted by Gemzell-Danielsson et al. [28], misoprostol for the treatment of incomplete abortion is a suitable option for all women, whether provided in a context where abortion is highly restricted or where abortion is legal.

This study was conducted in two large maternity hospitals located in capital cities. Additional data from nontertiary care settings may provide useful insight into “real world” service delivery, now that an alternative dose has been established. Only 2% of cases in this study were lost to follow-up in part because women unable or unwilling to return for follow-up care were not offered enrollment in the study. The issue of return for follow-up is of practical concern, and in the real world, women who are unable or unwilling to return should not necessarily be denied this safe and effective treatment. Our data suggest that provided with sufficient information on treatment, expected side effects and warning signs, women are capable of recognizing clinical signs that necessitate a return to the clinic. Moreover, these data clearly establish that the overwhelming majority of women are able to predict their abortion status correctly as either complete or possibly incomplete. With proper information and support from providers, it is likely that women with legitimate concerns can and will seek out further care until successfully treated. This is all the more plausible in the context of postabortion care where women receiving treatment have already identified clinical signs and initiated the health-seeking process. Additional studies could further examine certain service

delivery aspects, in particular the option of eliminating the required follow-up visit for most women. Such data would be instrumental for developing guidelines to expand access and availability to the method where the need is most acute.

Misoprostol offers a promising alternative to standard surgical evacuation and MVA, because it is effective, easily tolerated by women and can be provided by practitioners without surgical skills. New data demonstrating that a lower 400-mcg sublingual regimen is as effective and acceptable as the previously established 600-mcg oral regimen may further increase access to this treatment by providing an alternative treatment option and expand the availability of services for this indication in Madagascar and Moldova as well as other low-resource countries. These findings are of particular importance looking towards the use of misoprostol as first-line treatment for incomplete abortion in rural areas and in other areas where services are sparse and resources are especially constrained.

Acknowledgments

The authors would like to thank all the women who participated in this study and each of the local investigators who provided their care, particularly Charline Raveloarisoa, Pierrette Razananary and Fenoarisoa Randrianantoanina at the Befelatanana Maternity in Antananarivo, Madagascar, and Irena Digol, Sergiu Ungureanu, Stelian Hodoroaga and Valentin Friptu at the State Medical and Pharmacy University in the Republic of Moldova.

References

- [1] de Jonge ET, Makin JD, Manefeldt E, De Wet GH, Pattinson RC. Randomized clinical trial of medical evacuation and surgical curettage for incomplete miscarriage. *BMJ* 1995;311:662.
- [2] Gronlund L, Gronlund AL, Clevin L, Andersen B, Palmgren N, Lidegaard O. Spontaneous abortion: expectant management, medical treatment or surgical evacuation. *Acta Obstet Gynecol Scand* 2002;81:781–2.
- [3] Bagratee JS, Khullar V, Regan L, Moodley J, Kagoro H. A randomized controlled trial comparing medical and expectant management of first trimester miscarriage. *Hum Reprod* 2004;19:266–71.
- [4] Demetroulis C, Saridogan E, Kunde D, Naftalin A. A prospective randomized control trial comparing medical and surgical treatment for early pregnancy failure. *Hum Reprod* 2001;16:365–9.
- [5] Moodliar S, Bagratee JS, Moodley J. Medical vs. surgical evacuation of first-trimester spontaneous abortion. *Int J Gynecol Obstet* 2005;91:21–6.
- [6] Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. National Institute of Child Health Human Development (NICHD) Management of Early Pregnancy Failure Trial. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. *N Engl J Med* 2005;353:761–9.
- [7] Shelley JM, Healy D, Grover S. A randomized trial of surgical, medical and expectant management of first trimester spontaneous miscarriage. *Aust N Z J Obstet Gynecol* 2005;45:122–7.
- [8] Blanchard K, Taneepanchskul S, Kiriwat O, et al. Two regimens of misoprostol for treatment of incomplete abortion. *Obstet Gynecol* 2004;103:860–5.
- [9] Ngoc NTN, Blum J, Durocher J, Quan TTV, Winikoff B. A randomized controlled study comparing 600 versus 1200 mcg oral misoprostol for medical management of incomplete abortion. *Contraception* 2005;72:438–42.
- [10] Phuphong V, Taneepanchskul S, Kriengsinyot R, Sriyirojana N, Blanchard K, Winikoff B. Comparative study between single dose 600 mcg and repeated dose of oral misoprostol for treatment of incomplete abortion. *Contraception* 2004;70:307–11.
- [11] Pandian Z, Ashok P, Templeton A. The treatment of incomplete miscarriage with oral misoprostol. *Brit J Obstet Gynecol* 2001;108:213–4.
- [12] Coughlin LB, Roberts D, Haddad NG, Long A. Medical management of first trimester incomplete miscarriage using misoprostol. *J Obstet and Gynaecol* 2004;24:67–8.
- [13] Weeks A, Alia G, Blum J, et al. A randomized trial of oral misoprostol versus manual vacuum aspiration for the treatment of incomplete abortion in Kampala, Uganda. *Obstet Gynecol* 2005;106:540–7.
- [14] Dao B, Blum J, Thieba B, et al. Is misoprostol a safe, effective, acceptable alternative to manual vacuum aspiration for post abortion care? Results from a randomized trial in Burkina Faso, West Africa. *BJOG* 2007;114:1368–75.
- [15] Shwekerea B, Kalumuna R, Kipingili R, et al. Misoprostol for treatment of incomplete abortion at the regional hospital level: results from Tanzania. *BJOG* 2007;114:1363–7.
- [16] Bique C, Ustá M, Debora B, Chong E, Westheimer E, Winikoff B. Comparison of misoprostol and manual vacuum aspiration for the treatment of incomplete abortion. *Int J Gynecol Obstet* 2007;98:222–6.
- [17] Tang OS, Schweer H, Seyberth HW, Lee SW, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. *Hum Reprod* 2002;17:332–6.
- [18] Tang OS, Lau WNT, Ng EH, Lee SW, 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.
- [19] Wagaarachchi PT, Ashok PW, Smith NC, Templeton A. Medical management of early fetal demise using sublingual misoprostol. *BJOG* 2002;109:462–5.
- [20] Ayudhaya O, Herabutya Y, Chanranchakul B, Ayudhaya N, Prasertsawat P. A comparison of the efficacy of sublingual and oral misoprostol 400 microgram in the management of early pregnancy failure: a randomized controlled trial. *J Med Assoc Thai* 2006;89(suppl 4):S5–S10.
- [21] Sharma D, Singhal SR, Rani XX. Sublingual misoprostol in management of missed abortion in India. *Trop Doct* 2007;37:39–40.
- [22] Henshaw RC, Cooper K, El-Refaei H, Smith NC, Templeton AA. Medical management of miscarriage: non-surgical uterine evacuation of incomplete and inevitable spontaneous abortion. *BMJ* 1993;306:894–5.
- [23] Bhattacharjee N, Saha SP, Ghoshroy SC, Bhowmik S, Barui G. A randomised comparative study on sublingual versus vaginal administration of misoprostol for termination of pregnancy between 13 to 20 weeks. *Aust N Z J Obstet Gynaecol* 2008;48:165–71.
- [24] Mundle S, Elul B, Anand A, Kalyanwala S, Ughade S. Increasing access to safe abortion services in rural India: experiences with medical abortion in a primary health center. *Contraception* 2007;76:66–70.
- [25] Hamoda H, Ashok PW, Flett GM, Templeton A. A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation. *BJOG* 2005;112:1102–8.
- [26] Tang OS, Chan CC, Kan AS, Ho PC. A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12–20 weeks gestation. *Hum Reprod* 2005;20:3062–6.
- [27] Likert R. A technique for the measurement of attitudes. *Arch Psychol* 1932;140:5–53.
- [28] Gemzell-Danielsson K, Fiala C, Weeks A. Misoprostol: first-line therapy for incomplete miscarriage in the developing world. *BJOG* 2007;114:1337–9.