DOI: 10.1111/j.1471-0528.2007.01469.x
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Misoprostol for treatment of incomplete abortion at the regional hospital level: results from Tanzania

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Accepted 10 January 2007. Published OnlineEarly 5 September 2007.

Objective To investigate the safety, efficacy, and acceptability of misoprostol versus manual vacuum aspiration (MVA) for treatment of incomplete abortion.

Design A prospective open-label randomised trial.

Setting Kagera Regional Hospital, Bukoba, Tanzania.

Sample Three hundred women with a clinical diagnosis of incomplete abortion and a uterine size <12 weeks.

Methods A total of 150 women were randomised to either a single dose of 600 micrograms of oral misoprostol or MVA. If abortion was clinically complete at 7-day follow up, the woman was released from the study. If it was still incomplete, the woman was offered the choice of an additional 1-week follow up or immediate MVA. Cases still incomplete after a further week were offered MVA.

Main outcome measures Incidence of successful abortion (success defined as no secondary surgical intervention provided), incidence of adverse effects, patient satisfaction.

Results Success was very high in both arms (misoprostol: 99%; MVA: 100%; difference not significant). Most adverse effects were higher in the misoprostol arm, although the mean pain score was higher in the MVA arm (3.0 versus 3.5; $P < 0.001$). More women were very satisfied with misoprostol (75%) than with MVA (55%, $P = 0.001$), and a higher proportion of women in the misoprostol arm said that they would recommend the treatment to a friend (95% versus 75%, $P < 0.001$).

Conclusion Misoprostol is as effective as MVA at treating incomplete abortion at uterine size of <12 weeks. The acceptability of misoprostol appears higher. Given the many practical advantages of misoprostol over MVA in low-resource settings, misoprostol should be more widely available for treatment of incomplete abortion in the developing world.

Keywords Incomplete abortion, miscarriage, misoprostol, rural health, Tanzania.

Please cite this paper as: Shwekerela B, Kalumuna R, Kipingili R, Mashaka N, Westheimer E, Clark W, Winikoff B. Misoprostol for treatment of incomplete abortion at the regional hospital level: results from Tanzania. BJOG 2007;114:1363–1367.

Introduction

The failure of early pregnancy is among the most widely experienced medical conditions in the world. Up to 20% of recognised pregnancies miscarry, and perhaps 25% of women will experience a miscarriage at some point in their lives. Beyond this, however, there are approximately 46 million induced abortions worldwide each year. Many of these are performed under unsafe conditions, often in countries where abortion is illegal. Unsafe abortion is estimated to lead to 78 000 deaths per year,[1] with many times that number of women experiencing serious morbidity.

Both spontaneous and induced abortions (between which it is often difficult or impossible to distinguish in the clinic) can lead women to seek care at health facilities. Not surprisingly, these women make up a major part of the obstetric patient load. At Kagera Regional Hospital in Bukoba, Tanzania, where this study was conducted, unpublished hospital data reveal that incomplete abortion constitutes 39% of all admissions to the gynaecological ward. Finding safe, effective, acceptable, and affordable means of treating incomplete abortion is therefore a priority, especially for facilities in low-resource settings.

Until recently, the treatment for incomplete abortion has usually been surgery of some kind (dilatation and curettage [D + C] or manual vacuum aspiration [MVA]). While these treatments are effective, they require specialised equipment and skills. Furthermore, they subject the woman to the

dangers attendant on a surgical procedure—trauma, perforations, infections, bleeding due to instrumentation, and reactions to anaesthesia, among others. For these reasons, determining an effective nonsurgical approach to treatment is a priority.

Some studies have indicated that expectant management is effective in most cases of incomplete abortion.[2–4] However, the particulars of low-resource settings may reduce the attractiveness of this option:[5] if women live in a long distance from medical facilities and do not have access to dependable transportation, they may be required to remain at the hospital for an extended period, which can be inconvenient and costly for both patient and facility. And particularly in some parts of sub-Saharan Africa, where many women may be immunocompromised due to HIV infection, the risk of sepsis argues against a lengthy period of waiting. Finally, in all settings, women may be anxious to feel like the abortion process is 'finished' so that they can get this generally painful event behind them. Such women may not want to 'wait and watch'.

Many studies[6–20] have indicated that the uterotonic and cervical ripening properties of the prostaglandin E1 analogue misoprostol make it a safe and highly effective method of evacuating the uterus in cases of incomplete abortion. All research on misoprostol for this indication to date, however, has taken place either in developed or middle-income countries[7–19] or in the capital cities of developing countries at major, tertiary care facilities.[6,20] Misoprostol's stability at room temperature and low cost could make it an ideal treatment in low-resource settings, as well, should it prove safe and effective in such locales. The present study was designed to fill an important gap in the research by testing misoprostol for incomplete abortion at a regional hospital with a large rural catchment area in a low-income country.

The 600 micrograms dose and oral route of misoprostol administration were chosen on the basis of two earlier dose-finding studies conducted in Thailand and Vietnam[16,20] and a further recent large study in Kampala, Uganda.[6] Two of these,[6,20] which achieved the highest success rates reported by a large study to date (≥95%), used a single 600 micrograms oral dose of misoprostol, the same dose we use here. While some studies of misoprostol for incomplete abortion have employed the vaginal route of administration,[10,12–15,17–19] the majority of such studies have employed the oral route.[6–9,11,12,14,16,20] Furthermore, there are women who find vaginal administration more invasive and less acceptable than oral use, and there is an unconfirmed possibility that this route may be associated with greater rates of infection. Given that the studies cited above suggest that excellent results can be achieved with oral administration as well, we chose to employ this route here.

Methods

This was an open randomised trial to compare the efficacy, safety, and acceptability of misoprostol and MVA (the established standard of care) for treatment of incomplete abortion. A total of 300 women in the Kagera Region who were diagnosed with incomplete abortion were randomised to receive either 600 micrograms of oral misoprostol in one dose or standard surgical treatment (MVA).

Randomisation was performed by computer-generated random code, created in blocks of ten at Gynuity Health Projects' office in New York City. The code was used by a Gynuity employee who was not part of the research team as a basis for sealing cards in consecutively numbered envelopes; the cards read either 'Misoprostol' or 'MVA'. When a new participant was enrolled in the study, site staff would open the next envelope in the numbered series and the woman would receive the treatment specified therein.

All women who presented to the study site (Kagera Regional Hospital) with confirmed eligible incomplete abortion and who lived and worked within 1 hour of the hospital were invited to participate in this study. An eligible incomplete abortion was diagnosed when all of the following criteria were met:

1 Past or present history of bleeding during this pregnancy.
2 Cervical os open by visual/digital inspection.
3 Uterine size of no greater than 12 weeks since last menstrual period (LMP).
4 Woman in generally good health.
5 Woman willing to return for follow up.

Women were excluded if they had signs of severe infection (foul-smelling discharge, fever > 39°C, or pulse > 110/minute) or a known allergy to misoprostol.

Women who met the above requirements were given a full description of the study and asked if they would like to participate. Those who gave written informed consent were randomly assigned to one of the two study regimens using sequentially numbered envelopes. Women who were unable to read the consent form had the form read to them in their native language. Those who did not wish to participate were given standard treatment and care.

All women were observed at Kagera Regional Hospital for a maximum of 3 hours after treatment and, in the absence of any danger signs, discharged. No admission was offered. Antibiotics were given as needed, not routinely. Those women who were randomised to surgical treatment with MVA were managed according to the standard of care at the hospital, using 'verbal anaesthesia' (i.e. reassurance) alone during the procedure.

Each woman was requested to return to the hospital 7 days after treatment. If the abortion was found to be complete at the follow-up visit, the woman was released from the study. If the abortion was still incomplete, the woman was offered the choice between an additional follow-up visit in 1 week with no further intervention during this period or immediate surgical evacuation. If after the additional week of follow up the abortion was still not complete, the woman underwent MVA.

The study protocol did not call for routine ultrasonography (either for initial diagnosis or for determination of treatment success), administration of prophylactic antibiotics, or haemoglobin testing.

The primary outcome was the achievement of complete uterine evacuation after initial treatment (either misoprostol or MVA). The incidence of adverse effects from the treatments was assessed by observation after administration of misoprostol and at an exit interview, where women were asked to report on the adverse effects they had experienced, without interviewer prompting. Intensity of pain was assessed through a Likert scale based on women choosing which of seven increasingly larger circles depicted on a card (the smallest equalling no pain, the largest the worst imaginable pain), best represented what they experienced in connection with their abortions. The level of bleeding immediately after treatment was assessed by hospital staff during the period the woman remained in the hospital after the initial treatment (range: 1–15 hours; mean 2.75, median 3.0). Bleeding during the period between initial treatment and follow-up visit was assessed as an adverse effect, as described above. The presence of infection at follow up was assessed clinically—microbiological or blood tests were not available for verification.

This study was originally conceived as a feasibility study, employing an approach to uterine evacuation which had proved successful in a major urban area in Uganda but testing it in a more rural East African setting. As such, the sample size of 300 women,150 in each study arm,was not based on a power calculation but rather was meant to ensure a sufficient number of participants to allow the benefits and drawbacks of the approach to present themselves fully. The sample, nonetheless, is large enough to provide 90% power to detect a difference (one tailed) of 6% or greater in the effectiveness of the treatments, assuming 99% effectiveness for MVA. Data were analysed using SPSS statistical software (SPSS Inc., Chicago, IL, USA). Chi-square tests were used for categorical data, and *t* tests were used for continuous data. The main analysis of the data included success rates (defined as the percentage of women receiving each regimen who experienced a complete abortion without recourse to additional intervention), frequency of particular adverse effects, and acceptability.

The study was conducted in accordance with the current version of the declaration of Helsinki—women were only enrolled after counselling and informed consent, and the study was approved by the Western Institutional Review Board, Olympia, WA, USA, before the first study participant was enrolled. All laboratory specimens, evaluation forms, and records were identified only by code number and initials to maintain confidentiality. All records were kept locked in a filing cabinet, and women were assured that no clinical information would be released without their express permission.

Results

Overall, between July 2004 and April 2005, 150 women were randomised into the misoprostol group and 150 women into the MVA group (Figure 1). On most background characteristics the two groups did not differ (Table 1). However, a significantly larger percentage of women in the misoprostol group were married (67 versus 49%; $P = 0.006$) and had spontaneous rather than induced abortions (based both on self-report or on staff suspicions, Table 1). No woman was lost to follow up.

The success rates in the two arms (defined as not requiring a secondary surgical procedure) were very high and not statistically different (misoprostol: 99%, MVA: 100%; Table 2). The single failure in the misoprostol group was a woman who presented at the hospital several weeks after misoprostol treatment. Hospital staff, not aware of the study, performed a routine MVA without verifying that the abortion was still incomplete and without offering the woman a chance to wait and see if it would resolve spontaneously on its own.

Although the protocol did not require it, 48 women (17 in the misoprostol group and 31 in the MVA group) received prophylactic antibiotics on the day of their abortions, while 3 women (all in the misoprostol group) had the success of their abortions verified by ultrasound examination. No woman was noted as having posttreatment pelvic infection upon return for follow up.

Women in the misoprostol arm experienced a significantly higher rate of most adverse effects (Table 2), including bleeding immediately after treatment (31 versus 1%) and in subsequent days (82 versus 7%). In contrast, the mean reported pain score was significantly higher among MVA patients (3.0 versus 3.5). Perhaps in consequence, patients' feelings about adverse effects present a mixed picture: while a significantly larger percentage of women in the MVA group reported no adverse effects at all, a higher percentage of women in the misoprostol group found that adverse effects were 'easily tolerable' as opposed to 'tolerable' or nonexistent (Table 3).

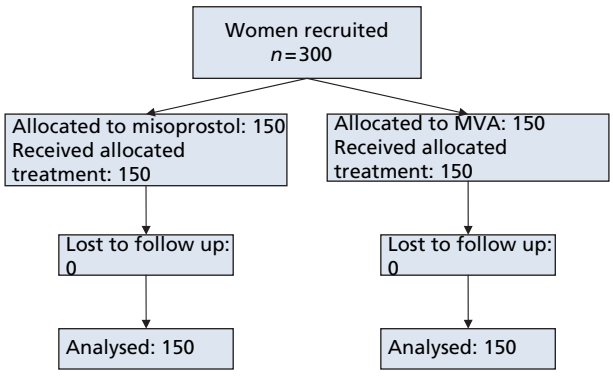

Figure 1. CONSORT flow chart.

Table 1. Background characteristics of study sample

Characteristics	Misoprostol arm (n = 150)	MVA arm (n = 150)	P value
Age (mean years)	25.8	24.7	0.093
Education (mean years)	7.2	7.3	0.766
Married, % (n)	67 (100)	49 (74)	0.008
Parity = 0, % (n)	29 (43)	33 (50)	0.382
As reported by woman, abortion was (% [n])			
Spontaneous	78 (117)	65 (98)	0.015
Induced	22 (33)	35 (52)	
According to staff suspicion, abortion was (% [n])			
Spontaneous	68 (102)	53 (80)	0.009
Induced	32 (48)	47 (70)	

When women were questioned about satisfaction with their treatment, a clearer picture emerges. Women were significantly more likely to report being 'very satisfied' with misoprostol than with MVA, and larger proportions of women in the misoprostol arm informed that they would choose the treatment again and would recommend it to a friend (Table 4).

Discussion

In this study, both misoprostol and MVA were very effective in treating incomplete abortion. Although women in the misoprostol arm experienced more adverse effects, they did not find these adverse effects difficult to tolerate, perhaps because, in comparison with women in the MVA arm, they experienced lower levels of pain. Whether measured through direct questioning or through expressed willingness to choose the treatment again and to recommend it to a friend, women in the misoprostol arm appeared more satisfied with their treatment than those undergoing MVA.

Table 2. Efficacy and adverse effects

	Misoprostol arm* (n = 150)	MVA arm* (n = 150)	P value
Success**	99 (149)	100 (150)	1.00
Failure	1 (1)	0 (0)	
Bleeding immediately after treatment	31 (46)	1 (2)	<0.001
Bleeding in 2 weeks after treatment	82 (123)	7 (11)	<0.001
Nausea	25 (38)	6 (9)	<0.001
Vomiting	11 (17)	4 (6)	0.017
Fever	4 (6)	1 (1)	0.060
Pain (mean score)	3.0	3.5	<0.001

*Except for pain (mean score), figures represent % (n).
**Defined as no surgical intervention required (beyond original MVA, for those in MVA arm).

Table 3. Tolerability of adverse effects

	Misoprostol arm, % (n)	MVA arm, % (n)
% Reporting no adverse effects	23 (34)	32 (47)
% Reporting adverse effect 'easily tolerable'	61 (91)	45 (67)
% Reporting adverse effects 'tolerable'	16 (24)	24 (35)

Differences significant at P = 0.02.

There have been at least 15 previous studies of misoprostol for treatment of incomplete abortion.[6–20] Of these, however, only two[6,20] were conducted in low-income countries, and both of these took place in the capital city at a larger tertiary hospital. This, then, is the first trial of misoprostol for this indication at a lower level health facility in a developing country. Its findings generally parallel those of the one previous study conducted in East Africa.[6]

In this study, misoprostol was successful in evacuating the uterus in 99% of cases. This is an extremely high success rate, but it is not out of line with those previously reported. Ten of the 15 earlier studies[6,7,10,13–15,17–20] showed rates of at least 90%; two report 100% success, albeit with very low numbers of incomplete abortion cases.[13,17] There is, furthermore, some reason to believe that as practitioners become more familiar with this method and as the base of experience grows, success rates are improving: while four of the five studies that report rates lower than 90% were conducted in 2001 or earlier, eight of the ten showing rates of 90% and above took place between 2001 and 2005. The two previous studies of this method conducted in the developing world, which included samples of 160 and 300 women, report rates of 96 and 95% (weighted average), respectively. Together with the current study, this record strongly suggests that misoprostol is an effective treatment for incomplete abortion, in both developed and developing countries.

Table 4. Satisfaction

	Misoprostol arm, % (n)	MVA arm, % (n)	P value
Satisfaction with treatment			
Very satisfied	75 (113)	55 (83)	0.001
Satisfied	24 (36)	45 (67)	
Unsatisfied	0	0	
Very unsatisfied	1 (1)	0	
Would choose method again	98 (147)	93 (139)	0.029
Would recommend method to a friend	95 (142)	75 (112)	<0.001

This study may seem unusual in that none of the 300 women who participated was lost to follow up. By comparison, in the previous study of misoprostol for incomplete abortion conducted in East Africa,[6] one-third of women in the misoprostol arm did not return for their next scheduled visit . However, the other similar trials which have been conducted either in a developing country[20] or in sub-Saharan Africa[17,19] had lost to follow up rates of 1.7, 0, and 0%, respectively. Clearly, it is possible for dedicated staff to maximise retention of subjects. The fact that this study was not conducted in a large city with a transient and relatively anonymous population may have given it an advantage in this respect.

The main strength of this study is that, as noted above, it is the first to be conducted at a lower level health facility in a developing country. A case could be made that it is in such facilities—or in facilities even lower down in the health system hierarchy—that most cases of incomplete abortion with potentially serious consequences are likely to present. The main weakness of the study is that, as ultrasound was not used to diagnose incomplete abortion, the study population may have included women with inevitable or even already completed abortions. While this is true, it is also true that the study, as conducted, accurately reflects 'real-world' conditions. It is unlikely that any healthcare facility in a low-income country,particularly one in a smaller city or rural area, is going to have the resources to verify incomplete abortion status through ultrasound for all presenting women. In such cases, a facility is likely to do exactly what was done in this study, that is, presumptively treat all women who appear to have an incomplete abortion as if they do have one. The current study shows that, in such real-world circumstances, misoprostol can be as effective an incomplete abortion treatment as MVA.

This study demonstrates that use of misoprostol for treating incomplete abortion is effective and feasible at the regional hospital level in Tanzania. Although other similar trials will need to be conducted to fully establish misoprostol's value in such settings, this study strongly suggests that misoprostol may prove a valuable treatment at secondary healthcare facilities. Full exploitation of misoprostol for this indication might make an important impact on reducing maternal death in rural areas of developing countries.

Unfortunately, misoprostol is not registered for obstetric use in most jurisdictions. Many women who could benefit from the drug are thus unable to get it. Future work should address itself to the political and regulatory context, striving to make the case for the approval of misoprostol for obstetric uses, and its regular inclusion in pharmacies as an essential medicine. Additionally, the next round of research should focus on the feasibility of treating incomplete abortion with misoprostol at the subregional level, where MVA is often not available and where misoprostol's low cost and ease of storage and use might make it especially valuable. ■

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