Misoprostol for safe motherhood: one tablet, two life-saving indications

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Abstract

Misoprostol is a safe, acceptable, feasible, and effective alternative for both postpartum hemorrhage (PPH) and the treatment of incomplete abortion and miscarriage when no other interventions are available, which is often the case in resource-challenged regions. This article reviews the use of misoprostol for these two leading causes of maternal death globally and presents data on the implementation of misoprostol for PPH in Zanzibar as a case study. An evaluation was conducted to assess the uptake of misoprostol in public facilities in Zanzibar through a record review at nine facilities on various indicators from April 2008 to March 2009. For comparison, pre-intervention data were also collected from the same nine facilities for the 12 months preceding the PPH management trainings in April 2008.

Following the introduction of misoprostol for PPH, the need for additional interventions among PPH cases significantly declined. The post-intervention period showed significantly fewer blood transfusions, PPH referrals, and PPH-related maternal deaths. Among PPH cases, the need for blood transfusion decreased from 30 (19.2%) in the pre-intervention period to 7 (2.4%) in the post-intervention period. Rates of PPH-related referrals and maternal deaths also declined from 7.7% pre-intervention to 3.1% post-intervention ($P<0.05$).

Misoprostol has the potential to make an immediate impact on the number of maternal deaths resulting from PPH and treatment of incomplete abortion and miscarriage.

The World Health Organization (WHO) (2007) estimated that in 2005 nearly 536 000 women died from complications related to pregnancy and childbirth; this translates to a woman dying every minute in the developing world, where 99% of all maternal deaths occur. Recent studies (Khan et al, 2006; WHO, 2007) have found that postpartum hemorrhage (PPH) accounted for 25–34% of these deaths, predominantly in resource-poor settings in Africa and Asia, where women are often unable to deliver in a facility.

The second leading cause of maternal deaths is attributed to complications from unsafe abortion, from which a woman dies every 8 minutes (WHO, 2007). Similar to PPH, a woman may not be able to return to a facility for proper care for these complications, or may be at a facility that does not have the technology or skilled provider to properly treat the woman for the incomplete abortion or miscarriage.

For both the management of PPH and the treatment of incomplete abortion, there are multiple proven interventions available. However, some often require several conditions, such as needing the woman to be at a health facility—which usually requires transport, money, and time; a trained birth attendant who can administer an injection; a trained health care worker who can perform manual vacuum aspiration for the treatment of incomplete abortion; and a guaranteed supply of effective medical tools and drugs. There is another intervention, however, that provides a simple alternative when these conditions are not possible: misoprostol. It is a tablet that can easily address these two leading causes of maternal death until further progress is made with strengthening the overall health-care systems in developing countries.

Misoprostol has an excellent safety profile with over 1500 studies published on its use. It has been widely used in obstetrics for decades and is a proven, evidence-based drug that reduces postpartum blood loss as a result of uterine atony (Alfirevic et al, 2007). Studies have shown that misoprostol, a prostaglandin-E1 analogue, is effective in causing the uterus to contract; it stops PPH within minutes (Goldberg et al, 2001; Lokugamage et al, 2001). Misoprostol has also been shown to be as effective as MVA in treating incomplete abortion at uterine size less than 12 weeks (Weeks et al, 2005; Bique et al, 2007; Dao et al, 2007; Shwekerela, 2007). It is not only easily given orally or rectally but also easily administered by lower level providers and effectively used at peripheral levels of a health system. Misoprostol has minimal, if any, occasional side effects such as shivering, increased body temperature, nausea, vomiting and/or diarrhea. These symptoms are not life-threatening and can be managed at the household level. Because misoprostol is an off-patent, generic drug, it is inexpensive at $0.10 USD per tablet. It is also easy to store at room temperature for up to 3 years, depending on the manufacturer.

The use of misoprostol for both PPH and the treatment of incomplete abortion has been endorsed by key international bodies such as the International Federation of Gynecologists and Obstetricians (FIGO) and International Confederation

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of Midwives (ICM). Specifically for PPH, these two groups recommend misoprostol in precisely the settings where maternal health programmemes are needed most: poor, often rural, communities where women deliver at home and are out of reach of the health-care system (ICM/FIGO, 2007). In 2009, the WHO included misoprostol in its Model List of Essential Medicines for treatment of incomplete abortion and miscarriage and went on to say that the evidence for misoprostol showed that it is as effective as surgery and may be safer and cheaper in some settings (WHO, 2009).

Misoprostol for PPH management

The active management of third stage of labour, which includes the use of a routine uterotonic drug to prevent PPH by addressing the uterine atony causing the PPH, can decrease maternal deaths by 40% (Prendiville et al, 1988). Active management of third stage of labour is a three-component procedure: the administration of a uterotonic, controlled cord traction and uterine massage. Ergometrine and oxytocin are two widely known uterotonics. Ergometrine is contraindicated in women with hypertension in pregnancy. Where skilled providers are available, the WHO recommends oxytocin as the first-line drug in the practice of active management of third stage of labour. A large multicentre hospital study showed that, for PPH prevention, oxytocin is statistically significantly better than misoprostol given orally, as evidenced by a reduction of blood loss of 1000 ml or more, from 4–3% (Gulmezoglu et al, 2001). In a hospital setting, these findings are critical to note; but in settings far from any health facility, these findings are difficult to apply. Because oxytocin requires both refrigerated storage and skilled attendance, it remains a challenge with inconsistent power sources and often undertrained and/or unauthorized health-care workers left to administer the oxytocin.

In busy hospitals where conventional uterotonics are available, it has been documented that misoprostol is as effective and preferred for both prevention and treatment of PPH (Prata et al, 2006). Langenbach (2006) conducted a meta-analysis of all randomized control trials (RCT) that tested the ability of misoprostol to prevent PPH and concluded that, when there are little to no other alternatives, the use of misoprostol should not at all be discounted but be considered as a viable and potent option when there are none to choose from otherwise. Derman et al (2006) found that oral misoprostol is statistically significantly better than placebo in preventing acute PPH when used as prophylaxis. In a commentary published in the same *Lancet*, Chong and Su (2006) deemed this the:

> *'best evidence so far that oral misoprostol can be given by skilled birth attendants in a low-resource community setting to prevent PPH safely and effectively.'*

For the prevention of PPH, 600 mcg of misoprostol, usually three tablets, is taken orally immediately after all infants, if there is more than one, are delivered. If the woman has already lost more than 500 ml of blood and was not already given a prophylaxis dose, the treatment dose calls for 1000 mcg administered rectally. Recent studies (Blum et al, 2010; Winikoff et al, 2010) have shown that 800 mcg administered sublingually is also an effective treatment dose. There is also a growing body of evidence supporting the safety and feasibility of misoprostol use at the community level for the prevention of PPH (Rajbhandari et al, 2010; Sanghvi et al, 2010). Using mathematical models, Pagel et al (2009) propose that community distribution of misoprostol coordinated with health-facility strengthening could prevent 32% of maternal deaths from PPH.

Misoprostol for the treatment of incomplete abortion and miscarriage

Annually, over 5 million women in developing countries are admitted to hospitals for complications from induced abortion, with the vast majority stemming from unsafe abortion (Singh, 2006). Maternal mortality from abortion-related complications accounts for 13% of all maternal deaths, around 63 000 in total (WHO, 2007). Acute and long-term morbidities can include sepsis, hemorrhage and intra-abdominal injuries, while the resulting economic and emotional burden on families and communities is substantial.

Current protocols for post-abortion care services include evacuation of the uterus with surgical methods, such as manual vacuum aspiration. Surgical techniques require sterilized equipment along with providers skilled in their use. The inclusion of misoprostol in post-abortion care services broadens the range of health-care workers allowed to provide post-abortion care, thereby contributing to increased service availability. In resource-poor settings, misoprostol can be a complementary strategy to existing post-abortion care services and have a potentially synergistic effect on service availability and quality.

Use of misoprostol for medication-based post-abortion care services has the capacity to increase women's access to treatment of incomplete abortion and reduce the financial burden on the health-care system. Because misoprostol is simple to use, it can be administered by trained providers at the primary care level, bringing post-abortion care services closer to women. With closer proximity to services, women will not only be able to seek care earlier, but fewer cases will need to be referred to higher level facilities. Coupled with increased community awareness and access to misoprostol, this intervention has the potential to greatly reduce maternal morbidity and mortality resulting from complications of unsafe abortion.

A number of studies have shown that misoprostol is as safe and as effective as MVA (Bique et al, 2007; Dao et al, 2007) and is more accepted among women (Shwekerela et al, 2007; Weeks et al, 2005) for its ease and comfort of administration as well as its lower cost. Like PPH, 600 mcg of misoprostol is given orally to the woman for treatment of incomplete abortion and miscarriage and 400 mcg sublingual is also an effective regimen (Diop et al, 2009).

Case study: Zanzibar

With 28% of maternal deaths caused by PPH in Zanzibar (AbouZahr, 2003; Ministry of Health and Social Welfare, 2008), the government has prioritized active management of third stage of labour to address this since every delivery faces the risk of PPH. In 2007, misoprostol was registered in Tanzania and Zanzibar for the prevention and treatment of PPH and is included in the national Essential Medicines List for this indication. In April 2008, Venture Strategies Innovations (VSI), in

conjunction with Danida, initiated training on the management of PPH with misoprostol for public sector mid-level providers, ultimately training 425 providers. VSI then initiated an evaluation in May 2009 to assess the uptake of misoprostol within public sector facilities; the effect on referral rates and need for additional interventions; and any challenges to its adoption to make recommendations for scale-up activities on the islands.

Methods

Data collection and analysis

Regular supervision by Ministry of Health and VSI personnel was conducted for 1 year following the first PPH management trainings and the introduction of misoprostol. Facilities chosen were based upon a convenience sample of active maternity facilities on both Pemba and Ugunja, including both large referral facilities and rural health clinics where providers trained in the VSI-Danida programme were stationed and record keeping was ongoing.

Quantitative data collection focused on record review at nine facilities and documented total number of births, number of deliveries that received misoprostol prophylaxis, incidence of PPH, use of uterotonics for treatment, need for referral and additional interventions and the number of PPH-related maternal deaths from April 2008 through March 2009. All data collection forms were manually reviewed for completion and accuracy. For comparison, pre-intervention data was also collected from the same nine facilities for the 12 months preceding the PPH management trainings in April 2008. Delivery logs were reviewed to record the monthly total number of births, PPH cases, treatment received, referrals to higher level facilities and PPH-related maternal deaths from April 2007 through March 2008. Data entry and preliminary analyses were restricted to 10 months (May 2008–February 2009) for which records were complete and conducted at VSI, Anaheim office, using Stata 10.0 (Stata Corp, College Station, TX, USA). Results were summarized using frequency distributions and cross tabulations. Two-tailed student t-test for comparison of two proportions or two means was estimated, and statistical significance was established at $P<0.05$.

Ten key informant interviews were also conducted at five facilities purposively selected to be representative of geographic location (three on Pemba and two on Unguja) and facility level (three higher level and two lower level). At each facility, the person in charge of the maternity ward and one midwife were interviewed by the same interviewer in Kiswahili or English, depending upon the providers' preferences, using a standard nine-question interview guide. Interviews were recorded by hand and translated into English. The first author thematically analyzed the qualitative data in the USA in consultation with the interviewer.

Results

Facility delivery data

Tables 1 and *2* present data on key variables of interest preceding and following the PPH trainings and introduction of misoprostol in public sector facilities (jointly called 'the intervention'). For the 12 months preceding the intervention, 19 303 births were recorded at the nine facilities, compared to 17 033 births the 10 months following the intervention (*Table 1*). The vast majority of births occurred at facilities on Unguja both before (75.2%) and after (72.1%) the introduction of active management of third stage of labour and misoprostol. Mnazi Mmoja, Mwembeladu and Chake Chake Hospitals reported the greatest delivery rates. From May to September 2007, Vitongoji Cottage Hospital was converted to a cholera camp and witnessed lower delivery rates over the period, referring all

Table 1. Total number of births by facility

	Pre-intervention April 2007–Mar 2008 *n*=19 303 (%)	Post-intervention May 2008–Feb 2009 *n*=17 033 (%)
Pemba	4794 (24.8)	4749 (27.9)
Chake Chake D. Hospital	2049 (10.6)	2243 (13.2)
Micheweni Cottage Hospital	352 (1.8)	379 (2.2)
Mkoani D. Hospital	1220 (6.3)	1011 (6.0)
Vitongoji Cottage Hospital	81 (0.4)	156 (0.9)
Wete D. Hospital	1092 (5.7)	960 (5.6)
Unguja	14 509 (75.2)	12 284 (72.1)
Kivunge Cottage Hospital	1162 (6.0)	1107 (6.5)
Makunduchi Cottage Hospital	340 (1.8)	319 (1.9)
Mnazi Mmoja Hospital	7644 (39.6)	6682 (39.2)
Mwembeladu Maternity Hospital	5363 (27.8)	4176 (24.5)

Table 2. Outcomes of PPH cases recorded at facilities

	Pre-intervention April 2007-Mar 2008	Post-intervention May 2008-Feb 2009	*P*-value
Number of births	19 303	17 033	
Number of PPH cases	156 (0.8)	289 (1.7)	<0.0001
Number of blood transfusions	30 (19.2)	7 (2.4)	<0.0001
Number of PPH-related referrals*	12 (7.7)	9 (3.1)	0.02
Number of PPH-related maternal deaths **	12 (7.7)	9 (3.1)	0.02
Other medical treatment	102 (65.3)	262 (90.7)	<0.0001

*Excludes referral facilities on each island: Chake Chake, Mkoani and Mnazi Mmoja
**Comparisons between PPH-related referrals and maternal deaths are coincidental

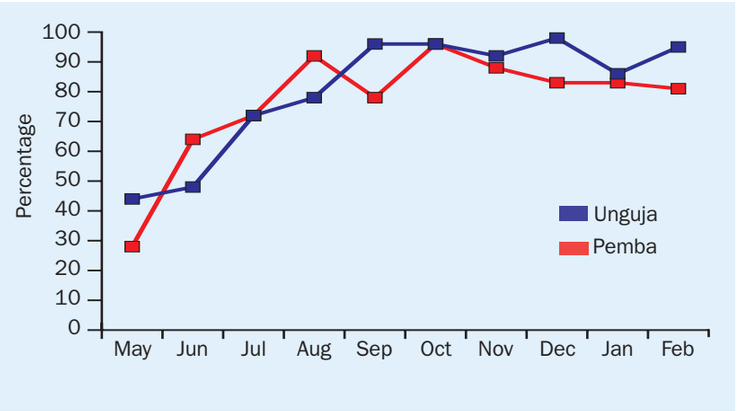

Figure 1. Percentage of protected births with misoprostol prophlyaxis May 2008–February 2009

deliveries to Chake Chake District Hospital.

Following the introduction of misoprostol for PPH, there was a significant decline in the need for additional interventions among PPH cases. In particular, the post-intervention period shows significantly fewer blood transfusions, PPH referrals and PPH-related maternal deaths. Among PPH cases, need for blood transfusion decreased from 30 (19.2%) in the pre-intervention period to 7 (2.4%) in the post-intervention period. Among PPH cases, rates of PPH-related referrals and maternal deaths both declined from 7.7% pre-intervention to 3.1% post-intervention ($P<0.05$).

The incidence of PPH both pre- and post-intervention is much lower than the global average. This may be owing to under-diagnosis and/or underreporting. Reported cases of PPH increased significantly post-intervention. This was expected, given the training aimed to increase provider awareness and improve the accuracy of diagnosis and record keeping. This will be discussed further in the next section.

Misoprostol use

Since the introduction of misoprostol, there has been a steady upward trend in its use for prevention of PPH in the nine facilities surveyed. (*Figure 1*). Several facilities achieved 100% coverage of deliveries with misoprostol prophylaxis over the 10 months of supervision was conducted. Overall, of 17033 deliveries in 10 months, 12497 received misoprostol for prevention of PPH, or 73.4% of all facility deliveries. When data is excluded from the initial 2 months (May and June 2008) during which the misoprostol supply was inconsistent, coverage of births with misoprostol prophylaxis goes up to 87.8% of all facility deliveries for July 2008–February 2009 (data not shown). For purposes of the report, births wherein the delivering woman received a uterotonic for PPH prevention are considered 'protected'. It was not possible to compare rates of protected births pre- and post-intervention, because use of uterotonics was not systematically recorded before the intervention.

Before the introduction of misoprostol, all PPH cases were treated using available injectable uterotonics (oxytocin or ergometrine) and commonly used intravenous fluids (e.g. ringer lactate). The introduction of misoprostol has allowed providers to effectively treat PPH with tablets when standard uterotonics are unavailable or fail.

Discussion

Use of misoprostol for PPH rapidly increased over the 10-month period surveyed, and the outcomes of PPH cases improved. The need for blood transfusions was significantly reduced, and significantly fewer PPH-related referrals and maternal deaths were witnessed. This suggests that more women were being treated successfully for PPH post-intervention. The overwhelming perception among key informants interviewed was that delivery care and maternal outcomes were improving—specifically a reduction in PPH and maternal death, and misoprostol was a driver of that change.

Recorded PPH cases were significantly greater in the post-intervention period. However, interpretations of this difference must take into account that the incidences of PPH pre- and post-intervention are extremely low compared to the global incidence for PPH (0.8% and 1.7% respectively, compared to 10.5% global incidence (WHO, 2005)). The reported incidences are even more drastically different than those previously reported from Tanzania, which was 22% (Prata, 2005).

The increase in the number of PPH cases may be explained by changes in provider practice brought about by the training component of the intervention. An aim of the training was to increase awareness of the seriousness of PPH and to improve notification of the case, whether through visual diagnosis or intention to treat. For example, providers were taught that two blood-soaked kangas were approximately equivalent to 500 ml blood loss, the common definition of PPH. During the training, some providers mentioned that they would not visually diagnose PPH until five kangas were soaked with blood. Record keeping is also expected to have improved since books dedicated to tracking PPH cases and misoprostol use were specially placed on the maternity units of participating facilities. Finally, diffusion of innovation may have resulted in an increase in referrals of women with PPH complications after home births, though this was not a specific component of the intervention.

Misoprostol uptake was rapid in facilities surveyed. From both anecdotal evidence during supervision visits and qualitative findings, ease of use of tablets by any level provider was the overwhelming factor contributing to this trend. In understaffed, ill-equipped and overburdened settings, misoprostol has been shown to be the preferred drug among busy providers (Prata et al, 2006). This may be the case in facilities surveyed in Zanzibar. Nevertheless, misoprostol is not intended to replace oxytocin as the first-line drug and should be seen as a complementary strategy for addressing PPH prevention, used only in the absence of oxytocin.

Conclusions

As this article shows, misoprostol has the potential to immediately impact the number of maternal deaths in places where no other uterotonic is available. Not only is it simple to use, misoprostol also has the ability to address more than one obstetric indication and bring services closer to women through community-based distribution and lower level facilities. This is not to say that misoprostol will not be subject to similar challenges

with the supply chain as other drugs, but adding misoprostol to the current list of uterotonic drugs will only increase the chance of facilities having at least one uterotonic agent available.

For many women in developing countries, delivering in a facility is not yet a feasible option and they continue to deliver at home, thus placing them at risk for PPH and further away from preferred interventions. For this reason, strategies addressing safe motherhood need to consider the realities of community-level interventions to meet the women where they are and be able to access health care by training providers on active management of third stage of labour, while emphasizing oxytocin as the first-line drug. As the data from Zanzibar shows, over the course of 10 months, there were decreases in blood transfusions, PPH-related referrals, and PPH-related maternal deaths once misoprostol was implemented. However, it is important to note that there may also have been other interventions that both directly and indirectly contributed to these improved outcomes as well since the misoprostol was not put into practice in isolation.

The integration of misoprostol for the treatment of incomplete abortion and miscarriage will give even more health-care providers another treatment option and allow women to access services at lower level facilities. As with PPH, training providers in the use of misoprostol for this indication is more simple than other surgical alternatives. By building the capacity of various providers, there will be more health-care staff authorized to provide post-abortion care services to women.

Misoprostol is a life-saving technology, when made available to women, that can quickly address the two leading causes of maternal death: PPH and complications from unsafe abortion. **AJM**

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Key Points

- **Misoprostol has the potential to make an immediate impact on the number of maternal deaths resulting from postpartum hemorrhage when no other uterotonic drug is available.**
- **Misoprostol offers a safe, simple and effective alternative to surgical treatment for the treatment of incomplete abortion and miscarriage.**
- **Misoprostol should be considered a key intervention to curb maternal mortality.**