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Misoprostol in Practice

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In the early 1990s, misoprostol was virtually unknown amongst obstetricians and gynecologists. Today, it has become an essential drug used in every part of the world by all those involved in women's health. It has gone from a limited role in gastric ulcer disease to the focus of obstetric care and an essential part of fertility regulation. As a low-cost, easy-to-administer, powerful uterotonic with an excellent safety profile and long shelf-life, misoprostol has the revolutionary potential to reduce death and morbidity from postpartum hemorrhage (PPH) in precisely those situations where it is most common – among the 40–50 million women who deliver at home without a skilled birth attendant.

The different obstetric uses of misoprostol are inextricably mixed. Misoprostol can be used for the prevention and treatment of PPH, for the treatment of incomplete abortion, and for induced abortion, as well as for labor induction, cervical dilation and the treatment of intrauterine fetal death. Millennium Development Goal (MDG) 5, to reduce maternal deaths by three-quarters between 1990 and 2015, is unlikely to be achieved in many low resource settings without the widespread distribution of misoprostol. The drug has performed superbly, but availability, accurate knowledge regarding its correct use and the regulatory framework for its approval have lagged behind the potential of misoprostol to save the lives of women on a large scale.

Women have searched for botanical uterotonics for thousands of years. In 1932, Moir reported the use of ergometrine to control PPH[1]. During that same decade, Von Euler isolated the first prostaglandins[2], but it was another 30 years before the systematic study of the obstetric and gynecological uses of various prostaglandins began. Ravenholt proposed the use of prostaglandins as an emmenagogue in 1968[3] and in 1970, Karim and Filshie demonstrated that prostaglandin F2α could be used to induce abortion[4]. However, therapeutic options were limited by high cost, the need for injection and refrigeration requirements. This changed in 1988 when the Upjohn Company began clinical trials of a synthetic prostaglandin E1 analogue called misoprostol (Cytotec®) for the treatment of gastric ulcers[5]. With the potential of a large market for long-term daily use, the company invested in developing a thermostable oral tablet. Typically, 200 μg four times per day was – and still is – prescribed for gastric ulcers. The United States Food and Drug Administration label for Cytotec states that, 'cumulative total daily doses of 1600 μg have been tolerated, with only symptoms of gastrointestinal discomfort being reported'[6].

The off-label use of misoprostol as a uterotonic began in the 1990s[7]. By 2001, over 300 papers had been published in peer-reviewed journals on the obstetric and gynecological uses of misoprostol[8]. Research has demonstrated that misoprostol can be delivered orally, vaginally, rectally, buccally and sublingually. *In utero* exposure to misoprostol, as in cases of attempted abortion, has been associated with congenital defects, but the absolute risk is low[9]. Side-effects, including pyrexia and shivering have been reported with misoprostol use, but these are often resolved with conservative treatment. In a 2010 review of 46 randomized controlled trials of misoprostol, involving more than 40,000 patients, only 11 deaths were reported; eight of these were reported as deaths associated with PPH, while the other three deaths were from causes unrelated to PPH or causes were not provided[10].

The uterotonic effect of misoprostol varies greatly over the course of gestation. Misoprostol dosages as low as 25 μg are safe and effective in the induction of labor when given orally or vaginally. The drug is also effective, when administered sublingually or rectally, for intractable PPH in single doses of 800 μg or 1000 μg, respectively[11–13]. Misoprostol is an unusually powerful drug, and some of the doses now in clinical practice may be lowered as more clinical experience is gained.

CLINICAL USE IN POSTPARTUM HEMORRHAGE

Delivery with a trained birth attendant

When active management of the third stage of labor (AMTSL) with oxytocin is compared to expectant management, the relative risk of losing 1000 ml of blood at the time of birth is 0.34 (CI 0.14–0.87)[14]. In 2001, the World Health Organization (WHO) coordinated a randomized controlled trial testing 600 μg of oral misoprostol against 10 units of oxytocin in well resourced hospitals. It was found that oxytocin was marginally more effective than misoprostol (RR 1.39, 95% CI 1.19–1.63), although there was only 1%

difference in the frequency of blood loss of 1000 ml or more between participants in each arm of the study[15]. Shannon and Winikoff, while accepting the statistical significance of this difference, question its clinical relevance[16].

In a randomized controlled placebo trial in Belgaum, India, 600 μg of oral misoprostol was associated with a significant reduction in severe PPH compared to placebo (RR risk 0.20, 95% CI 0.04–0.91)[17]. A pre- and postintervention comparison of the use of misoprostol and standard of care with other uterotonics, including oxytocin, was conducted in a busy hospital setting in Egypt and found that misoprostol performed consistently better than oxytocin (Figure 1)[18].

Use in low resource settings

The 1987 Nairobi Safe Motherhood Conference drew attention to the unacceptably high maternal mortality ratios (MMR) around the world. As noted, MDG 5 is not being achieved in low resource settings, where the highest death rates occur during home births that take place farthest from hospitals and without trained birth attendants. Based on a study from Zimbabwe, which found the total MMR to be 725 per 100,000, and of which 14.4% were due to PPH alone, it can be calculated that the MMR due to PPH is approximately 104/100,000 live births[19]. WHO and the International Federation of Gynecology and Obstetrics (FIGO) have emphasized the need to extend the reach of emergency obstetric care, and this should be a long-term goal for all countries. However, for the foreseeable future, lack of trained staff, reluctance to work in deep rural areas and migration from countries of the south to those of the north, will continue to stall the extension of emergency obstetric care[20].

The first national drug regulatory authority to approve the use of misoprostol for PPH was that of Nigeria in 2006, facilitated by Venture Strategies for Health and Development. Prior to the availability of misoprostol, it was impossible to do anything to significantly reduce mortality associated with PPH among the most vulnerable women, many of whom live on less than one or two US dollars per day. Most efforts to train traditional birth attendants have failed to show a significant positive impact on the MMR[21]. PPH is difficult to predict, a traditional birth attendant may miss diagnosing pre-eclampsia, and exhorting traditional birth attendants to wash their hands, while a good idea, does not have a measurable impact on the MMR. Misoprostol changes this dynamic. It is the first life-saving technology that can be used during home delivery without a trained birth attendant[22]. Operations research in Tanzania has demonstrated that trained birth attendants can diagnose and treat PPH with 1000 μg of misoprostol given rectally[23]. In Nepal, Afghanistan, Bangladesh and elsewhere, tens of thousands of women have been taught to self-administer 600 μg of misoprostol orally after delivering their babies without serious side-effects or systematic misuse[24–26].

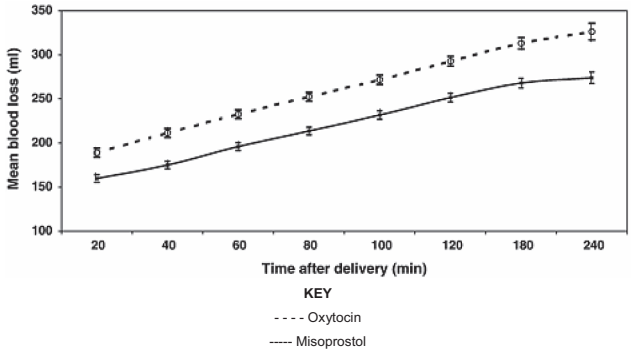

Figure 1 Cumulative mean blood loss and 95% confidence intervals. From Prata *et al.*, 2006[18], with permission

Induction of labor

All over the world, the induction of labor is an integral part of the management of serious conditions such as pre-eclampsia, diabetes and chorioamninotis. Even in middle income countries, prior to the introduction of vaginal misoprostol, women endured long hours of induction of labor with a Syntocinon® infusion because the available prostaglandins were too expensive (costing the equivalent of a month's disposable income) to use. The arrival of misoprostol removed this inequity. Clinicians around the world have learnt to divide misoprostol tablets into one-eighth parts, though this can be difficult, and certain manufacturers are now producing 25 μg tablets. An optimal method of delivery is to prepare a solution with 200 μg tablets and administer it orally for smaller divided doses[27].

ABORTION AND EVACUATION OF THE PREGNANT UTERUS IN THE FIRST TRIMESTER

Abortion remains illegal in most of the world to date, inaccessible to millions of women around the globe. The unmet demand for abortion is often met illicitly and is criminalized. Of the estimated 43.8 million abortions that occurred globally during 2008, nearly half of those were unsafe. The proportion of unsafe abortion is even higher in certain regions of the world, with an estimated 65% and 97% of all abortions being unsafe in South Central Asia and Africa, respectively, in 2008[28].

Where abortion is illegal, unsafe procedures to interrupt pregnancy are commonly one of the most frequent causes of maternal death after PPH. The estimated 47,000 abortion deaths in 2008 accounted for nearly 13% of all maternal deaths[29]. Women who try to achieve abortion themselves have resorted to herbal medications, the use of sharp needles and jumping from stairs. Many of these women suffer physical and mental trauma as a result, and many also end up seeking medical or paramedical help to achieve the abortion. Such help is often only available in clandestine fashion. The surgery for termination of pregnancy

was, and is, performed in suboptimal circumstances. Anesthetics and sterilization of instruments are compromised and doctors may or may not have received proper training in the procedure. The morbidity of illegal and illicit abortion on hospital admissions is very well documented.

The rise of misoprostol in women's health around the globe led to a substantial drop in abortion morbidity on two fronts. First, it changed the nature of illicit abortion from a surgical procedure to a semi-medical procedure. A failed illicit abortion that started with misoprostol is arguably a safer intervention than a surgical one. In those same countries where abortion is illegal, but misoprostol is available to replace the use of more dangerous traditional methods, admissions for complicated incomplete abortions fall, as has been recorded in the Dominican Republic[30]. Second, the development of mifepristone, and subsequently medical induction of abortion, was a landmark in reproductive freedom. Originally, the regimen involved the use of mifepristone and a prostaglandin analogue. Two of the most widely used prostaglandin analogues available prior to misoprostol included sulprostone and gemeprost. The former is administered parenterally, while the latter is a vaginal pessary. Neither of these were appropriate technologies for use in developing countries, as both required cold chain transfer and specific storage requirements. The introduction of misoprostol as a thermostable agent heralded yet another chapter of equality in reproductive freedom around the world. Where abortion is legal, as in Ethiopia, a pilot project using community health extension workers to offer medical abortion using misoprostol in the first 9 weeks of pregnancy led to hospital admissions for abortion complications plummeting from the number one most common reason for hospital admission to the tenth reason[31].

INTRAUTERINE FETAL DEATH IN THE SECOND AND THIRD TRIMESTER

Intrauterine fetal death is a tragedy for any pregnant mother and a cause of concern to all involved. Evacuating a pregnant uterus in the second or third trimester is a biological challenge since the cervix is not ripe and the myometrial receptors are not primed for uterine contractility. Prior to misoprostol this biological challenge had no clear or pharmacological answer. In North America, dilation and evacuation or hysterectomy were widely practiced with significant physical and psychological morbidity. In Europe, the use of prostaglandins replaced the use of high dosages of Syntocinon regimens in the 1980s. Extra-amniotic administration of prostaglandins compared with intra-amniotic prostaglandins or vaginal pessaries were also explored as alternative technologies. Again, misoprostol has ushered in a new era for women throughout the world. The drug has proved effective and well tolerated in the management of fetal death in advanced pregnancies.

WHERE NEXT?

Over the past decade, misoprostol has moved from an exciting new drug to one which is widely thought can revolutionize obstetrics and reproductive health worldwide. While it takes time to assimilate this remarkable expansion of research and clinical practice, the life-saving potential of misoprostol has been unnecessarily hindered by a mixture of medical conservatism and controversy over abortion. Regulatory approval has been slow and policies for community distribution have been resisted.

Despite many years of advocacy by groups, such as FIGO, the International Confederation of Midwives, Venture Strategies Innovations, Jhpiego, Gynuity and experienced obstetricians with clinical experience with PPH, WHO delayed placing misoprostol on the Essential Medicines List for PPH until 2011. One reason for the delay was that the WHO Department for Making Pregnancy Safer imposed the 'gold standard' of randomized clinical trials to assess the strength of the evidence base for making the recommendations. However, randomized clinical trials involving misoprostol for prevention of PPH cannot be implemented during home births without a trained birth attendant. It would be ethically unacceptable to randomize misoprostol against a placebo where no alternative to save the life of a hemorrhaging woman is available, especially when we know that misoprostol is an effective uterotonic and can and does save lives.

Governments such as those of Nigeria and Bangladesh have already approved community distribution of misoprostol to pregnant women for self-administration after delivery. Prata *et al.*[32] demonstrate that reducing deaths from PPH and unsafe abortion will result in the greatest gains in maternal deaths averted in low resource settings (Figure 2). Their models also demonstrate that the most cost-effective interventions to reduce maternal mortality in low resource settings include family planning and safe abortion services, as well as antenatal care with misoprostol. Safe delivery, eclampsia and standard antenatal care services, which do not include the distribution of misoprostol, were found to be the least cost-effective interventions. There is an order of magnitude difference in cost per death averted between the provision of safe deliveries in a facility with trained health

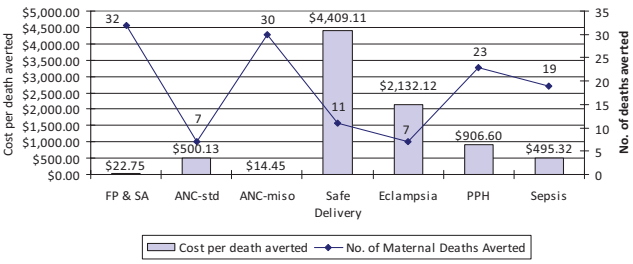

Figure 2 Average cost and number of maternal deaths averted in low infrastructure setting. ANC, antenatal care; FP, family planning; SA, safe abortion. From Prata *et al.*, 2010[32], with permission

professionals plus emergency obstetric care, estimated at $4410 per death averted, compared to the distribution of misoprostol for home deliveries without a trained birth attendant, estimated at $15 per death averted[32].

The power of misoprostol reaches beyond medical practice into many communities. It is a potentially low cost medicine, with a wholesale price ranging from 15 to 90 US cents per tablet. However, while life-saving, any one woman may need misoprostol perhaps only once in a life time, and a low-volume, low-cost medicine is not commercially attractive to many retailers. Most women will recognize the power of a self-administered means of bringing on a delayed period, whether abortion is legal or illegal in the country where they live. Consequently, where misoprostol is difficult to obtain, as in parts of Sub-Saharan Africa, the retail price can exceed $10 US dollars per tablet.

For misoprostol to reach its full potential, women need access to a low cost or free product supported by correct information on doses and side-effects. In Bangladesh, the government purchases misoprostol tablets from local manufacturers and distributes them to women in free birthing kits to control PPH. In Nigeria, the government is buying misoprostol tablets from China and plans to distribute them at the community level. Misoprostol can also be delivered through social marketing of a branded product and it is also possible that women's groups will have the ability to distribute misoprostol in low resource settings.

Perhaps the least explored aspect of the use of misoprostol is how women who obtain this medicine through informal channels can find the information they need on its correct and safe use, and on its side-effects. For prevention of PPH, options include training front line health workers, community volunteers and the use of media. Mobile phones are now ubiquitous even in many relatively remote parts of Africa and Asia, and can be used to distribute reproductive health information.

There will always be different perspectives on abortion, even when completed early in pregnancy. However, there is consensus that in situations where abortion is illegal and a woman undergoes an unsafe abortion, she should still be given the best possible clinical care, treated with respect and offered contraceptive advice if she wants it. Every obstetrician and gynecologist knows that once a woman decides to end a pregnancy, she may go as far as risking her own life to do so. Does the ethical responsibility of professionals extend to thinking of ways to spread correct knowledge about the use of misoprostol, even where access to legal abortion is constrained?

CONCLUSIONS

Misoprostol is the 'penicillin' of reproductive health. Just as penicillin introduced a new era of large scale antibiotic use with a measurable impact on global death rates, so too can misoprostol begin to lower maternal mortality ratios worldwide. No other medicine crosses the divide between the joy of a safe delivery of a wanted child and the despair of an unintended pregnancy. The fact that misoprostol is also the first uterotonic that women can self-administer to control PPH, bring on a late period, or induce an early abortion, is also the reason it is certain to remain controversial. The self-administration of misoprostol by lay people is not ideal, but it is an order of magnitude safer than the absence of any therapy for PPH or the alternative of highly unsafe traditional methods of bringing on a late period or inducing abortion.

The first full decade of widespread use of misoprostol has been marked by a revolution in the treatment of PPH and the spread of medical abortion. The next decade is likely to see a further scaling up of use. For the hundreds of million fertile women living on a dollar a day or less, the International Conference on Population and Development (ICPD) and MDG targets to reduce maternal mortality remain as remote today as they were when each was set. Unless technologies and distribution systems to control PPH during home births in the absence of trained birth attendants can be set up, then taking into account the rapid increase in the number of women of fertile age in the poorest countries, it is possible that more women living on a dollar or two a day will die in childbirth each year in the current decade, than died around the time of the 1987 Nairobi Safe Motherhood Conference. Bringing the use of misoprostol to scale has the power to reverse this most tragic of outcomes.

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