Clarifying the role of misoprostol in obstetrics
African Health Sciences Editorial

Andrew Weeks
Visiting Lecturer in Obstetrics, Department of Obstetrics and Gynaecology, Makerere University, Kampala, Uganda

When Searle announced in 1988 that they were launching an orally active prostaglandin E1 analogue for the treatment of peptic ulcers, a ripple of excitement went through the African obstetrics community. Oxytocics are crucial drugs in obstetrics, used for treating abortions, inducting of labour and, perhaps most importantly, controlling postpartum haemorrhage. Despite the importance of oxytocics, the currently available preparations are very unsatisfactory. Ergometrine and oxytocin require a cold chain and can only be given by injection, whilst the current prostaglandins are unstable and very expensive. But misoprostol is a stable, inexpensive, orally active prostaglandin to which the uterus is very sensitive. The potential of misoprostol seemed immense, especially in the developing world where product stability, cost, and ease of use is crucial.

Correspondence
Andrew Weeks
Visiting Lecturer in Obstetrics
Department of Obstetrics and Gynaecology
Makerere University, Kampala, Uganda
Tel: 077-615410
e-mail: aweeks@doctors.org.uk

Thirteen years later the place of misoprostol in the obstetric armoury is clearer, illuminated by some important recent trials. The article by Nikintu in today's *African Health Sciences* sheds further light on its role. She randomised 120 women with intra-uterine fetal demise at a wide range of gestations (18 weeks to term) to induction with either an oxytocin infusion or with wetted misoprostol administered vaginally. The sensitivity to both misoprostol and oxytocin varies greatly with gestation becoming more sensitive as pregnancy progresses. To cope with this she used

a titrated dosage regimen for the misoprostol – 50 mcg of vaginal misoprostol doubled every 6 hours until effective contractions were achieved. This allowed the same protocol to be used for all gestational ages. The choice of wetted tablets is also important. The bioavailability of misoprostol when inserted vaginally appears to be greatly increased when the tablets is wetted – this aspect of the regimen was probably crucial for achieving good results.

The results showed misoprostol's overall superiority to oxytocin, with the mean induction to delivery interval in the misoprostol group being almost half of that in the oxytocin group. The mean cost of the drugs and consumables in the misoprostol group was less than a US dollar compared to over 8 dollars in the oxytocin group. Subgroup analysis showed that the benefits were restricted to those who were unfavourable for induction – those with intact membranes, Bishops scores of less than 6, and those with gestations of less than 28 weeks. These are the groups in whom induction with oxytocin is well known to be difficult. In the developed world prostaglandins have been shown to be superior to oxytocin alone for these groups at term.[1] For pre-term intrauterine fetal demise the standard induction regimen has become treatment with the anti-progesterone mifepristone followed 48 hours later with vaginal misoprostol. This regimen was adopted because the efficacy of vaginal misoprostol alone was found to be low in the early trials where dry tablets were used. With the discovery of the importance of moisture for the efficacy of the vaginal misoprostol, this policy may need to be re-evaluated. Work conducted in the first trimester has demonstrated that if the misoprostol is moistened, then the mifepristone is not necessary for the induction of abortion in the first trimester.[2] If this is the case for other gestations then it will simplify the regimen, as well as removing the 48 hour delay. A randomised trial of moistened misoprostol with or without mifepristone pre-treatment is needed for second trimester inductions to assess whether the anti-progesterone is really necessary.

For induction of viable pregnancies in the third trimester, vaginal misoprostol is quickly becoming the standard prostaglandin, not only because it is far cheaper than the alternatives, but because it appears to be more effective.[3] The one remaining concern is with the frequency of uterine hyperstimulation which appears to be more frequent when a dose of 50 microgrammes 6 hourly is used. It may be that a titrated dosage regime similar to that used by Nakintu is the ideal. A recent trial in which titrated misoprostol was used for induction *and augmentation* of labour found that the incidence of hyperstimulation was no higher than in the controls.[4] More research is awaited.

So should misoprostol be available in every pharmacy across Africa? For induction of labour it appears ideal, and there are multiple other uses in obstetrics. A huge multicentre WHO trial has also recently reported, defining its use for the prophylaxis of post partum haemorrhage (PPH).[5] In a randomised comparison with parenteral oxytocin 10 i.u. they demonstrated that the frequency of a PPH of over 1000mls was 4% with oral misoprostol 600 mg compared with 3% in the oxytocin group ($p<0.0001$). The authors therefore recommend that in places where oxytocin is currently available it should not be replaced with misoprostol. The attention has therefore turned to home births in rural areas where no oxytocics are currently given, and to the use of misoprostol for the *treatment* of PPH. Trials of the former are ongoing, but a recently reported trial suggests that when used rectally in a dose of 800 mg, misoprostol is at least as good as a regimen of intra-muscular oxytocin-ergometrine (Syntometrine®) followed by an oxytocin infusion.[6]

Misoprostol also appears effective in the treatment of incomplete abortions. In the developed world where dilatation and curettage under general anaesthetic is the norm, oral misoprostol in a dose of 600 mg is highly effective and has the benefit of avoiding the dangers of anaesthetic and intra-uterine instrumentation.[7] But it is in using misoprostol in the first trimester that all the trouble begins, for moistened misoprostol given vaginally also appears to be a highly effective inducer of abortions.[2] The manufacturer Searle is well aware of this fact. They are also aware that since the drug company Roche produced the ' abortion pill' (mifepristone), the company has come under intense political pressure to withdraw it, and its workers have received physical threats from the anti-abortion lobby. Eager to protect its image (and its workers' health) Searle has therefore refused to participate in any research of misoprostol in pregnancy, and have constantly sought to remind the medical profession that it is contra-indicated in pregnancy. The unique situation has now arisen where many health provider groups, including the WHO, the American College of Obstetricians and Gynaecologists and the Royal College of Obstetricians and Gynaecologists, are recommending the use of misoprostol in pregnancy against the express wishes of the manufacturer. And Searle is not the only one with anxiety. Many governments are also being cautious about licensing the drug for import, aware of the potential for widespread abortion use. Hence in Africa, South Africa and Ghana remain the only countries in which it is licensed for use.

Misoprostol is the answer to many obstetricians prayers. It is effective, cheap, easy to administer, stable and can be used in a variety of clinical situations. It has an important role to play in modern obstetrics and deserves a place in every doctor's bag. Of course, as with any powerful instrument, it requires close control to prevent it being misused. But African governments should set about licensing its import quickly so that their women can receive the full benefit of this effective and potentially life-saving drug. They may wish to restrict it to controlled drug status, but not to allow its import just because it could be misused would be to deprive their women of the chance to take another step away from the scourge of maternal mortality.

REFERENCES

1. Tan BP & Kelly AJ. Intravenous oxytocin alone for induction of labour. Cochrane Database Syst Rev 2001; Issue 3.
2. Blanchard K, Winikoff B, Ellertson C. Misoprostol used alone for the termination of early pregnancy. Contraception 1999;59:209-17.
3. Hofmeyr GJ & Gulmezoglu AM. Vaginal misoprostol for induction of labour. Cochrane Database Syst Rev 2001; Issue 2.
4. Hofmeyr GJ, Alfirevic Z, Matonhodze B, Brocklehurst P, Campbell E, Nikodem VC. Titrated oral misoprostol solution for induction of labour: a multicentre, randomised trial. Br J Obstet Gynaecol 2001;108:952-9.
5. Gulmezoglu AM, Villar J, Ngoc NTN, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001;358:689-95.
6. Lokugamage AU, Sullivan KR, Niculescu I, et al. A randomized study comparing rectally administered misoprostol *versus* Syntometrine combined with an oxytocin infusion for the cessation of primary post partum haemorrhage. Acta Obstet Gynecol Scand 2001;80:835-9.
7. Pandian Z, Ashok P, Templeton A. Treatment of incomplete miscarriage with oral misoprostol. Br J Obstet Gynaecol 2001;108:213–4.