

Maternal mortality: one death every 7 min

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99% of all deaths in childbirth are in the least developed countries. Annually, 45 million women deliver without a skilled birth attendant, a situation in which the greatest number of maternal deaths occur. In many low-resource settings, having enough skilled birth attendants remains a distant goal. The commonest single cause of maternal death is from post-partum haemorrhage, from which one woman dies every 7 min.

The report by Mariana Widmer and colleagues¹ in *The Lancet* today is a good example of the type of high-quality clinical research being done in well-resourced hospitals. In this large trial (in more than 1400 women), the investigators used 600 µg sublingual misoprostol to treat clinically diagnosed (blood loss ≥500 mL) post-partum haemorrhage, after routine use of oxytocin in the third stage of labour. The study did not detect a difference between misoprostol and placebo. Today's study complements two trials published earlier this year by the same group. One study² found that 800 µg sublingual misoprostol and intravenous oxytocin were equally effective in controlling post-partum haemorrhage in women who had not received oxytocin in the third stage of labour, although the total amount of blood loss was less in the oxytocin group. The second³ found that 800 µg sublingual misoprostol was clinically equivalent to oxytocin in stopping post-partum haemorrhage in women who had already received prophylactic oxytocin and who were suspected of having uterine atony.

These large, well-conducted randomised trials are part of an ongoing effort to build a solid and unambiguous evidence base to further improve obstetric care in well-resourced settings. However, as today's paper concludes, "Any further research on misoprostol should focus on the possible effectiveness of misoprostol in settings where standard uterotonics are not available." Here, an increasingly polarised debate is taking place about the nature of scientific evidence and clinical guidelines in the treatment of post-partum haemorrhage.

For prevention of post-partum haemorrhage, pregnant women delivering at home without a skilled birth attendant can self-administer 600 µg misoprostol orally as soon as possible after their baby is delivered. Studies in Afghanistan, Nepal, and Bangladesh show that women use misoprostol consistently and safely (even for twin deliveries) when the drug is distributed at the community level.^{4,5} Misoprostol 1000 µg rectally has also been used successfully by traditional birth attendants (village midwives) to treat post-partum haemorrhage.⁶ In 2006, the International Federation of Gynecology and Obstetrics (FIGO) and the International Confederation of Midwives agreed that "in home births without a skilled attendant, misoprostol may be the only technology available to control [post-partum haemorrhage]".⁷ In 2006, a WHO expert meeting recommended that "auxiliary nurse-midwives, community midwives, village midwives and health visitors...if they have been specially trained" can distribute misoprostol.⁸ However, in 2009, WHO's Department of Making Pregnancy Safer issued a statement saying "WHO does not recommend distribution of misoprostol to community level health workers or women and their families for routine or emergency use".⁹

The evidence base for establishing policy guidelines in the treatment of post-partum haemorrhage is disputed. What do we do when the type of randomised trial done by Widmer and colleagues is logistically, ethically, or financially impossible to implement? A placebo cannot be used when we know misoprostol makes the uterus contract and no alternative therapy exists. It follows that historical or geographical controls are the only plausible source of evidence about home births without a skilled birth attendant. Are such

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studies to be dismissed as “weak evidence”, as Widmer and colleagues do, or is the standard we should seek the most accurate measurement that is possible in a particular environment? Even the best randomised trial is informative only about the setting in which it was done. For example, Gülmezoglu and colleagues showed that oxytocin performed marginally better than misoprostol did in controlling blood loss in well-resourced hospitals,¹⁰ but in a historical comparison of misoprostol with oxytocin in Egyptian hospitals (where not every woman had a drip and the storage of oxytocin was problematic), blood loss was consistently lower with misoprostol than with oxytocin.¹¹

WHO’s statement also raised concerns about safety.⁹ Misoprostol is a heat-stable uterotonic, costing as little as US\$0.10 a tablet and, since its introduction in 1985, the drug has been used by millions of people to treat gastric ulcers at high doses (800 µg a day) for far more extended periods than those used in obstetrics. The common side-effects of fever and chills are self-regulating. Tens of thousands of women are now self-administering misoprostol in Bangladesh and elsewhere, and no drug-induced deaths and remarkably few serious side-effects have been reported. Are deaths occurring and going unregistered, or is misoprostol not only a highly effective drug but also a remarkably safe one?

WHO’s policy reversal is causing confusion and the need for consensus is urgent. An analysis based on maternal mortality ratios from sub-Saharan Africa showed that targeting post-partum haemorrhage, family planning, and unsafe abortion all have a dramatic effect in the reduction of maternal deaths, but that managing post-partum haemorrhage at the community level with misoprostol has the single greatest effect.¹² Without widespread community use of misoprostol, it is unlikely that Millennium Development Goal 5 will be achieved in sub-Saharan Africa. In a country such as Niger, where 84% of deliveries are at home and where the number of fertile women is increasing by nearly 4% a year, there might be more maternal deaths in this decade than in any previous decades in the country’s history.

The Nigerian National Council of States on Health has just approved the use of misoprostol to prevent post-partum haemorrhage at the community level. However, in countries such as Madagascar, last year’s WHO statement⁹ on the use of misoprostol in the community put the brake on what some consider

potentially life-saving work. On a public highway, applying the brakes can save a life. On the road to safe motherhood an inappropriate application of the brakes by WHO, which inhibits the scaling-up of community-based use of misoprostol during home births, could cause thousands of deaths. We suggest that WHO and FIGO call a joint emergency meeting to explore whether that brake needs to be applied or released.

*Malcolm Potts, Ndola Prata,

Nuriye Nalan Sahin-Hodoglugil

Bixby Center for Population, Health and Sustainability, University of California, Berkeley, Berkeley, CA 94720, USA (MP, NP); and Venture Strategies Innovations, Anaheim, CA, USA (NNS-H) potts@berkeley.edu

MP is a member of the board of Venture Strategies for Health and Development (VSHD), a non-profit organisation that started, at the request of African obstetricians, to make misoprostol available in countries with high levels of maternal mortality, and is married to Martha Campbell, the president and CEO of VSHD. NP and NNS-H work for Venture Strategies Innovations (VSI), set up by VSHD as an independent organisation, to which the focus on misoprostol in multiple countries has been transferred. MP and Martha Campbell receive no funding from VSI or its funders.

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