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World Health Organization

Department of Reproductive Health and Research

Statement

Clarifying WHO position on misoprostol use in the community to reduce maternal death

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Clarifying WHO position on misoprostol use in the community to reduce maternal death

Misoprostol has been arguably the most discussed and researched drug in sexual and reproductive health since the early 1990s. The uterotonic effects of misoprostol to terminate pregnancy were first reported in Brazil. Since then, misoprostol has been researched in many areas of sexual and reproductive health in numerous randomized trials and systematic reviews. WHO currently includes misoprostol in its evidence-based guidelines and *Model List of Essential Medicines* for early pregnancy termination together with mifepristone, medical management of miscarriage and labour induction. An application to include misoprostol for postpartum haemorrhage (PPH) prevention has been deferred until the publication of a large trial in Pakistan and review of its dose-related safety in the immediate postpartum period.

The most controversial use of misoprostol has been its use in PPH prevention and treatment. In a commentary in *The Lancet*, Potts et al. recommend community distribution of misoprostol to pregnant women as the key intervention to achieve Millennium Development Goal 5 – improve maternal health – and further state that rigorous evaluation of benefits and harms of this approach is logistically, ethically and financially impossible.[1] These authors also allege that WHO has changed its position regarding its recommendations on misoprostol use after childbirth. WHO disagrees on both. This technical brief reiterates the WHO position on the use of misoprostol for PPH prevention and management and the issues highlighted by Potts et al.

WHO's work on misoprostol follows the principles of evidence-based decision-making and includes randomized controlled trials,[2] systematic reviews[3] and development of evidence-based guidelines on PPH prevention[4] and management.[5]

For PPH prevention, WHO recommends that *"in the absence of active management of the third stage of labour, a uterotonic drug (oxytocin or misoprostol) should be offered by a health worker trained in its use for prevention of PPH. For misoprostol, this recommendation places a high value on the potential benefits of avoiding PPH and ease of administration of an oral drug in settings where other care is not available, but notes there is only one study. The only trial relevant to this recommendation used 600 µg of misoprostol.[6] The efficacy of lower doses has not been evaluated. There is still uncertainty about the lowest effective dose and optimal route of administration."* [4]

The supporting evidence comes from a trial in India where auxiliary nurse-midwives attending births at home or in primary health centres used misoprostol without any other component of active management of the third stage of labour.[6] This recommendation for misoprostol administration after birth appears to have been misinterpreted as a recommendation for community *distribution during pregnancy* (i.e. advance provision) for use when the need arises after birth.

In July 2009, at the request of Member States for clear guidance in the presence of conflicting information on the use of misoprostol for PPH prevention and management, WHO published a statement, clarifying its position.[7] Potts et al. refer to this publication to claim that WHO has changed its position from what was published in the guidelines. This is incorrect. While WHO does not condemn the community distribution of misoprostol during pregnancy, WHO does not recommend such practice because its potential benefits and harms are currently unknown and recommends proper research to evaluate its role in reducing maternal deaths.

Potts et al. ask the question of whether the deaths are going unregistered or whether misoprostol is highly effective and remarkably safe. This is the most important question and the answer is not yet known. There are clearly potential benefits but also potential harms of misoprostol use, especially with advance distribution during pregnancy. Among 52 mostly facility-based randomized controlled trials with more than 40 000 participants, 15 maternal deaths were reported in seven trials with 24 609 participants.[8] Eleven deaths occurred among women receiving misoprostol compared with 4 women receiving other uterotonics or placebo. All deaths occurred in

women receiving 600 µg or more. It is counterintuitive but plausible that misoprostol at high doses could have adverse effects that may overshadow its benefits. As a prostaglandin 1 (PGE1) analogue, misoprostol induces various systemic effects which have been observed in numerous research studies. Furthermore, advance provision may lead to inappropriate use for labour induction at very high doses with catastrophic results (doses for PPH are about 20 times those needed for labour induction). It is well documented that both oxytocin and ergometrine have been used in inappropriate doses and routes before delivery when they were first introduced causing many unnecessary deaths.[9] Such practices are still believed to be prevalent in some parts of the world.[10]

The studies Potts et al. refer to as evidence of safe and effective misoprostol use are all nonrandomized studies with significant risks of bias. All of these studies have been conducted by groups who firmly believe that misoprostol works and that rigorous research in those contexts is a luxury. Most have indicated only appropriate timing of the administration as a safety endpoint. In addition, Potts et al. are incorrect in claiming that misoprostol 800 µg was as effective as oxytocin in women without previous oxytocin prophylaxis according to the trial published in January 2010.[11] In this trial, additional blood loss ≥500 mL after treatment was experienced by 53 (11%) women given misoprostol versus 20 (4%) women given oxytocin (RR: 2.84 (1.63–5.01)) and the drop in Hb≥30 g/L or blood transfusion was observed in 199 (41%) women given misoprostol and 148 (30%) women given oxytocin (RR: 1.35 (1.14–1.60)). These outcomes strongly suggest that for women with no prophylaxis, oxytocin is clearly more effective than misoprostol in the doses used.

Finally, as Sir Iain Chalmers stated "Because professionals sometimes do more harm than good when they intervene in the lives of other people, their policies and practices should be informed by rigorous, transparent, up-to-date evaluations."[12] It is with this line of thought that WHO has taken a cautious approach regarding the advance community distribution of misoprostol during pregnancy and recommends rigorous research. WHO monitors research in this area very closely and as new evidence becomes available will review the evidence critically and update its guidance to its Member States.

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