

Application to include Misoprostol for prevention of postpartum haemorrhage in WHO Model List of Essential Medicines

Comments from Departments of Making Pregnancy Safer & Reproductive Health and Research

This application should be considered within the context of WHO Recommendations for Prevention of Postpartum Haemorrhage published in 2007¹. Those recommendations relate to the procedures and medications to be used for PPH prevention in the third stage of labour.

WHO recommends active management of the third stage of labour by skilled attendants for the prevention of PPH. This package includes the following interventions: administration of an uterotonic after birth of the baby, clamping and cutting the cord, followed by delivery of the placenta by controlled cord traction. WHO does not recommend active management by non-skilled providers based on potential life threatening risks such as uterine inversion that may result from inappropriate cord traction.

Oxytocin is the recommended uterotonic. Although oxytocin and ergometrine have similar benefits for preventing PPH and have comparable acquisition costs, oxytocin is preferred because of less side effects compared to ergometrine¹.

Misoprostol was not recommended as the first line uterotonic for active management of the third stage of labour.¹ The WHO recommendation placed high value on the relative benefits of oxytocin in preventing blood loss compared to misoprostol, as well as the increased side effects of misoprostol compared to oxytocin. Blood loss of 1000 ml or more was increased with misoprostol compared to oxytocin 10 IU IM (RR 1.34; 95% CI 1.16, 1.55) in three trials of over 18000 women. More additional uterotonics was used with misoprostol (RR 1.41; 95% CI 1.31; 1.5). Shivering (RR 3.29; 95% CI 3.03, 3.56); diarrhoea (RR 2.52; 95% CI 1.6, 3.98) and temperature higher than 38°C (RR 6.62; 95% CI 5.45, 8.05) were more common with misoprostol.

In the absence of active management of the third stage of labour (i.e. passive or expectant management), WHO recommends that an uterotonic drug (oxytocin or misoprostol) should be offered by a health worker trained its use for prevention of PPH. For misoprostol, the recommendation placed a high value on the potential benefits of avoiding PPH and the ease of administration of an oral drug in settings where other care is not available although this was based on one study². In this study, the interventions were administered at births in health centres and at home conducted by auxiliary nurse midwives.

Both oxytocin and ergometrine are administered by injection. Ergometrine is sensitive to light and high environmental temperatures. Oxytocin also deteriorates in high environmental temperatures but over a longer period of time. If oxytocin is stored for 12 months at 30°C, there was 14% loss of potency (range 9-19%). Storage for the same period at 25°C was associated with 7% loss of potency (range 5-9%) but no loss when kept under refrigeration for the same time period³.

Overall, though misoprostol is not the first choice, it can be used by skilled health workers in settings where oxytocin is not available.

Points for considerations:

1. PPH is a major cause of maternal deaths. Fifty to 70% of PPH follows uterine atony; uterotonics reduce the risk of this type of PPH but not risks due to other types of PPH - following trauma, retained placenta, etc. Only a skilled attendant can differentiate between the causes of PPH and initiate appropriate actions.
2. One advantage in favour of misoprostol is its reported stability compared to oxytocin. However unlike oxytocin stability which was studied extensively in laboratory and field studies ⁴, we are not aware of large field studies on stability of misoprostol in tropical climates. Misoprostol is reportedly less stable when exposed to water ⁵. If oxytocin is used routinely for active management of third stage in all cases, the time of exposure to high temperatures is limited ⁶.
3. Buyer prices for oxytocin 10 IU (median USD 0.1645/ml; range USD 0.0879-0.7187) is less than for misoprostol 200 mcg (median USD 0.2233; range USD 0.0900-0.3565) as listed in the International Drug Price Indicator Guide (11 Feb 09). The dose recommended for prevention of PPH is 600 mcg i.e. 3 tablets. Thus at current prices, misoprostol which is less effective than oxytocin is also significantly more expensive than oxytocin.
4. Oral medications are preferable to injectable medicines if they are at least equally effective. However where the injectable medicine is more effective and less expensive, it should be considered the preferred option. While concerns about injection safety, need for skilled personnel, refrigeration, etc are valid, it should be noted that immunization programmes working in similar settings manage well to address these concerns.
5. Internationally, WHO, UNICEF and UNFPA recommend that there should be at least four facilities offering basic emergency obstetric care (EmOC) for every 500,000 people ⁷. Basic emergency obstetric care includes the administration of uterotonics, parenteral antibiotics, magnesium sulfate and provision of manual removal of the placenta. Therefore, at this level of care which includes health centres and small maternity homes in rural areas, oxytocin and active management of the third stage of labour should be promoted and made available as the gold standard uterotonic for PPH prevention.
6. Misoprostol administration is associated with high rates of shivering (NNH 8) and fever (NNH 19) ¹. While these symptoms are not considered life threatening, shivering and high fever can continue for a few hours. No studies have addressed the effects of shivering and high fever on bonding and breast feeding. It would be difficult for a mother to hold or breast feed her baby while shivering. The implications of these side effects on newborn health and survival in resource poor settings, and the potential use and costs of other medications - antipyretics, antimalarials and antibiotics - for fever have not been addressed.
7. The economic assessments of interventions for reducing PPH in developing countries ^{8,9} assume that oxytocin will be administered only by skilled attendants while misoprostol will

be administered by traditional birth attendants even at home births. Community distribution of misoprostol for self administration by the mother after childbirth (or by non-skilled workers) is currently being promoted in many countries based on the results of a study in Indonesia¹⁰. In this study, eligible women in one district were given misoprostol tablets with guidance on use after birth of the baby. Women in the "control" district did not receive these tablets. Women in the intervention area were reportedly "25% less likely to perceive excessive bleeding" (OR=0.76; 95% CI 0.55-1.05; p=0.094) and "45% less likely to need an emergency referral for PPH" (OR=0.55; 95% CI 0.24-1.23; p=0.144) compared to women in the comparison areas. This study has major methodological flaws and its results have not been published in a peer reviewed journal.

WHO colleagues in many countries in SEARO, WPRO and AFRO have reported concerns of their national MOH colleagues that similar projects are being or have been initiated in countries based on the "successful experience in Indonesia". These colleagues have also reported increasing reports of uterine rupture following misoprostol administration. It is unclear if these ruptures are related to misoprostol use for induction of labour or because of administration of this drug for hastening labour. WHO Model List of Essential Medicines includes 25 microgram tablets of misoprostol to be used for labour induction. In settings where such formulation is not available it is likely that small 100 or 200 microgram tablets may be used by dividing those tablets resulting in uneven and unreliable doses. Oxytocin and ergometrine have been misused by untrained workers for augmenting labour and adverse effects have been reported. Unfortunately, monitoring of routine information is poor in many countries where misoprostol for community distribution is promoted. It is also unlikely that systematic monitoring of adverse events will be possible in these countries.

Some organizations are reported to vigorously promote use of misoprostol by **non-skilled workers** citing the WHO recommendation (No 7) on use of misoprostol by trained workers (in the absence of active management of the third stage) in support of their proposal. This WHO recommendation was based on the results of one well-conducted trial² where auxiliary nurse midwives (ANM) administered misoprostol after birth of the baby. It should be noted that although an ANM was considered a skilled health worker earlier¹¹, this category of health worker does not fully satisfy current criteria¹² for the skilled attendant, and hence the reference to "trained health worker". All but one of the RCTs included in the Cochrane review on prostaglandins¹³ have used skilled health workers to administer the intervention. There is therefore insufficient data to recommend the use of misoprostol by non-skilled workers.

Conclusion:

Oxytocin is the best uterotonic for prevention and treatment of PPH. Every effort should be made to make oxytocin available for this purpose.

Misoprostol is an important drug for sexual and reproductive health of women globally. There is evidence of beneficial effects on blood loss when used by health workers trained in its use and while the results of other trials are being awaited, it can be recommended only under circumstances where a trained health worker is present and oxytocin has not been made available.

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