Prevention of Post-Partum Haemorrhage with Misoprostol

FIGO GUIDELINE
ANNOTATED VERSION

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Background Evidence

Post-partum haemorrhage (PPH) is the most important direct cause of maternal mortality in low resource countries, and one of the most preventable. As the most common cause for PPH is the failure of the uterus to contract adequately (atonic uterus), a key aspect in prevention of PPH is uterotonic therapy. The most widely used agent is injectable oxytocin. However, it requires parenteral administration, and, therefore, skills to give injections as well as sterile equipment; and refrigeration. For this reason, misoprostol, an E1 prostaglandin analogue, has attracted considerable attention as an alternative to oxytocin for the prevention of PPH in resource poor settings. Misoprostol is effective, simple to administer, and presents none of the logistical difficulties associated with use of oxytocin.

In 2011, the World Health Organization added misoprostol (600 µg orally) to its Model List of Essential Medicines for the prevention of PPH [WHO prevention guidelines, WHO EML 2011].

Misoprostol versus conventional injectable uterotonics in the prevention of PPH

A systematic review of 16 randomised controlled trials (RCTs) of misoprostol versus injectable uterotonics, involving in total 29,042 women, has shown that oral misoprostol is less effective than injectable uterotonics in preventing severe PPH (blood loss >1000 mL: 3.3% v. 2.4%, relative risk (RR) 1.32; 95% confidence interval (CI) 1.16 to 1.51) [Gülmezoglu 2007].

There is less data on the use of ergometrine for the prevention of PPH. In one double blind RCT involving 1,229 home births attended by traditional birth attendants (TBAs) in rural Gambia, 600 µg oral misoprostol was compared with 2 mg oral ergometrine. While there were no significant differences in measured post-partum blood loss ≥ 500 mL or post-partum Hb < 8 g/dL, misoprostol was more effective at reducing pre- to post-partum Hb ≥ 3 g/dL (16.4% vs. 21.2%; RR=0.77, 95% CI 0.60-0.98). Shivering was significantly more common with misoprostol, but vomiting more common with ergometrine [Walraven 2005].

A review of six studies that used a combination of oxytocin 5 IU and ergometrine 500 µg (Syntometrine®) injected intramuscularly indicates that it is slightly more effective than IM oxytocin alone in reducing PPH > 500 mL (odds ratio (OR) 0.82,

95% CI 0.71 to 0.95), but with higher rates of hypertension and vomiting [McDonald 2004]. Furthermore, the one study that tested IV ergometrine as part of an active management package with physiological management found improvements in PPH rates but a large increase in the rate of retained placenta [Begley 1990]. It is on this basis that FIGO and WHO recommend the use of IM oxytocin 10 IU in preference to the ergometrine containing products.

Misoprostol in the prevention of PPH in situations without access to oxytocin

Early placebo-controlled trials of misoprostol conducted in hospital settings had variable results, and meta-analysis showed variable effects on PPH rates [Gülmezoglu 2007]. They did, however, consistently show that misoprostol markedly reduced the need for postnatal blood transfusion (RR 0.31; 95% CI 0.10 to 0.94). In addition, the three large scale placebo-controlled studies published since 2005 have all consistently shown positive effects of misoprostol in reducing post-partum blood loss [Høj 2005, Derman 2006, Mobeen 2011]. All three trials used misoprostol 600 µg, orally or sublingually, in community or primary health care settings without access to conventional injectable uterotonics. The first was a randomised trial of 661 women attended by midwives in a primary health centre in Guinea-Bissau. Findings indicated sublingual misoprostol 600 µg was significantly better than placebo at reducing severe PPH (blood loss ≥ 1000 mls) [Hoj 2005]. The second, involving 1,620 home births attended by auxiliary nurse midwives in rural India showed 600 µg oral misoprostol to be significantly better than placebo at reducing most indicators of PPH: blood loss ≥ 500 mL, ≥ 1000 mL, need for transfer to a health facility, blood transfusion, and surgical interventions [Derman 2006]. The third, involving 1,119 home births attended by trained TBAs in Pakistan, showed that compared with placebo, 600 µg oral misoprostol significantly reduced the rate of PPH (≥ 500 mL) (16.5% versus 21.9%, RR 0.76, 95% CI 0.59-0.97) and incidence of postpartum declines in haemoglobin > 3 g/dl [Mobeen 2011].

Doses of under 600 µg have also been studied in an attempt to reduce the incidence of shivering and fever. However, results across trials have been inconsistent. While there is some data to suggest that a lower dose of misoprostol may also be effective and could reduce the incidence of side effects, there is a greater body of evidence in support of a 600 µg regimen, and prolonged or serious side effects are uncommon.

Regimen

A single dose of misoprostol **600 µg orally** is indicated for prevention of PPH in settings where oxytocin is not available. The recommended dose does not change according to the woman's weight.

Course of Treatment

Misoprostol should be administered immediately after delivery of the newborn. It is good practice to first do an abdominal palpation to confirm that there are no additional babies *in utero*.

Contraindications

History of allergy to misoprostol or other prostaglandin.

Side Effects

Temperature changes: Shivering, chills and/or fever are all commonly associated with misoprostol. Shivering is the most common side effect and is occasionally accompanied by fever. In the large WHO multicentre study using 600 µg oral misoprostol, shivering was experienced by 18% of women, but temperatures of over 38°C or 40°C were found in only 6 and 0.1%, respectively [Gülmezoglu 2001]. Similarly, when Derman et al. used 600 µg in rural India, shivering occurred in 52.2% of women, but fever in only 4.2% [Derman 2006]. The shivering is self-regulating and even if high temperatures occur, they are transient and settle with reassurance and symptomatic treatment.

Gastro-intestinal effects: Transient diarrhoea, nausea and vomiting may occur following misoprostol, but are rare, occurring in less than 1% women [Gülmezoglu 2001]. An anti-emetic can be used if needed, but in general no action is required except to reassure the woman and her family.

Breast feeding: Small amounts of misoprostol or its active metabolite may appear in breast milk. No adverse effects on nursing infants have been reported.

Self-Administration

In community settings where oxytocin is not available, there are ongoing programmes in which women are given misoprostol tablets for self-administration after delivery. Reports from these programmes suggest that this can be done safely and effectively, but further research is in progress that will clarify the matter. Those providing misoprostol in this way are advised to monitor its use, effectiveness and side-effects; and to make an effort to ensure that, in cases of multiple pregnancies, misoprostol is not administered until after all babies have been delivered.

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Abbreviations

CI	confidence interval
FIGO	International Federation of Gynecology and Obstetrics
Hb	haemoglobin
G/dl	gramme per decilitre
IM	intramuscular
IU	international unit
IV	intravenous
µg	microgramme
Mg	milligramme
ML	millilitre
OR	odds ratio
PPH	post-partum haemorrhage
RCT	randomised controlled trial
RR	relative risk
TBA	traditional birth attendant
WHO	World Health Organization

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