WHO recommendation on the uterotonic drug of choice for the prevention of postpartum haemorrhage in settings where oxytocin is unavailable

21 September 2012

Recommendation

In settings where oxytocin is unavailable, the use of other injectable uterotonics (e.g. ergometrine/methylergometrine or the fixed drug combination of oxytocin and ergometrine) or oral misoprostol (600 µg) is recommended.

(Strong recommendation, moderate-quality evidence)

Publication history

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Assessed as up-to-date: September 2012

Remarks

- Available comparisons are limited, but a significant difference between the benefits of oxytocin and ergometrine is unlikely. This recommendation places a high value on avoiding the adverse effects of ergometrine and assumes a similar benefit from using oxytocin and ergometrine for the prevention of postpartum haemorrhage.
- Caution should be exercised when opting for ergot derivatives for the prevention of PPH as these drugs have clear contraindications in women with hypertensive disorders. Thus, it is probably safer to avoid the use of ergot derivatives in unscreened populations.
- Misoprostol (600 µg PO) was regarded by the GDG as an effective drug for the prevention of PPH. However, the GDG considered the relative benefits of oxytocin compared to misoprostol in preventing blood loss, as well as the increased adverse effects of misoprostol compared to oxytocin.
- The recommendations concerning alternative uterotonics should not detract from the objective of making oxytocin as widely accessible as possible.
- In view of past concerns regarding the community-level distribution of misoprostol and the potential for serious consequences of administration before birth, the GDG places emphasis on training persons administering misoprostol and monitoring community distribution interventions with scientifically...
sound methods and appropriate indicators.

**Background**

Postpartum haemorrhage (PPH) is defined as blood loss of 500ml or more within 24 hours after birth. PPH is the primary cause of nearly one-fifth of all maternal deaths globally. Most of these deaths occur during the first 24 hours after birth. The majority could be prevented through the use of prophylactic uterotonics during the third stage of labour, and by timely and appropriate management.

It is generally assumed that by preventing and treating PPH, most PPH-associated deaths could be avoided. The prevention and treatment of PPH are therefore vital steps towards improving the health care of women during childbirth and the achievement of the Millennium Development Goals. To reach these objectives, health workers in developing countries should be given access to appropriate medications and be trained in procedures relevant to the management of PPH. Countries also need evidence-based guidance to inform their health policies and improve their health outcomes.

**Methods**

The recommendation was developed using standardized operating procedures in accordance with the process described in the “WHO handbook for guideline development”, based on the GRADE approach. (1, 2) Outcomes used for this recommendation were the prioritized outcomes from the WHO recommendations on prevention and treatment of postpartum haemorrhage (2012).(3)

Three systematic reviews provided evidence. (4-6). Randomized controlled trials relevant to the key question were screened by review authors, and data on relevant outcomes and comparisons were extracted. Evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgments for each outcome, and the estimated risks.

WHO convened a Guideline Development Group (GDG) meeting in March 2012. This group of independent experts used the evidence profiles to assess evidence on effects on the pre-specified outcomes. GDG members discussed the balance between desirable and undesirable effects, overall quality of supporting evidence, values and preferences, magnitude of effect, balance of benefits versus disadvantages, resource usage, and feasibility, to formulate the recommendation. Remarks were added to clarify the recommendation, and aid implementation.

Further information on procedures for developing this recommendation are available [here](#).

**Recommendation question**

For this recommendation, we aimed to answer the following question:

For all women giving birth in settings where oxytocin is unavailable (P), does other uterotonic administration during the third stage of labour (I) compared to placebo or no treatment (C) improve maternal outcomes, including postpartum haemorrhage prevention (O)?

**Evidence Summary**
Alternative uterotonic drugs were evaluated in two systematic reviews (20 trials, 18 266 women).(4,5) The treatments compared were: ergometrine (or derivatives) versus oxytocin; ergometrine only versus the fixed dose combination of ergometrine and oxytocin; ergometrine-oxytocin versus oxytocin (the doses and routes varied); IV oxytocin versus IV ergometrine; IM oxytocin versus IM ergometrine; IM oxytocin/ergometrine (as a fixed combination) versus IM ergometrine only; and IV oxytocin versus IM oxytocin/ergometrine (as a fixed combination).

The doses of oxytocin varied in the different trials and ranged between 2 IU and 10 IU, while the doses of ergometrine ranged between 0.2 mg and 4 mg. The fixed drug combination consisted of a 5 IU dose of oxytocin with a 0.5 mg dose of ergometrine.

All the trials were conducted in settings with skilled attendants.
- None of the trials reported maternal deaths.

**Oxytocin versus ergot alkaloids (nine trials, 3960 women)**
- There were no observed differences in critical outcomes between the use of oxytocin versus ergot alkaloids.
- A reduction in blood loss >500 ml was observed (RR 0.8; 95% CI 0.65 to 0.99) with the use of oxytocin when compared with the use of ergot alkaloids. However, the data quality was low and there is a high risk of bias for this outcome.
- Among the adverse outcomes rated as important, the comparison of oxytocin versus ergometrine (or derivatives) showed a lower rate of adverse effects in women treated with oxytocin only. These included nausea (RR 0.13; 95% CI 0.08 to 0.21; NNT 5, 95% CI 4 to 6); vomiting (RR 0.08; 95% CI 0.05 to 0.14; NNT 4, 95% CI 3 to 5) and headache (RR 0.03; 95% CI 0.01 to 0.14).
- There was no observed difference in high blood pressure in women treated with oxytocin only (RR 0.53; 95% CI 0.19 to 1.52), though the quality of evidence was low.
- A lower rate for the manual removal of the placenta was reported in women treated with oxytocin (RR 0.60; 95% CI 0.45 to 0.8)

**Oxytocin versus fixed drug combination oxytocin-ergometrine (seven trials, >10 000 women)**
- The use of the fixed drug combination of oxytocin and ergometrine (IM) was not associated with a reduction in the use of additional uterotonics (RR 1.27; 95% CI 0.91 to 1.76) when compared with the use of IV oxytocin only (two trials, >1600 women). No significant difference was observed between the two groups when blood loss or the need for blood transfusion was compared.
- Among the adverse outcomes rated as important, the fixed dose of oxytocin-ergometrine was associated with a significant increase in vomiting (RR 3.33; 95% CI 1.21 to 9.2) as well as the elevation of diastolic blood pressure (OR 1.96; 95% CI 1.16 to 3.30) compared with a dose of IV oxytocin only.

**When the fixed drug combination of oxytocin and ergometrine (IM) was compared with IM oxytocin only (five trials, 8341 women)**
- Reductions in the use of additional uterotonics (RR 0.78; 95% CI 0.66 to 0.91) and blood loss >500 ml (RR 0.84; 95% CI 0.74 to 0.96) were reported. No differences were found in blood loss >1000 ml, the use of blood transfusion, or the use of the manual removal of the placenta.
- The side-effects among those receiving oxytocin plus ergometrine, as well as those receiving IV oxytocin, included more frequent nausea, vomiting and hypertension.

**Ergometrine versus the fixed drug combination of oxytocin-ergometrine (five trials, >4200 women)**
A significant reduction in blood loss >500 ml (RR 0.57; 95% CI 0.4 to 0.81) was reported in women who received the fixed dose combination of oxytocinergometrine compared with those who received ergometrine only. This finding was not reported for blood loss >1000 ml (RR 1.67; 95% CI 0.4 to 6.94), though the sample size was small and the event rate was noted to be lower.

No differences were found in the use of blood transfusion or the manual removal of the placenta.

Other priority adverse outcomes were not reported for this comparison.

There is currently no evidence to support the use of either oxytocin or ergometrine for the prevention of PPH by non-skilled attendants. Before recommending the general use of injectable drugs that may have adverse effects, appropriate studies of their use by non-skilled attendants should be conducted.

**Oxytocin versus misoprostol**

Evidence for this comparison is based on one systematic review which included seven trials (>22 000 women) which compared the two treatments directly. The oxytocin doses varied between the studies and ranged from 2.5 IU to 10 IU. In the largest trial, which included more than 18 000 women, a dose of 10 IU of oxytocin was used and the misoprostol dose was 600 mcg.

- Among the priority outcomes, two maternal deaths were reported in each arm of the largest trial.
- In six trials (21 977 women), blood loss >1000 ml was reported to have increased with the use of misoprostol compared with the use of 10 IU oxytocin IM (RR 1.36; 95% CI 1.17 to 1.58; NNT 105, 95% CI 70 to 200). There was no statistically significant difference in the use of blood transfusion when misoprostol was used compared with oxytocin (RR 0.77; 95% CI 0.59–1.02). However, there was a greater use of additional uterotonics when misoprostol was used compared with oxytocin (RR 1.4; 95% CI 1.31 to 1.5; NNT 22, 95% CI 19 to 28).
- Among the important adverse effects reported, misoprostol was associated with an increase in shivering (RR 3.3; 95% CI 3.0 to 3.5; NNH 7, 95% CI 7 to 8), diarrhoea (RR 2.52; 95% CI 1.6 to 3.98; NNH 261, 95% CI 177 to 494), and temperatures higher than 38 °C (RR 6.8; 95% CI 5.5 to 8.3; NNH 18, 95% CI 16 to 19).

The evidence provided came from studies conducted in hospital settings in which the interventions were provided by skilled attendants.

**Sublingual misoprostol 600 mcg versus injectable uterotonics**

There was one systematic review of eight relevant trials (>1000 women) that compared the use of sublingual misoprostol versus other uterotonics.

Only two of these trials (220 women) compared the use of sublingual misoprostol (600 mcg) versus IV syntometrine (one trial) and IV oxytocin (5 IU) (one trial).

- There was no difference in blood loss >1000 ml, although the sample size was insufficiently large to rule out potentially relevant differences.
- An increased risk of side-effects was reported, namely shivering (RR 27; 95% CI 1.63 to 446.10; NNH 6, 95% CI 4 to 11), and pyrexia ≥38 °C (RR 33; 95% CI 2.02 to 540.22; NNH 5, 95% CI 3 to 8).

**Sublingual misoprostol (any dose) versus injectable uterotonics**

A further five trials compared a sublingual 400 mcg dose of misoprostol versus injectable uterotonics (0.2 mg methylergometrine IV, and 5 IU and 20 IU of IV oxytocin), one study compared a dose of 200 mcg misoprostol versus 0.2 mg methylergometrine, and another compared a 50 mcg misoprostol dose with either oxytocin 16 IU or methylergometrine 0.2 mg.

- Maternal deaths were not reported.
- There were no observed differences in critical outcomes between the use of sublingual misoprostol
(any dose) and injectable uterotonic, except for a significant increase in the use of additional uterotonic among those receiving injectable uterotonic compared with those receiving sublingual misoprostol (RR 0.61; 95% CI 0.44 to 0.85).

- Among the adverse outcomes rated as important, higher incidences of shivering (RR 9.06; 95% CI 4.46 to 19.39) and maternal temperatures above 38 °C were reported among women who received sublingual misoprostol (RR 13.04; 95% CI 4.77 to 35.62) compared with those women who had received injectable uterotonic. There was no difference between the groups in reported diarrhoea, headache, nausea and vomiting, or the need for the manual removal of the placenta.

**Rectal misoprostol 400 mcg versus injectable uterotonic**

Lower doses of rectal misoprostol (400 mcg) were used in five studies (>2100 women). In one of these trials, misoprostol was dissolved in 5 ml of saline and administered rectally as a micro-enema. Two trials used IM oxytocin (10 IU and 20 IU) as the comparator, and one used oxytocin 5 IU IV or IM, or 10 IU IM. A combination of ergometrine and oxytocin was used in two trials.

- No difference between the treatments was reported regarding the priority outcomes except with regard to the use of additional uterotonic. This outcome measure was reported in three of the five trials (1210 women) and this was reported to be higher in the groups that received misoprostol (RR 1.64; 95% CI 1.16 to 2.31; NNH 8; 95% CI 5 to 27). The relatively low number of subjects, however, suggests that small differences may not have been detected.

- Among the important adverse outcomes, rectal misoprostol 400 mcg was associated with more shivering (RR 2.34; 95% CI 1.88 to 2.92), and pyrexia >38 °C (RR 2.08; 95% CI 1.21 to 3.57)

**Rectal misoprostol 600 mcg versus oxytocin**

Only one study (200 women) in the systematic review compared the use of 600 mcg misoprostol administered rectally versus 10 IU oxytocin IM.

- Maternal deaths, severe PPH (blood loss >1000 ml) and the use of blood transfusions were reported in this trial.

- There were no differences in blood loss >500 ml, the manual removal of the placenta, or the use of additional uterotonic.

- Among the important adverse effects, there were no observed differences reported in nausea, shivering, or temperatures above 38°C, although the sample size was very small.

**Rectal misoprostol 800 mcg versus oxytocin**

- Two trials (>950 women) compared higher doses of rectal misoprostol (800 mcg) versus oxytocin (5 IU IV or 10 IU IM). There were no significant differences between the groups in terms of the critical outcomes.

- Among the adverse outcomes reported, there was a significant increase in shivering among women treated with misoprostol (RR 38.6; 95% CI 11.04 to 134.95). However, serious inconsistency between the trial results was noted and there was significant statistical heterogeneity (I² = 82%).

**Carboprost versus oxytocin**
Evidence came from one systematic review of 10 trials in which the use of injectable prostaglandins (sulprostone, carboprost, and prostaglandin F2 alpha) was compared versus the use of other injectable uterotonic (s >1300 women). Carboprost was compared versus IV ergometrine in four trials (600 women), versus IM syntometrine in one (115 women) and versus IV oxytocin in another (132 women). Sulprostone was compared versus IV oxytocin in one trial (74 women), and versus IV oxytocin and IM ergometrine in another (69 women). Prostaglandin F2 alpha was compared versus IV methergin in two trials (400 women) and versus IV oxytocin in another (60 women). No study was identified in which the use of carboprost/sulprostone was compared versus the use of 10 IU of oxytocin IM.

- Overall, there were no differences in the priority outcomes in the trials of injectable prostaglandins.
- Among the important adverse effects reported, intramuscular prostaglandins were associated with more vomiting (RR 2.33; 95% CI 1.06 to 5.11), more diarrhoea (RR 12.28; 95% CI 4.47 to 33.70), and more abdominal pain (RR 4.99; 95% CI 1.46 to 17.05).
- Maternal high blood pressure and shivering were not assessed.

Further information on evidence supporting this recommendation are available here.

Implementation considerations

- The successful introduction of evidence-based policies related to the prevention and management of PPH into national programmes and health care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. These processes may include the development or revision of national guidelines or protocols based on this recommendation.
- The recommendation should be adapted into locally-appropriate documents and tools that are able to meet the specific needs of each country and health service. Modifications to the recommendation, where necessary, should be justified in an explicit and transparent manner.
- An enabling environment should be created for the use of this recommendation, including changes in the behaviour of health care practitioners to enable the use of evidence-based practices.
- Local professional societies may play important roles in this process and an all-inclusive and participatory process should be encouraged.

Research implications

The GDG identified these research priorities related to this recommendation:

- What is the minimum effective dose of oxytocin for the prevention of PPH?
- What are the effects of IM oxytocin (versus IV oxytocin) for the prevention of PPH?
- Can oxytocin be administered safely by unskilled attendants?
- What are the effects of buccal and sublingual use of oxytocin for the prevention of PPH?
- What is the appropriate time to administer oxytocin for PPH prevention, relative to cord clamping and placental delivery? (i.e. before/after cord clamping, before/after placenta delivery).
Related Links

WHO recommendations on prevention and treatment of postpartum haemorrhage (2012) - full document and evidence tables

Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice

Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors (2nd ed)

VIDEO: Active management of third stage of labour

Education material for teachers of midwifery. Managing postpartum haemorrhage.

Links to supporting evidence:


References


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