SAFETY PROFILE OF MISOPROSTOL FOR OBSTETRICAL INDICATIONS

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INTRODUCTION
Cervical ripening, full-term labour induction, and postpartum haemorrhage (PPH) are obstetric conditions that require proper and early interventions in order to save maternal and fetal lives. These interventions include pharmacological (uterotonic agents, mainly) and non-pharmacological methods that have been tested and compared throughout the past decade.

Regarding injectable uterotonic medicines (such as oxytocin, ergometrine, syntometrine, prostaglandins, and, more recently, carbetocin), factors limiting their use in low-resource settings have been their cost, instability at high ambient temperatures, and difficult requirements of administration. In poor and rural settings, birth attendant skills are limited, transport facilities are inadequate, and injectable uterotonics and blood are hardly available. In contrast, misoprostol, a synthetic prostaglandin E1 analogue, presents low cost, storage at room temperature, and widespread availability. Misoprostol could also be easily administered by unskilled attendants or the women themselves, thus making them available for women giving birth at home or in isolated areas. These are benefits that make it particularly appealing for developing poor countries.1

Despite the built evidence of efficacy, induction of full-term labour in women with a live fetus, as well as prevention and treatment of PPH, remains as a major challenge in modern obstetrics. Safety profile of misoprostol is still a matter of concern, especially relating to doses and routes used for the mentioned purposes.2

Misoprostol can be effectively administered vaginally, rectally, bucally, orally and sublingually. Pharmacokinetic studies have demonstrated the properties of misoprostol after various routes of administration. The rate of absorption varies considerably between routes, and care must be taken to use the correct dose and frequency for the specified route. The dosage range is also widely variable for different obstetric indications, working as a confounder relating to safe dosages for reproductive health indications. If unsafe dosage is used, side effects are more prone to occur because they seem to be dose-related.3

Regarding safety, current publications emphasize and compare lower doses of misoprostol for all indications, because they have proved efficacy and low incidence of side effects.

For preparing uterine cervix and inducing labour, misoprostol main adverse effects refer to contraction abnormalities (tachysystole, hypertonus and hyperstimulation), and uterine rupture, which may be life-threatening for both mother and fetus. Hyperstimulation may result from excessive or repeated doses of misoprostol when used for labour induction. Uterine rupture is considered a rare complication of labour induction with misoprostol, but it can happen even with a low-dosage use. It is important to keep in mind that uterine rupture could also be associated with other inductive methods.

Regarding fetal and perinatal outcomes, data are sparse but some trials reported increased frequencies of meconium passage, neonatal acidaemia and caesarean delivery for fetal distress, apparently dose-dependent events. Also they have suggested
associations between labour induction and stillbirth or neonatal resuscitation or neonatal intensive care unit (NICU) admission.

Misoprostol use for prevention and treatment of postpartum haemorrhage (PPH) is consistently associated with increased risk of shivering and pyrexia, reported in the majority of clinical trials as a transient and dose-dependent finding.4

Other reported side effects are nausea, vomiting, diarrhoea, and abdominal cramps. Abdominal cramps usually develop within the first few hours and may start as early as 10 minutes after administration. Diarrhoea is the most common gastrointestinal side effect and it is usually mild and self-limiting within a day; vomiting usually resolves in less than 6 hours. These events seem to be associated to determined doses and routes. They are more common after oral or sublingual administration.3

A few maternal deaths were reported in a recent large meta-analysis, which had occurred during misoprostol use for management of PPH. Some deaths were due to severe haemorrhage, while others did not seem to be directly related to haemorrhage.5

Perinatal outcomes linked to misoprostol preventive use in PPH are rarely reported. A negligible amount of misoprostol was detected incolostrum 5 hours after oral intake. The concentration of misoprostol acid in colostrum per kilogram of body weight of the newborn is very small, probably insufficient to cause side effects in the breast-fed infant.6 A pharmacokinetic study measured single oral doses of misoprostol 200 µg in breast milk of 10 lactating women who require postpartum uterotonic therapy. Milk misoprostol levels rose and declined rapidly, consequently lowering infant exposure.7

Despite the international interest, expressed through government and professional society meetings, and the reinforced evidence published in peer-reviewed journals during the past 13 years, there are uncertainties regarding misoprostol administration schedule, specifically involving safety-related dose-response curve.

Therefore, evidence-based information about the safest misoprostol regimens – taking into account the accuracy of accomplishment to regimens recommended in international protocols – should be discussed, both to prevent its inappropriate use and to define the real safety profile of misoprostol.

This review focuses on safety of misoprostol in pre-induction and induction of labour, as well as on prevention or treatment of postpartum haemorrhage, by means of comparisons among different uterotonic agents and different misoprostol regimens.

**OBJECTIVES**

The aim of this review is to clarify the safety profile of misoprostol, as well as how it may be affected by dose and route of administration, when used for management of cervical ripening and labour induction in the third trimester of pregnancy, and for prevention and treatment of PPH in the third and fourth stages of labour.

**METHODS**

Medline, PubMed (using tools: Mesh Browser [(", Induced"[Mesh] OR (", Induced/adverse effects"[Mesh] OR ", Induced/mortality"[Mesh] AND "Misoprostol" [Mesh] ) and Limits, such as publication date, any language, humans, meta-analysis, randomized controlled trial); EMBASE; The Cochrane Library; Cochrane Central Register of Controlled Trials (CENTRAL); Lilacs and Scielo databases; Sietes (Sistema de Información Esencial en Terapéutica y Salud); BMJ Clinical Evidence; and [http://www.misoprostol.org](http://www.misoprostol.org) website were searched for relevant articles published
between 1995 and 2010, with concentration on randomized controlled trials (RCTs) and systematic reviews focusing misoprostol maternal and neonatal safety, and using the keywords “misoprostol”, “labour/induction”, “cervical ripening”, “postpartum haemorrhage/hemorrhage”, “maternal and fetal misoprostol side effects.” Additional references from identified articles were reviewed. Each article was screened for relevance and the full text acquired if determined to be relevant. Each full-text article was critically appraised regarding misoprostol safety in labour pre-induction and induction and in postpartum haemorrhage prevention and treatment. This review excluded studies about efficacy and safety of misoprostol used for abortion, labour induction in the first two trimesters of pregnancy, and cervical ripening in other medical indications.

The search for eligible systematic reviews and randomised controlled trials found altogether 15 systematic reviews and 193 RCTs related to cervical ripening/labour induction management, and 12 systematic reviews and 137 RCTs that assessed safety in prevention/treatment of PPH. From all these publications, 17 systematic reviews and 70 RCTs remained for critical appraisal and inclusion. Almost all of individual studies included in the systematic reviews are not mentioned in the text.

The endpoints of interest consist in comparisons among different uterotonics, different doses and different routes referring to maternal and fetal safety.

**FINDINGS**

**MISOPROSTOL FOR CERVICAL RIPENING AND FULL-TERM LABOUR INDUCTION**

Sometimes it is necessary to bring on labour artificially because of safety concerns for the mother or child. The procedure may be performed for medical reasons or on request by the woman (elective induction). Worldwide prevalence of labour induction varies greatly between countries. It seems to be higher in developed countries than in developing ones, ranging between 22.1% in the United States in 2004 and 11.4% in eight selected Latin American countries.9

For women with unfavourable cervix, uterine cervical ripening favours the success of induced labour. For cervical ripening10 and labour induction,1 misoprostol has confirmed comparative effectiveness. However, the use of oxytocin is very common in the induction process. Even in Brazil, where misoprostol is officially available as 25 μg vaginal tablets for cervical ripening and labour induction since 2001, its use alone was reported in only 4.1% of cases in a survey carried out in Latin America.9

Some authors contraindicated misoprostol for labour induction in women with a previous caesarean section, due to an increased risk of uterine rupture and adverse neonatal outcomes.11 Such opinion is contradicted by other studies that have shown good results even in those women.

Despite the high number of publications, the results about misoprostol schedules are variable and sometimes contradictory, as well as the misoprostol safety profile in cervical ripening and labour induction. So, some evidences that aim to clarify these issues were searched.

**Safety comparisons between misoprostol and other uterotonics**

Cervical ripening and labour induction involve the use of uterotonic agents. The considered gold standard for induction protocols is cervical ripening with a vaginal
Misoprostol versus oxytocin

A Cochrane systematic review included seven trials (1017 participants) comparing oral misoprostol with intravenous oxytocin for labour induction. In terms of safety, the only significant difference between the groups was an increase in meconium-stained liquor in women with ruptured membranes following administration of oral misoprostol (RR = 1.72; 95%: 1.08 - 2.74).

Another Cochrane systematic review showed that vaginal misoprostol was associated with more uterine hyperstimulation in comparison to oxytocin for labour induction.

In contrast, a meta-analysis that compared misoprostol to oxytocin for labour induction (9 studies) showed that misoprostol was not associated with an increased risk of tachysystole, hypertonus, or hyperstimulation syndrome, and had similar risks for adverse neonatal and maternal outcomes.

Another meta-analysis showed that misoprostol might increase the risk of precipitous labour, abnormal uterine contractions or meconium stained amniotic fluid in comparison to oxytocin for labour induction.

A recent pilot study investigated the effects of oxytocin infusion and 25 μg vaginal misoprostol 4-hourly within 24 hours in 100 neonates who were born via the vaginal route after labour induction. The bilirubin levels in the oxytocin group were significantly higher than those in the misoprostol group on day one (P = 0.035), but not in day four. However, the levels of bilirubin in both groups were within normal ranges.

A study compared misoprostol and oxytocin for cervical ripening. There was no difference between the 2 groups with regard to hyperstimulation, tachysystole, postpartum haemorrhage, blood transfusions, intraamniotic infection, or endometritis. Similarly, there was no difference in the 2 groups with respect to neonatal outcome. Macrosomia, Apgar scores, umbilical artery blood pH and gases, and neonatal intensive care unit admissions were all similar between the 2 groups.

In another trial, 62 consecutive patients for induction of labour were randomized into vaginal misoprostol (50 μg 6-hourly to a maximum of four doses) or intravenous oxytocin (maximum of 48 IU/min) study groups. There were no significant differences in the mean Apgar score and perinatal mortality rate in the two study groups. There were two cases of primary postpartum haemorrhage in the oxytocin group but none in the misoprostol group. One case of ruptured uterus was encountered in the misoprostol group. No case of maternal mortality was recorded. Four patients in the misoprostol group had minor side effects, mainly nausea and vomiting.

A randomized controlled trial compared 25 μg intravaginal misoprostol every 4 hours, not exceeding 8 doses, with intravenous oxytocin in a continuous infusion for cervical ripening and labour induction in 210 pregnant women with unripe cervices. With regard to uterine tonus alterations, tachysystole was significantly more common.
in the misoprostol group. However, there was no difference in hypoxia and neonatal morbidity between the groups.

**Misoprostol versus dinoprostone**

A systematic review\textsuperscript{22} of 14 eligible articles did not find difference in the risk of caesarean delivery between misoprostol and PgE2 groups (RR = 0.99; 95% CI = 0.83-1.17). Misoprostol was associated with higher risks of tachysystole and hyperstimulation compared with PgE2 (RR = 1.86, 95% CI: 1.01-3.43 and RR = 3.71, 95% CI = 2.00-6.88, respectively). A trend towards increased meconium staining was observed (RR = 1.22; 95% CI: 0.96-1.55).

A Cochrane systematic review\textsuperscript{14} included 9 trials (2627 participants) comparing oral misoprostol with vaginal dinoprostone. Uterine hyperstimulation was more common after oral misoprostol (RR=1.63; 95%CI: 1.09 - 2.44) although this was not associated with any adverse perinatal events. There were fewer studies comparing oral misoprostol and intracervical dinoprostone, but these found that the oral misoprostol (at doses of 50 and 100 μg) resulted in stronger contractions than the dinoprostone. This led to higher rates of hyperstimulation, but with no effect on fetal outcomes.

Another Cochrane review\textsuperscript{15} found that vaginal misoprostol presented higher rates of uterine hyperstimulation and meconium stained liquor than vaginal or intracervical dinoprostone. Whether the latter effect was secondary to uterine hyperstimulation or due to a direct effect of misoprostol on the fetal bowel remained undefined.

With the lower misoprostol doses now recommended (25 μg vaginally or 20 μg orally), the incidence of hyperstimulation is similar to that of dinoprostone.

A systematic review of five trials that estimated the efficacy and safety of 20 μg oral misoprostol solution administered every 2 hours versus dinoprostone showed no statistically significant differences in risks of uterine hyperstimulation or need for oxytocin augmentation.\textsuperscript{23}

Two randomised clinical trials,\textsuperscript{24,25} with a similar study design, compared efficacy and safety vaginal misoprostol with dinoprostone vaginal insert for labour induction in term pregnant women with unfavorable cervices. Both of them did not demonstrate significant differences referring to tachysystole and uterine hyperstimulation, and admission to neonatal intensive care units. In one of them, Cesarean delivery for a non-reassuring fetal heart rate tracing was more common with misoprostol, while in the other this outcome was not significantly different between groups.

A non-blinded, randomised, controlled trial (n=588 women)\textsuperscript{26} directly compared intravaginal dinoprostone (2 mg once every 6 hours) or misoprostol (25 μg once every 4 hours) or a transcervical balloon catheter. Dinoprostone, misoprostol, and the catheter were shown to be equally safe. There were no significant differences in the three study groups relating to birthweight, Apgar score at 5 minutes, cord pH, and neonatal intensive care unit admissions. The incidence of uterine hyperstimulation was low and similar in all the three groups. None of the participants suffered uterine rupture. There was a tendency towards more frequent occurrence of meconium in the amniotic fluid in the misoprostol group.

A randomised, open-label, non-inferiority study\textsuperscript{27} compared misoprostol (initially 25 or 50 μg followed by 25 μg after 4 and 8 hours) with dinoprostone (initially 3 mg followed by 3 mg after 6 hours) in 626 nulliparous or multiparous women eligible for
induction of labour. Maternal and fetal adverse events were similarly distributed across the misoprostol and dinoprostone groups.

A randomised controlled trial compared 50 μg intravaginal misoprostol every 6 hours for a maximum period of 24 hours versus 0.5 mg dinoprostone cervical gel for cervical ripening and labour induction. Among 130 patients evaluated, the tachysystole and hyperstimulation syndrome rates were slightly increased in the misoprostol group than in the dinoprostone group without reaching the level of statistical significance.28

Another randomised study29 compared effectiveness, safety, and side effects of 50 μg intravaginal misoprostol (204 women) versus 3 mg intravaginal PGE2 (211 women) for labour induction. In both groups, the dose was repeated every 6 hours for a maximum of 3 doses until active labour was achieved. Tachysystole occurred without oxytocin augmentation and was observed more frequently in the misoprostol group than in the PGE2 group (18.6% vs. 9%, respectively; \( P < 0.05 \)). However, there was no significant difference in the occurrence of uterine hypertonia (17 and 19 cases, respectively). No statistically significant differences were observed in neonatal events (abnormal fetal heart rate patterns, Apgar scores, cord blood pH, need for neonatal resuscitation or admission to the neonatal intensive care unit) or maternal side effects attributed to the medication (nausea, vomiting, diarrhoea, and fever). The last side effects occurred in a total of nine cases in both groups.

Regarding frequency and timing of cardiotocographic abnormalities associated with the use of misoprostol (50 μg every 6 hours in 2 doses), dinoprostone gel (0.5 mg every 6 hours in 2 doses), and dinoprostone vaginal pessary (10 mg in 1 dose for 12 hours), as preinduction agents in 111 women undergoing induction of labour with an unfavorable cervix, those events were more frequent after misoprostol administration compared with the dinoprostone analogues.30 These results were already seen in another comparison between misoprostol and dinoprostone gel, in which pathological CTG tracing was more frequent in the misoprostol-treated group \( (P < 0.001) \).31

A randomised multicentre trial (n= 681 women)32 compared vaginal misoprostol (25 μg, every four hours, maximum three times daily) or dinoprostone gel (1 mg, every four hours) for labour induction. Adverse neonatal outcome (5-minute Apgar score <7 and/or umbilical cord pH <7.15) was found to be similar in both groups: 21% in the misoprostol and 23% in the dinoprostone groups. Significantly fewer neonates were admitted to NICU in the misoprostol group compared with the dinoprostone group \( (RR = 0.7; 95\%CI: 0.5-0.98) \).

Safety comparisons between lower and higher doses of misoprostol

Former studies compared higher misoprostol dosage, such as 100 μg versus 50 μg, in repeated administrations, for preinduction and induction of labour. One example is a double-blind controlled trial33 carried out in 203 women who randomly received 50 μg or 100 μg sublingual misoprostol. Sublingual misoprostol is more effective with the highest dose. However, the incidence of tachysystole was significantly higher in the 100 μg group \( (P = 0.02) \). The incidence of hyperstimulation syndrome was higher in the same group, but not statistically significant \( (P = 0.46) \). With respect to the perinatal outcome, no significant differences between treatment groups were observed.

Subsequently other studies have been published comparing even lower doses. A Cochrane review13 showed that lower doses of vaginal misoprostol (not exceeding 25 μg 4-hourly) appeared to have similar effectiveness and risk of uterine
hyperstimulation as conventional labour inducing methods. Compared to higher
doses, lower doses were associated with more need for oxytocin augmentation, less
uterine hyperstimulation, with and without fetal heart rate changes, and a non-
significant trend to fewer admissions to neonatal intensive care unit. Use of a gel
preparation of misoprostol versus tablet was associated with less hyperstimulation.

A systematic review34 that included five published randomized controlled trials
(RCTs) compared the safety and efficacy of 25 μg versus 50 μg repeated doses of
intravaginal misoprostol for cervical ripening and induction. Tachysystole and
hyperstimulation syndrome appear to occur less frequently among women who
received 25 μg of misoprostol than 50 μg. However, neonatal outcomes appear to be
comparable with the two doses.

Various studies, with similar methodological design, compared doses of 50 μg
versus 25 μg, via different routes, of misoprostol for induction at term. The incidence
of tachysystole was significantly higher in the 50 μg groups than in the 25 μg groups,
without significant difference with respect to incidence of hyperstimulation syndrome,
and no ruptured uterus. Comparable neonatal outcomes were found with both doses
in terms of assigned Apgar score at 1 and 5 minutes, meconium stained amniotic fluid,
birth weight, and referral of the infants to the pediatrician.35-37

A randomised trial38 compared efficacy and safety of oral misoprostol solution (1
μg/ml, every 1 hour for four doses) titrated against individual uterine response and
vaginal misoprostol (25 μg every 4 hours until attaining a more favourable cervix) for
labour induction in women at term with an unfavourable cervix. The incidence of
hyperstimulation was 0.0% in the titrated oral group compared with 11.3% in the
vaginal group (RR =0.08; 95% CI: 0.01-0.61). Although more women experienced
nausea (10.9%) in the titrated oral group (RR= 27.07; 95% CI: 1.57-465.70), fewer infants
had Apgar scores of less than 7 at 1 minute in the titrated oral group than in the
vaginal group (RR= 0.10; 95% CI: 0.01-0.76).

Another randomised controlled trial (n=758)39 compared a titrated low-dose
misoprostol regimen (50 μg oral or 25 μg vaginal initial dose, the latter for
unfavourable cervix, followed, 4 hours later, by the titrated 2-hourly 25 μg or 50 μg
oral misoprostol regimen, according to the need of uterine contractions, up to 24 hours)
versus a standard induction method (vaginal dinoprostone followed by intravenous
oxytocin if the cervix was unfavourable or intravenous oxytocin alone if the cervix was
favourable) for induction of labour in the presence of prelabour rupture of membranes.
The maximum possible dose in a 24-hour period for the unfavourable cervix subgroup
was 525 μg, and for the favourable cervix subgroup was 600 μg. There was no
difference in the uterine hyperstimulation or hyperstimulation syndrome. Overall,
misoprostol was associated with more maternal adverse effects, but no significant
difference was seen for individual side effects (nausea, vomiting, diarrhoea, shivering,
and pyrexia > 38 °C during labour). The majority of maternal complications (three cases
in misoprostol group) were due to postpartum haemorrhage. There were no cases of
uterine rupture or maternal death. There were no differences in neonatal outcomes,
and in general, the incidence of markers of neonatal morbidity was low. There were no
neonatal deaths and only one neonatal complication (a case of neonatal sepsis) in the
control group.

A double-blind pilot clinical trial40 randomly assigned 62 term pregnant women, to
receive 25 μg (32) or 12.5 μg (30) vaginal misoprostol each four hours, until the
maximum of eight doses. The two groups did not significantly differ in relation to efficacy outcomes, as well as Apgar scores below seven at the fifth minute (3.3 versus 6.25%, P=0.533) and tachysystole frequency (3.3 versus 9.3%, P=0.533). The average total administered dose was significantly higher in the 25 μg misoprostol group than in the 12.5 μg misoprostol group (61.2 μg vs. 40 μg, respectively; P<0.03).

Currently, the recommended doses for induction of labour using misoprostol are 25 μg vaginally or 50 μg orally every 4 hours for a maximum of six doses. Another option is 20 μg oral misoprostol solution every 1 or 2 hours for a maximum of 12 doses.

**Safety comparisons between different routes of misoprostol**

Misoprostol administered orally and sublingually has the advantage of rapid onset of action, while the sublingual and vaginal routes have the advantage of prolonged activity and greatest bioavailability. It has been shown that the route of administration of misoprostol has a strong impact on the pharmacokinetic profile that results in different clinical efficacy.

Head to head comparisons of low-dose oral and vaginal misoprostol are few, but one study has shown that 20 μg oral misoprostol solution administered 2 hourly is as effective as vaginal misoprostol in achieving vaginal delivery, but with a much lower rate of uterine hyperstimulation. A systematic review of two studies compared oral with vaginal low-dose misoprostol. Women using oral misoprostol were significantly less likely to experience uterine hyperstimulation with fetal heart rate changes (2% versus 13%; RR=0.19; 95% CI: 0.08-0.46), but there were no significant differences in other outcomes.

A Cochrane review that included sixteen trials (3645 participants) compared oral and vaginal misoprostol and found less uterine hyperstimulation without fetal heart rate changes in those given oral misoprostol (RR=0.37; CI95%: 0.23-0.59). Oral misoprostol was associated with more meconium-stained liquor (RR=1.27; 1.01-1.60).

In a quasi-experimental study, 50 μg misoprostol (maximum 150 μg) was administered, either by oral or vaginal route, to 80 at term pregnant patients. There was no significant difference between both groups with regard to maternal complications and neonatal outcome.

Another study (n=310 term pregnancies) compared the safety and efficacy of 50 μg misoprostol orally or vaginally every 4-6 hours to a maximum of six doses for induction of labour. As secondary outcome, the study included frequency of tachysystole/hyper stimulation, maternal side effects, caesarean section rate, and neonatal outcome (Apgar score, need of neonatal intensive care). In the vaginal group there was an increased incidence of hyperstimulation and tachysystole (8.3% vs. 1.8%). A higher incidence of neonatal intensive care unit admission in the vaginal group was mainly due to respiratory distress syndrome. So, the vaginal route demonstrated more efficacy than the oral route, but a slightly lesser safety relating maternal and neonatal outcomes.

A Cochrane systematic review (3 studies; 502 participants) compared various routes (buccal, sublingual, vaginal and oral) and doses (200, 100, and 50 μg) of misoprostol for cervical ripening and induction of labour. When the same dosage was used by both routes, the sublingual route was associated with better effectiveness outcomes. However, none of the differences reached statistical significance, as well as when a smaller dose was used sublingually than orally. In both subgroups, the
numbers with uterine hyperstimulation with and without fetal heart rate changes and Apgar scores less than seven at five minutes were too few for meaningful statistical analysis. The buccal route was associated with a trend to fewer caesarean sections than with the vaginal route, but there were no significant differences in any other outcomes.

A systematic review of 5 trials (740 participants) compared sublingual to vaginal misoprostol routes of administration for induction of full-term labour with a live fetus. No statistically significant difference was found between the sublingual and the vaginal misoprostol groups with respect to the uterine hyperstimulation syndrome (OR = 1.20; 95% CI: 0.61-2.33) or caesarean section (OR = 1.33; 95% CI: 0.96-1.85). An increased risk of uterine tachysystole was found in the sublingual misoprostol group (OR = 1.70; 95% CI: 1.02-2.83). When the studies were grouped according to the initial dose of misoprostol, no significant difference was found between sublingual or vaginal groups.

**MISOPROSTOL FOR PREVENTION AND TREATMENT OF POST-PARTUM HAEMORRHAGE**

Post-partum haemorrhage (PPH) is defined as blood loss in excess of 500 ml, and severe PPH, as blood loss equal or in excess of 1000 ml, occurring at a variety of sites (uterus, cervix, vagina and perineum) in the first 24 hours after birth. Primary PPH due to uterine atony occurs when the relaxed myometrium fails to constrict uterine blood vessels, thereby allowing haemorrhage. This is responsible for the majority of cases. However, obstetrical injury can also cause primary PPH, as well as retained placenta, invasive placenta, and coagulopathies. PPH is a clinical problem of indisputable importance to patients. Even the mild self-limiting cases have consequences for the patient’s puerperium in the form of fatigue, tiredness, failure to breast-feed and possible need for haematinics or blood transfusion. More severe cases can cause maternal mortality and morbidity, mainly in poor developing countries, where the risk of dying is 100 times higher than in developed countries.

The prevalence of postpartum haemorrhage and severe postpartum haemorrhage is approximately 6% and 1.86% of all deliveries, respectively, with a wide variation across regions of the world. The differential risk of death from PPH is of 1 per 16 in Africa and 1 per 300 in Latin America compared with 1 in 3700 in the United States. According to Karoshi and Keith, this represents the difference in the accessibility of medical care to patients who live in areas devoid of public and private health systems that provide appropriate conditions related to women’s and children’s health care.

The incidence of PPH is reduced by about 60% when some form of prophylaxis is practised versus expectant management of the third stage of labour in hospital setting. The most recommended strategy is active management during the third stage of labour (AMTSL) that includes uterotonic use, controlled cord traction, and fundal massage, and can reduce the occurrence of severe PPH by approximately 60-70%. This estimated benefit might be lower in non-hospital settings, because AMTSL requires skills and training to be performed appropriately. Controlled cord traction is one of those components that need training in manual skill for it to be performed appropriately. Currently, a research group aims to investigate whether a simplified package of AMTSL can be recommended without increasing the risk of PPH. By avoiding this manual procedure that requires training, the third stage management could be more feasible at low-resource settings.
In seven tertiary centers in southwest Nigeria, with a high rate of compliance with most of the individual components of AMTSL, the frequencies of PPH and severe PPH were 4.9% and 0.8%, respectively. Frequencies of PPH, postpartum anemia, and mean blood loss among women who received AMTSL were significantly lower than for those who did not ($P < 0.05$).\textsuperscript{31}

In spite of the availability of evidence and international recommendations and protocols, there is little use of AMTSL in developing countries. Correct use of AMTSL was found in only 0.5% to 32% of observed deliveries due to multiple deficiencies in practice.\textsuperscript{32}

The role of misoprostol in PPH prevention and treatment is controversial, as a consequence of a large number of studies in which inconsistencies occur by means of a multiplicity of schedules (doses, routes and frequency in variable combinations) and different execution of procedures. The last issue is more visible in studies carried out in hospital-settings versus those performed in resource-poor communities. In these communities, a randomised controlled trial\textsuperscript{33} estimated that one case of PPH (blood loss $\geq$ 500 ml) could be prevented for every 18 women that received 600 μg oral misoprostol. Thus, in less-developed countries, misoprostol, even if slightly less effective than conventional uterotonics, appears as a useful alternative. A pharmacoeconomic analysis\textsuperscript{34} concluded that misoprostol is a cost-effective maternal mortality intervention for home births carried out in rural settings.

A large meta-analysis (22 studies; 30,017 participants)\textsuperscript{35} conducted on the efficacy of misoprostol for the prevention of PPH demonstrated that excess risk of PPH on misoprostol use was only 4% in comparison to oxytocics. This risk difference was well within the range of expected results for all uterotonic agents and does not warrant branding misoprostol as an inferior drug. Langenbach emphasized the need to stop comparing misoprostol with established oxytocics in hospital situations. Additionally, prophylactic injectable uterotonics could have lesser effectiveness in the remote locations, due to a non-appropriate management.

So, in low-resource settings, some authors advocate to perform comparisons between misoprostol and placebo regarding the definition of side effects. For instance, the maternal and neonatal side effects were investigated in 1620 women delivering at home or subcentres in rural India who randomly received 600 μg oral misoprostol or placebo in the third stage of labour. Women who received misoprostol had a significantly greater incidence of shivering (52% vs. 17%; $P < 0.001$) and fever (4.2% vs. 1.1%; $P < 0.001$) at 2 hours postpartum compared with women who received placebo. At 24 hours, women in the misoprostol group experienced significantly more shivering (4.6% vs. 1.4%; $P < 0.001$) and fever (1.4% vs. 0.4%; $P < 0.03$). There were no differences in nausea, vomiting or diarrhea between the two groups. There were no differences in the incidence of vomiting, diarrhea or fever in the newborns.\textsuperscript{36}

PPH occurs in approximately 3% of all women in a variety of populations, despite the preventive active management of the third stage of labour with the routine administration of uterotonics, such as oxytocin or oxytocin and ergometrine or misoprostol. For women that excessively bleed after childbirth, oxytocin is regarded as the gold standard for treatment of PPH. However misoprostol has been proposed as a low-cost, easy-to-use alternative.\textsuperscript{49} Nevertheless, the authors of a Cochrane systematic review\textsuperscript{57} and another review\textsuperscript{58} affirmed that there is insufficient evidence to show that the addition of misoprostol would be superior to the
combination of oxytocin and ergometrine alone for the treatment of primary PPH. Few randomised trials had been done, and, until now, there was a weak evidence supporting misoprostol use for treatment of PPH. Besides the doubts regarding efficacy and safety, there were queries about preferable and safe doses and routes of administration.

In January 2010, two well designed, conducted, and reported studies were published. Their objective was to answer a real key question: whether misoprostol can be recommended for treating primary postpartum haemorrhage, concerning efficacy and safety.

A large, multicentre, double-blind, randomised, controlled and non-inferiority trial was carried out in 31 055 women exposed to intravenous or intramuscular oxytocin for prophylaxis to PPH in the active management of the third stage of labour at five hospitals (two secondary-level and three tertiary-level facilities). Despite oxytocin prophylactic use, 809 (3%) women had PPH diagnostic and were randomly assigned to receive 800 μg sublingual misoprostol (n=407) or 40 IU intravenous oxytocin (n=402) and matching placebo. Efficacy outcomes, as active bleeding controlled within 20 minutes after initial treatment, time to active bleeding controlled, additional blood loss of 300 ml or greater after treatment, total blood loss when active bleeding stopped, haemoglobin after treatment, additional interventions, did not differ between groups. The authors concluded that misoprostol is clinically equivalent to oxytocin when used to stop excessive post-partum bleeding in women who have received oxytocin prophylactically during the third stage of labour.

A second multicentre, randomised, double-blind, controlled and non-inferiority trial, with a similar experimental design, was carried out in 9 348 women not exposed to prophylactic oxytocin for PPH in the second or third stages of labour. Blood loss was measured at four hospitals (one secondary-level and three tertiary-level facilities) in all women after vaginal delivery, of whom 978 (10%) women were diagnosed with primary PPH and randomly assigned to receive 800 μg sublingual misoprostol (n=488) or 40 IU intravenous oxytocin (n=490) and matching placebo. The same outcomes previously mentioned, excepting haemoglobin, demonstrated statistically significant differences favouring oxytocin. Severe blood loss of 1000 ml after treatment occurred in 1% or less of women in both treatment groups. Despite measured differences in blood loss, median haemoglobin measures after treatment were similar between the groups. This trial provided evidence that oxytocin is significantly better than is misoprostol for the treatment of PPH in women not given oxytocin prophylaxis.

**Safety comparisons between misoprostol and other uterotonics for PPH prevention**

*Misoprostol versus oxytocin*

A randomised controlled trial compared the effects of 800 μg oral misoprostol with 10 IU intramuscular oxytocin after delivery for the prevention of PPH. There was no significant difference between misoprostol and oxytocin groups with regard to the incidence of PPH. Shivering was significantly higher with misoprostol, but there were no differences in the other side effects.

A randomised controlled trial compared 800 μg rectal misoprostol with an intravenous infusion of 5 IU oxytocin, and matching placebos, as prevention of PPH in
514 women, immediately after delivery. Fever was significantly higher among misoprostol patients (18.7% vs. 0.8%; \(P<0.001\)).

A double-blind randomised trial (\(n=622\))\(^a\) compared oral misoprostol (400 \(\mu\)g) with intravenous oxytocin (5 IU) for the prevention of PPH in a hospital setting. Shivering was confined to the misoprostol group (6.8%). In all cases the shivering was self-limiting and not distressing to the participant. Fever (\(\geq38\) °C) occurred in 39 (12.5%) women in the misoprostol group and 1 (0.3%) woman in the oxytocin group (\(P=0.01\)). There were no blood transfusions, hysterectomies, or deaths in either group.

**Misoprostol versus methylergometrine**

A randomised, single-blinded, controlled trial\(^a\) compared 400 \(\mu\)g oral misoprostol with 500 \(\mu\)g intramuscular methylergometrine in the prevention of PPH in 864 low-risk pregnant women. Orally administered misoprostol was associated with more pyrexia. More subjects developed fever with temperature greater than 38°C within 1 hour of delivery in the misoprostol group than in the methylergometrine group (7.2% vs. 1.6%). Shivering occurred in not statistically significantly higher proportion in subjects in the misoprostol group than in subjects in the methylergometrine group. However, there were more subjects who had headache, nausea and vomiting in the methylergometrine group than in the misoprostol group (\(P<0.05\)). No subjects in either group developed diarrhoea during the study period.

In other study,\(^b\) 300 low-risk women received either 100 \(\mu\)g or 200 \(\mu\)g misoprostol sublingually or 200 \(\mu\)g methylergometrine intravenously, after the delivery of the anterior shoulder of the baby. PPH (\(>\) or = 500 ml blood loss) did not occur in any of the women. Shivering occurred with misoprostol in groups I (6%) and II (8%); 4% and 6% in groups I and II respectively reported a temperature >38°C. None of the women in the methylergometrine group had either shivering or a recorded temperature of >38°C. The side effects were mild, reversible and well accepted by the women.

**Misoprostol versus oxytocin plus ergometrine**

A double-blind randomised controlled trial (\(n=355\))\(^b\) compared 400 \(\mu\)g oral misoprostol with intramuscular syntometrine in the management of the third stage of labour. The incidence of shivering was significantly higher in the misoprostol group whilst that of vomiting was significantly higher in the syntometrine group. There were no differences in the incidence of nausea, headache, diarrhea and pyrexia between the two groups.

In another trial,\(^b\) 300 women were randomised to receive either 600 \(\mu\)g or 400 \(\mu\)g misoprostol sublingually or 5 IU intravenous oxytocin or 200 \(\mu\)g intravenous methylergometrine in active management of the third stage of labour. Pre- and post-delivery temperatures of patients were in the normal range in the oxytocin and methylergometrine groups. However, at 1 hour after delivery, 9 (12%) patients in the 400 \(\mu\)g misoprostol group and 16 (21.3%) in the 600 \(\mu\)g misoprostol group had pyrexia. The maximum rise in temperature was seen in patients in the 600 \(\mu\)g misoprostol group, followed by the 400 \(\mu\)g misoprostol group, which was significantly higher compared with the other groups (\(P<0.001\)). None of the patients was febrile at 4 hours after delivery. Shivering was observed in 6 patients in the 400 \(\mu\)g misoprostol group, 13 patients in the 600 \(\mu\)g misoprostol group, and none in the oxytocin and methylergometrine groups. The methylergometrine group had the highest incidence of
nausea and vomiting. A significant increase in blood pressure was seen in patients receiving methylergometrine (P <0.001). No difference in mean neonatal weight was seen in the 4 groups. There were no stillbirths, and mild birth asphyxia was recorded in 18 neonates who were observed in the neonatal intensive care unit for 6 to 14 hours. All neonates were discharged with their mothers.

**Misoprostol versus prostaglandin F2alpha and methylergometrine**

A trial included 200 low-risk pregnant women who were randomized to receive either 400 µg misoprostol sublingually or 0.2 mg methylergometrine intramuscularly or 125 µg 15-methyl PGF2alpha intramuscularly, after the delivery of anterior shoulder of the baby. The significant side effects in the misoprostol group were shivering, pyrexia (temperature >38°C) and vomiting, which were self-limiting. Diarrhea occurred significantly more in the 15 methyl PGF2alpha group. Three women in the methyl-ergometrine group underwent manual removal of placenta. One woman in the misoprostol group received blood transfusion.

**Safety comparisons between misoprostol and other uterotonics for PPH treatment**

**Misoprostol versus oxytocin**

In the referred non-inferiority trial that compared misoprostol versus oxytocin in women previously exposed to intravenous or intramuscular oxytocin for prophylaxis to PPH, shivering (37% vs. 15%; RR= 2.54; 95% CI: 1.95-3.32) and fever (22% vs.15%; RR=1.47; 1.09-1.99) were significantly more common with misoprostol than with oxytocin. Reports of other side-effects and their tolerability did not differ significantly between the two groups, and none resulted in extended stay in hospital. Serious adverse events were reported for seven participants and included six hysterectomies (four with misoprostol and two with oxytocin). Two of these women died of uncontrolled post-partum bleeding, one allocated to oxytocin and one (after hysterectomy) allocated to misoprostol.

The second non-inferiority trial performed in women not exposed to prophylactic oxytocin showed significantly more shivering (47% vs. 17%; RR=2.80; 95% CI: 2.25-3.49) and fever (44% vs. 6%; 8.07; 5.52-11.8) with misoprostol than with oxytocin. Pyrexia occurred in 66 women in the misoprostol group and in none in the oxytocin group. All side-effects after treatment were transient, and none resulted in additional complications or extended stay in hospital. No women had hysterectomies or died.

**Misoprostol in addition to oxytocin**

A double-blind, randomized and controlled trial was conducted in four Karachi hospitals to assess the benefit of oxytocin plus 600 µg sublingual misoprostol (n = 29) or oxytocin plus matching placebo (n = 32). All women had their third stage of labor actively managed as per standard hospital protocol (intravenous or intramuscular oxytocin or intravenous or intramuscular ergometrine in conjunction with oxytocin). Transient shivering and fever were more commonly reported in the misoprostol group. There was one case of high fever reported in the misoprostol group in which temperature at one hour post-treatment measured 40.1°C. There were no reports of severe side effects resulting in prolonged hospitalization or other adverse events in misoprostol group and all women made a full recovery. There were no hysterectomies or maternal deaths among study participants.
Safety comparisons between different doses of misoprostol

Maternal mortality and severe morbidity related to dosage are permanent concerns. A systematic review and meta-analysis evaluated the association between misoprostol to prevent and treat PPH and maternal deaths. In all the included studies (n=5) in which maternal deaths (n=8; 6 due to PPH) associated to misoprostol occurred, women were receiving 600 μg or more. Side-effects such as pyrexia and chills also appear to be dose-related.

Cases of temperatures of 40 °C or higher after misoprostol for PPH treatment at doses ranging from 600 μg to 1000 μg have been previously reported. All of them resolved with antipyretic treatment and cool compresses within several hours and without complication.

Regarding the results of the non-inferiority mentioned studies, Buekens and Althabe commented that 800 μg sublingual misoprostol was not differently associated with shivering and fever in comparison with lower dosage, both side-effects easily resolvable and without complication.

For evaluating the PPH treatment, a Cochrane systematic review included three trials. Only one of them presented 3 maternal deaths and 3 cases of hysterectomy in the 1000 μg misoprostol arm (n=117). However, this review was not large enough to evaluate the effects of misoprostol on maternal mortality, serious maternal morbidity or hysterectomy rates in women with primary PPH.

The single dose most commonly used in clinical trials is 600 μg administered orally or sublingually. This dose is more effective than placebo in preventing PPH in community births, but not in hospital settings. It is not as effective as injectable oxytocin. In the event of continued haemorrhage, a minimum of 2 hours should lapse after the original dose before a second dose is given.

A single 400 μg dose has been tested for preventing PPH. Meta-analysis of direct and adjusted indirect comparisons of the results of randomised trials showed very similar effectiveness between 600 and 400 μg for preventing blood loss > 1000 ml. In this meta-analysis, pyrexia was more common in the group given 600 μg misoprostol rather than 400 μg (RR: 2.53; 95% CI: 1.78–3.60). There was consistency between the estimates derived from the direct and the adjusted indirect comparisons.

Safety comparisons between different routes of misoprostol

Misoprostol is absorbed faster orally than vaginally, with onset of action in 8 minutes and plasmatic peak at about 30 minutes. Oral misoprostol had a significantly greater peak plasma concentration. However, oral misoprostol has a shorter duration to maximum concentration than either rectal or vaginal misoprostol (for both: P < 0.001). Orally absorbed serum level declines rapidly by 120 minutes after intake and remains low thereafter. Oral misoprostol tablet is also absorbed by the rectal and vaginal routes.

After oral administration, uterine tonus develops, which is not followed by uterine contractions, unless repeated doses are given.

Derman and colleagues found that one mother will have shivering for every three treated, and one will have pyrexia for every 32 receiving oral misoprostol.

Administration of misoprostol by sublingual route results in rapid absorption, highest serum concentrations, long-lasting duration of effect, and greatest bioavailability.
compared with other routes of administration. The sublingual route was identified as having the greatest potential for treatment of post-partum haemorrhage.

Hoj and colleagues evidenced that sublingual misoprostol will produce pyrexia in one mother for every five treated for severe PPH in a community setting.

After 400 µg misoprostol rectal administration, serum levels peaked earlier, and then dropped more abruptly. Rectal route produced lower peak serum level (202.2 vs. 264.8 pg/ml), lower serum concentration area under the curve at 5 hours (312.5 vs. 519.6 pg-hr/ml), lower peak uterine tone ($P < 0.001$) and total activity ($P = 0.04$) than after the buccal and vaginal routes used in a misoprostol pharmacokinetic study. Therefore, there is uncertainty about absorption and efficacy via rectal route.

**DISCUSSION**

The first remarkable issue is the variability of results referring to misoprostol use that does not allow a consensus about the best use of this medicine in obstetric indications. Based on the contemporary built evidence, there are many confounders in the available studies, due to mixed comparisons among different doses, routes, and procedures (such as time of repeated administration), even when the aim is to compare two uterotonic agents that admitted the same route and an equipotent dose. In the research of a unique medicine, it would more useful to isolate the variable of interest, for instance the same dose, but administered by different routes, for evaluating the best route to be used. There are several repetitive studies, despite the inconsistencies and contradictions which remained throughout the last decade. These ones, in my point of view, derived from the many simultaneous variables in the same study.

The second noticed fact is the difference in the efficacy and safety outcomes provided by studies carried out in hospital and non-hospital settings. In general, the first ones – even if performed at hospitals of different level facilities and placed in countries with different incomes and cultures – present a higher difference related to efficacy and safety between treatments, favouring injectable oxytocics. In the latter, there are lesser differences, maybe derived from a less appropriate execution of procedures that could mask the effects attributed to medicines considered the gold standard. The different results obtained in individual studies consequently influence the systematic reviews that include trials performed in hospital and community settings. Nowadays, many studies have found misoprostol to be slightly less effective than oxytocics in controlled clinical settings. In order to evaluate its efficacy and safety in the realistic perspective of community settings, some authors suggest that, where injectable uterotonic are not available, misoprostol should be compared with placebo or no intervention for preventing PPH. In PPH treatment this research design is not considered ethical.

Besides these methodological considerations, there are some issues to be discussed specifically related to labour pre-induction and induction and prevention or treatment of postpartum haemorrhage.

_Cervical ripening and labour induction_

The most reported maternal side effects are hyperstimulation and tachysystole, which appear to be dose-related, and are commonly transient and easily controlled. Uterine rupture is a rare event, as well as maternal death. Perinatal side effects linked
to misoprostol are uncommonly reported, including meconium-stained amniotic fluid, neonatal acidaemia, and neonatal intensive care unit admissions.

Currently, studies compare lower misoprostol doses (25 μg, 20 μg, 12.5 μg) with other uterotonics. Higher misoprostol doses were frequently associated with significantly increased risk of tachysystole and hyperstimulation. On the contrary, the lower misoprostol doses now recommended are consistently associated with lower incidence of those side effects. Neonatal outcomes do not show significant difference between doses. Regarding the comparison with other uterotonics, trials commonly show no statistically significant differences in neonatal morbidity or only a trend towards some side effects between the comparative groups.

So, lower doses compared with higher ones seem to maintain the therapeutic effectiveness with a more acceptable maternal safety profile. Neonatal outcomes appear to be comparable with any dose. In terms of safety, an alternative dose of 12.5 μg (only one study) presented similar rates of tachysystole and neonatal outcomes. Misoprostol titrated low-dose regimen, as well as the use of the 20 μg oral solution, appears as a good alternative regarding safety.

For labour induction, the vaginal route of low-dose misoprostol demonstrated similar efficacy as the oral route, but equal or a slightly lesser safety relating to maternal and neonatal outcomes. Sublingual versus oral or vaginal low-dose misoprostol showed no statistically significant difference in terms of maternal and neonatal outcomes. Thus, in general, different routes of administration of misoprostol for labour induction provide similar results regarding safety. However, in some studies, vaginal route was associated with more uterine hyperstimulation and tachysystole. Only one study showed an increased rate of NICU admissions.

Prevention of postpartum haemorrhage

Prevention of postpartum haemorrhage is of utmost importance because it reduces the risk of PPH by at least 50%.59,53 Prophylactic injectable oxytocin, either alone or in the context of active management of the third stage of labour (AMTSL), is recommended as the drug of choice in hospital settings.71 Misoprostol represents a useful alternative where the injectable uterotonics are not available, as well as the other AMTSL procedures. Its value increases in low-income countries where the risk of dying from PPH is higher than in developed countries.65 In Derman and colleagues’ trial, 53 oral misoprostol was associated with significant decreases in the rate of acute postpartum haemorrhage and mean blood loss.

A comparison between the two recently published studies on PPH treatment 59,60 confirms the reduced PPH occurrence as a result of oxytocin prevention in the third stage of labour: the PPH frequency fell from 10% in the trial without prevention to 3% in the trial with women receiving prophylactic oxytocin.

The most reported side-effects of misoprostol are maternal shivering and fever, consistently and significantly increased in comparison with placebo and injectable uterotonics. Usually these side-effects are mild, reversible, self-limiting and not distressing to the women. According to a large meta-analysis, 5 in prevention trials misoprostol showed slightly more adverse events in comparison with placebo; severe morbidity was low and similarly experienced by women on misoprostol and on conventional uterotonics; and five deaths occurred in misoprostol groups (in three trials controlled by placebo e one controlled by other uterotonic). Shivering and fever
occur even with low-dose misoprostol (400, 200 and 100 μg). However, in the referred review, pyrexia was more than twice as common among women who received 600 μg rather than 400 μg of misoprostol. Also, only higher single doses (equal or superior to 600 μg) were associated to maternal deaths. In this review, 400 μg of misoprostol were found to be safer than 600 μg and just as effective.

For prevention of PPH, misoprostol administered via oral and sublingual routes presents similar side-effects. Rectal route is not appropriate for this condition.

So, it seems better to use lower misoprostol doses via oral or sublingual routes in low-resource settings, especially outside hospital, since its common maternal side-effects balance favourably against morbidity and mortality of developed postpartum haemorrhage.

*Treatment of postpartum haemorrhage*

In comparison with studies that evaluated misoprostol versus oxytocin for prevention of PPH, fewer studies have dealt with treating PPH, despite the serious consequences of this disease on maternal mortality and morbidity. Considering the need for PPH treatment in resource-poor settings, where oxytocin is not always feasible to provide, it seems very useful to perform large non-inferiority trials like the two ones recently published in *The Lancet*. These studies especially differ in one aspect: one evaluates treatment for women receiving prophylactic oxytocin (study 1); in the other (study 2), women were not previously exposed to oxytocin.

In both studies, shivering and fever were significantly more common with misoprostol than with oxytocin. Pyrexia occurred in both studies, but was only significantly different between groups in the study 2. In the study 1, hysterectomies and maternal deaths were not significantly different between oxytocin and misoprostol. They were absent in the study 2.

The authors did a cross-study comparison and pointed out some differences between the two trials, regarding efficacy and safety. They suggest that oxytocin prophylaxis could have reduced the differences between the treatment groups (study 1) by selecting a specific group with poorer response to oxytocin PPH treatment, and a better response to misoprostol. In this subgroup of women the usual advantages of oxytocin over misoprostol, even if small, are effectively erased.

On the contrary, in the study 2, the more visible statistically significant differences relating to efficacy outcomes between groups favoured oxytocin, in spite the absolute differences recorded were quite small. However, in comparison to the previous study, the safety profile was similar, except by the different pyrexia occurrence that elapsed without complications.

In conclusion, these findings provide evidence that oxytocin remains as the gold standard for treatment of primary post-partum haemorrhage in hospital settings, but misoprostol could be a reasonable and valuable alternative, especially when oxytocin prophylaxis was performed during the third stage of labour.

**FINAL COMMENTS**

New information adds valuable evidence, useful for decisions about obstetric use of misoprostol.
Nevertheless, other questions remain unanswered. For instance, about the result of simultaneous introduction of misoprostol for both prevention and treatment of postpartum haemorrhage; also, if a lower treatment dose of misoprostol shows similar effectiveness with fewer undesirable side-effects.

In an overall view, misoprostol common maternal side-effects seem tolerable, and less prevalent with lower doses. In all obstetric indications here discussed, the neonatal side-effects do not appear as important findings, or different ones in comparison to the other treatments. The few number of deaths reported in PPH management is of utmost concern. However, they were mainly due to excessive bleeding that might represent unresponsiveness to medical treatment, instead of a misoprostol direct side-effect. In addition they must be counterbalanced with the higher number of deaths consequent to an uncontrolled PPH.

Finally, large, pragmatic trials are still crucial to elucidate the effectiveness and risks of obstetric use of misoprostol in low-resource settings, a real need under a social perspective. Besides this, lower doses might also deserve to be tested, as well as other alternatives, as new regimens of oxytocin or a simplified package of AMTSL.

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Prevention of postpartum hemorrhage with misoprostol

International Federation of Gynecology and Obstetrics

Background evidence

Postpartum hemorrhage (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 uterotonics 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 the use of oxytocin.

In 2011, the World Health Organization (WHO) added misoprostol (600 μg orally) to its “Model List of Essential Medicines” for the prevention of PPH [1].

Misoprostol versus conventional injectable uterotonics in the prevention of postpartum hemorrhage

A systematic review of 16 randomized controlled trials (RCTs) of misoprostol versus injectable uterotonics, involving 29,042 women, has shown that oral misoprostol is less effective than injectable uterotonics in preventing severe PPH (blood loss >1000 mL: 3.3% vs 2.4%, relative risk (RR) 1.32; 95% confidence interval (CI) 1.16–1.51) [2]. There is less information on the use of ergometrine for the prevention of PPH. In one double-blind RCT involving 1229 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 postpartum blood loss of 500 mL or greater, or postpartum hemoglobin levels of less than 8 g/dL, misoprostol was more effective at reducing pre- to postpartum hemoglobin of 3 g/dL or greater (16.4% vs 21.2%; RR 0.77, 95% CI, 0.60–0.98). Shivering was significantly more common with misoprostol, but vomiting was more common with ergometrine [3]. A review of 6 studies that used a combination of oxytocin 5 IU and ergometrine 500 μg (Syntometrine) injected intramuscularly indicates that it is slightly more effective than intramuscular oxytocin alone in reducing PPH greater than 500 mL (odds ratio [OR] 0.82; 95% CI, 0.71–0.95), but with higher rates of hypertension and vomiting [4].

Furthermore, the one study that tested intravenous 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 [5]. It is on this basis that FIGO and WHO recommend the use of intramuscular oxytocin 10 IU in preference to the ergometrine-containing products.

Misoprostol for the prevention of postpartum hemorrhage 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 [2]. They did, however, consistently show that misoprostol markedly reduced the need for postnatal blood transfusion (RR 0.31; 95% CI, 0.10–0.94). In addition, the 3 large-scale placebo-controlled studies published since 2005 have all consistently shown positive effects of misoprostol in reducing postpartum blood loss [6–8]. All 3 trials used misoprostol 600 μg, orally or sublingually, in community or primary healthcare settings without access to conventional injectable uterotonics. The first was a randomized trial of 661 women attended by midwives in a primary health center in Guinea-Bissau [6]. Findings indicated sublingual misoprostol 600 μg was significantly better than placebo at reducing severe PPH (blood loss ≥1000 mL) [6]. The second, involving 1620 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 of 500 mL or greater, blood loss of 1000 mL or greater, need for transfer to a health facility, blood transfusion, and surgical interventions [7]. The third, involving 1119 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% vs 21.9%; RR 0.76, 95% CI, 0.59–0.97) and incidence of postpartum declines in hemoglobin greater than 3 g/dL [8].

Doses of less than 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 adverse effects, there is a greater body of evidence in support of a 600-μg regimen, and prolonged or serious adverse 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.

These guidelines were reviewed and approved in May 2012 by the FIGO Executive Board.
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.

Adverse effects

Temperature changes: Shivering, chills, and/or fever are all commonly associated with misoprostol. Shivering is the most common adverse effect and is occasionally accompanied by fever. In the large WHO multicenter 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 [9]. Similarly, when Derman et al. [7] used 600 μg in rural India, shivering occurred in 52.2% of women, but fever in only 4.2%. The shivering is self-regulating and even if high temperatures occur, they are transient and settle with reassurance and symptomatic treatment.

Gastrointestinal effects: Transient diarrhea, nausea, and vomiting may occur following misoprostol, but are rare, occurring in less than 1% of women [9]. An antiemetic 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 programs in which women are given misoprostol tablets for self-administration after delivery. Reports from these programs 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 adverse 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.

References

PROPOSAL FOR THE INCLUSION OF MISOPROSTOL
IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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1. **Summary Statement of the proposal for inclusion, change or deletion**

The data presented in the following report demonstrates that misoprostol is a safe, effective and low cost pill that reduces postpartum bleeding after delivery. Based on the well-established efficacy of misoprostol for the prevention of postpartum hemorrhage (PPH), we propose that misoprostol be specifically listed for its PPH prevention indication in section 22.01.00.00 “Oxytocics” of the WHO List of Essential Medicines (EML) list. Of note, misoprostol is already included in the **WHO Model List of Essential Medicines (22.1 Oxytocic)** because of its proven safety and efficacy for medical abortion (with mifepristone), labor induction, and treatment of incomplete abortion and miscarriage.

Misoprostol has the potential to increase significantly the number of women who receive a uterotonic following childbirth to prevent excessive bleeding. Several countries in Asia and Africa have already included misoprostol for the prevention of PPH in their list of essential medicines. Inclusion of misoprostol in the WHO Model List of Essential Medicines could presumably lead to greater uterotonic coverage at all deliveries by bolstering the package of interventions available to providers seeking to prevent a postpartum hemorrhage. In places where standard injectable uterotonic are not available and/or feasible, misoprostol offers an alternative method of PPH prevention. The **WHO Recommendations for the Prevention of Postpartum Haemorrhage** (WHO 2007) indicate that misoprostol may be used as for PPH prevention in the absence of active management of the third stage of labor.

This proposal is based on the following evidence and considerations, described below:

1. Postpartum hemorrhage is one of the largest contributors to maternal morbidity and mortality in low resource countries and accounts for nearly one quarter of all maternal deaths worldwide.

2. Misoprostol is a proven, evidence-based drug that reduces post-partum blood loss.

3. Misoprostol can be safely used by providers of all levels for prevention of PPH. Evidence from randomized controlled trials shows that health workers trained in its use can safely and effectively administer misoprostol to women in any delivery setting.

4. Misoprostol is a low-cost alternative to conventional uterotonic, including oxytocin and ergometrine, which require skilled administration and are not yet consistently sustainable and/or available in many low resource countries.

5. Inclusion of misoprostol on the EML for its PPH prevention indication could contribute to efforts to achieve Millennium Development Goal #5 to reduce maternal mortality by three-quarters by the year 2015.

2. **Name of the focal point in WHO submitting or supporting the application**

A. Metin Gülmezoglu, MD, PhD, Department of Reproductive Health and Research
Matthews Mathai, MD, Department of Making Pregnancy Safer
3. Name of organization(s) consulted and/or supporting the application

Gynuity Health Projects, New York, USA
Venture Strategies Innovations, USA

4. International Nonproprietary Name (INN, generic name) of the medicine

The International Nonproprietary Name Modified (INNM) of the medicine is: Misoprostol

5. Formulation proposed for inclusion; including adult and pediatric (if appropriate)

200 mcg oral tablets
100 mcg oral tablets

6. International availability – sources, if possible manufacturers

Misoprostol is widely available throughout the world, and has been available in generic formulation for several years. The first patent was granted in the United States, to Searle (now Pfizer), for marketing of Cytotec®, which continues to be the most widely distributed misoprostol tablet. Misoprostol has been off-patent in the United States for several years and is currently manufactured by companies worldwide as shown in Appendix A.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

We request that misoprostol be listed as an individual medicine with multiple therapeutic uses in obstetrics and gynecology. Misoprostol is already included on the WHO Model List of Essential Medicines (22.1 Oxytocic) because of its proven safety and efficacy for early medical abortion (with mifepristone), induction of labor, and treatment of incomplete abortion and miscarriage.

8. Information support the public health relevance

8.1 Disease Burden

It is estimated that in 2008 more than 350,000 women died due to complications of pregnancy and childbirth (UNFPA, 2010). The burden of maternal mortality falls most heavily on low resource countries where 99% of maternal deaths occur. This accounts for the largest disparity between rich and poor countries of all the WHO health indicators (de Bernis et al. 2003; Hogan 2010). In low-resource countries, one woman in 16 may die of pregnancy-related causes, while only one death among 2,800 is attributed to these causes in developed countries (WHO 2004). Areas where the burden of maternal mortality is the highest have shown the least improvement. The maternal mortality ratio (MMR) in sub-Saharan Africa has remained static over the last 15 years; a decrease of less than 2% during this time. In fact, due to population increase, 50,000 more women lost their lives due to maternal causes in sub-Saharan Africa in 2005 than in 1990 (WHO 2004).
The main direct causes of maternal death include postpartum hemorrhage (PPH), sepsis, eclampsia, unsafe abortion, and obstructed labor. PPH is the leading single direct cause of maternal mortality, accounting for a quarter of all maternal deaths worldwide (Mousa and Walkinshaw 2001). As shown on Table 8.2, a systematic review of studies documenting causes of maternal death, found that hemorrhage was the leading cause of death in Africa and Asia (>30% of deaths) (Khan et al 2006). The clinical threshold for PPH as defined by the WHO is postpartum blood loss in excess of 500ml (WHO 1990). It has also been noted that anemic women in developing countries are more prone to blood loss after delivery (McCormick et al. 2002). Uterine atony, or failure of the uterus to contract after delivery, is the most common cause of PPH and accounts for 90% of PPH cases in most countries (Mousa and Walkinshaw 2001; Carroli et al 2008).

Although PPH occurs everywhere, the risk of maternal death from PPH is one hundred times greater in developing countries than it is in developed: 1 in 1000 deaths in developing countries versus 1 in 100,000 in the UK (Mousa and Walkinshaw 2001). Khan et al. (2006), using various datasets, estimated that hemorrhage is the main cause of maternal mortality in Asia and Africa – accounting for 30% or more of all maternal deaths (see Table 8.2). Of those women who survive

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**Table 8.1: Estimates of maternal mortality ratio.** (UNFPA, 2010)

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated MMR$^a$</th>
<th>Number of maternal deaths$^a$</th>
<th>Lifetime risk of maternal death$^a$: 1 in:</th>
<th>Range of uncertainty on MMR estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WORLD TOTAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developed regions$^b$</td>
<td>260</td>
<td>358 000</td>
<td>140</td>
<td>200 - 370</td>
</tr>
<tr>
<td>Countries of the Commonwealth of Independent States (CIS)$^c$</td>
<td>14</td>
<td>1700</td>
<td>400</td>
<td>13 - 15</td>
</tr>
<tr>
<td>Developing regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>290</td>
<td>355 000</td>
<td>120</td>
<td>220 - 410</td>
</tr>
<tr>
<td>Northern Africa$^d$</td>
<td>590</td>
<td>207 000</td>
<td>36</td>
<td>430 - 850</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>640</td>
<td>204 000</td>
<td>31</td>
<td>470 - 900</td>
</tr>
<tr>
<td>Asia</td>
<td>190</td>
<td>139 000</td>
<td>220</td>
<td>130 - 270</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>41</td>
<td>7800</td>
<td>140</td>
<td>27 - 66</td>
</tr>
<tr>
<td>South Asia</td>
<td>280</td>
<td>109 000</td>
<td>120</td>
<td>190 - 420</td>
</tr>
<tr>
<td>South-Eastern Asia</td>
<td>160</td>
<td>16 000</td>
<td>260</td>
<td>110 - 240</td>
</tr>
<tr>
<td>Western Asia</td>
<td>68</td>
<td>3300</td>
<td>460</td>
<td>45 - 110</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>85</td>
<td>9200</td>
<td>490</td>
<td>72 - 100</td>
</tr>
<tr>
<td>Oceania</td>
<td>230</td>
<td>550</td>
<td>110</td>
<td>100 - 500</td>
</tr>
</tbody>
</table>

$^a$ The MMR and lifetime risk have been rounded according to the following scheme: <100, no rounding; 100–999, rounded to nearest 10; >1000, rounded to nearest 100. The numbers of maternal deaths have been rounded as follows: <1000, rounded to nearest 10; 1000–9999, rounded to nearest 100; and >100 000, rounded to nearest 1000.

$^b$ Includes Albania, Australia, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, The former Yugoslav Republic of Macedonia, the United Kingdom, and the United States of America.

$^c$ The CIS countries are Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, the Republic of Moldova, the Russian Federation, and Uzbekistan.

$^d$ Excludes Sudan, which is included in sub-Saharan Africa.
PPH, 12% will experience anemia, resulting in 1.6 million women of reproductive age suffering from its long-lasting and debilitating consequences (AbouZahr 2003). It is estimated that the impact of PPH management on reducing MMR ranges from 55% to 82% (WHO 1994). With the high rates of maternal mortality in developing countries and the large proportion of these deaths attributable to PPH, making gains in the management of PPH in low resource settings will have a dramatic impact on the number of maternal deaths that occur each year and is thus an essential step towards achieving the fifth United Nations (UN) Millennium Development Goal # 5 to reduce the MMR by three-quarters by the year 2015 (UN 2007).

Table 8.2: Joint distribution of causes of maternal deaths (Khan et al. 2006)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Developed countries</th>
<th>Africa</th>
<th>Asia</th>
<th>Latin America and the Caribbean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of datasets</td>
<td>5</td>
<td>8</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Number of maternal deaths</td>
<td>2825</td>
<td>4508</td>
<td>3698</td>
<td>11777</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>15.4% (4.7-34.4)</td>
<td>33.5% (13.3-43.6)</td>
<td>30.6% (5.9-48.9)</td>
<td>20.8% (1.1-45.9)</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>26.1% (6.7-24.2)</td>
<td>9.1% (3.9-21.9)</td>
<td>9.1% (2.0-34.3)</td>
<td>25.7% (7.2-52.4)</td>
</tr>
<tr>
<td>Septic infections</td>
<td>2.1% (0.0-5.9)</td>
<td>9.7% (5.3-12.6)</td>
<td>11.5% (0.6-13.9)</td>
<td>7.7% (0.0-15.1)</td>
</tr>
<tr>
<td>Abortion</td>
<td>8.2% (0.0-48.6)</td>
<td>3.9% (0.0-23.3)</td>
<td>2.7% (0.0-33.6)</td>
<td>12.0% (0.0-52.4)</td>
</tr>
<tr>
<td>Obstructed labour</td>
<td>0.0%* (0.0-0.0)</td>
<td>4.3% (0.0-20.3)</td>
<td>9.4% (0.0-12.9)</td>
<td>13.4% (0.0-38.9)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0.0%* (0.0-0.0)</td>
<td>37.0% (0.0-12.1)</td>
<td>12.0% (0.0-57.3)</td>
<td>0.1% (0.0-3.9)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>0.0%* (0.0-0.0)</td>
<td>6.2% (0.0-13.3)</td>
<td>0.0%* (0.0-0.0)</td>
<td>0.0%* (0.0-0.0)</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>4.9% (0.0-7.4)</td>
<td>0.5% (0.0-2.2)</td>
<td>0.1% (0.0-2.2)</td>
<td>0.5% (0.0-4.5)</td>
</tr>
<tr>
<td>Embolism</td>
<td>14.9% (0.0-21.2)</td>
<td>2.0% (0.0-5.6)</td>
<td>0.4% (0.0-51.3)</td>
<td>0.0% (0.0-8.4)</td>
</tr>
<tr>
<td>Other direct causes</td>
<td>24.3% (0.0-33.9)</td>
<td>4.5% (0.0-10.3)</td>
<td>2.5% (0.0-25.9)</td>
<td>3.3% (0.0-27.9)</td>
</tr>
<tr>
<td>Other indirect causes</td>
<td>14.4% (0.0-51.2)</td>
<td>16.7% (0.1-29.2)</td>
<td>12.5% (0.0-29.2)</td>
<td>2.9% (0.0-52.2)</td>
</tr>
<tr>
<td>Unclassified deaths</td>
<td>4.8% (0.0-9.2)</td>
<td>5.4% (0.0-21.5)</td>
<td>6.1% (0.0-16.2)</td>
<td>11.7% (0.0-29.4)</td>
</tr>
</tbody>
</table>

Data are posed percentages (range), unless stated otherwise. *Zero indicates that the condition is not reported as a cause of death. Deaths from that cause could still have occurred but listed under either or unclassified deaths.

It is impossible to predict who will experience PPH. Of the few common risk factors known for PPH, most cannot be identified until labor has already begun, such as, large baby, and prolonged or augmented labor (Mousa and Walkinshaw 2001; Geller et al. 2008). Additionally, PPH occurs unpredictably in women without risk factors: two thirds of women who have PPH do not have any identifiable clinical risk factors. Therefore, a woman is not usually referred until she develops PPH. Even trained clinicians often underestimate blood loss (Lalonde et al. 2006; Schorn 2010). Any delay in seeking health care can be deadly - the average time to death from onset of PPH is two hours (Maine 1993; Walraven et al. 2008). This is particularly problematic in low resource settings where women often suffer delays in reaching and receiving effective care for their PPH (Walraven et al. 2008). Since many women do not present with risk factors, PPH prevention is extremely important especially in settings where access to care is scarce or non-existent (UNPF 2003; USAID 2008).

8.2 Prevention of PPH

To reduce blood loss after delivery, the WHO recommends the Active Management of the Third Stage of Labor (AMTSL) be offered to all women delivering with skilled attendants (WHO 2007). AMTSL is comprised of immediate administration of an uterotonic agent (preferably oxytocin), delivery of the placenta by controlled cord traction, and uterine massage. In a
Cochrane systematic review of five studies, AMTSL showed a significant reduction in PPH (relative risk 0.38, 95% CI 0.32 to 0.46) (Prendiville et al. 2000).

Uterotonic drugs have been recommended to reduce or stop postpartum bleeding. Ergometrine, oxytocin, and prostaglandins such as misoprostol all cause the uterus to contract to prevent and/or stop excessive bleeding. Oxytocin is the currently the drug of choice for PPH prevention (and treatment) because it is highly effective, has an excellent safety profile, and is free from the side effects associated with ergometrine (WHO 2007). However, oxytocin is administered by injection, which requires both a skilled health provider and a clean needle (Tsu and Shane 2004). Further, the active ingredient in oxytocin preparations has been shown to decrease gradually over time; and more rapidly when the drug is stored at temperatures above 30° Celsius (Hogerzeil and Walker 1996). Thus, injectable oxytocin has been limited to use in settings where appropriate storage facilities are available. Given the need for providers skilled in its use and appropriate storage facilities, the use of oxytocin for PPH prevention has been mostly limited to births occurring at a health facility and/or with a skilled provider.

Prostaglandins cause strong uterine contractions, but their cost and availability have inhibited their widespread use as uterotonics. Misoprostol, an E1 prostaglandin analog, was developed during the 1980s and was approved by the U.S. Food and Drug administration (FDA) to be taken orally in tablet form for the prevention of gastric ulcers associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in 1988. Off-label exploration of the drug for obstetric purposes began soon after its development, and the drug has been studied extensively for a number of gynecological and obstetric indications.

Despite the effectiveness of conventional uterotonics for prevention of post-partum hemorrhage, there is continued interest in the use of misoprostol as an alternative drug where other uterotonics are not available or cannot be administered. A recent systematic review of randomized controlled trials assessing the role of misoprostol in the prevention of PPH found that 600 mcg of misoprostol reduced significantly the risk of PPH when comparing post-partum administration of misoprostol to placebo in community settings (relative risk 0.59 95% CI 0.41-0.84) (Alfirevic et al. 2007).

8.3 Assessment of Current Use

The major advantage of misoprostol over oxytocin in the prevention of PPH is its ability to be used in low resource settings where oxytocin use is not feasible or sustainable (Tsu & Shane 2004). Misoprostol is a heat-stable tablet with a shelf life of several years and as such, provides an advantage over conventional injectable uterotonics in field conditions. A report from 2006 WHO Technical Consultation on the prevention of PPH recommends that, “In the absence of AMTSL, a uterotic agent (oxytocin or misoprostol) may be administered by a health care provider trained in its use” (WHO DoMPS 2007).

A number of international agencies are now partnering with Ministries of Health around the globe to introduce misoprostol for post-partum hemorrhage prevention and to train providers in its safe administration (see www.popphi.org, www.jhpiego.org and www.vsinnovations.org).
8.4 Target Population

As seen in Table 8.4, the regions with the highest MMR have the lowest proportion of births with skilled attendants and the least resources for their health systems. The primary strategies to reduce MMR by the international community have been to ensure that every woman has ready access to a skilled birth attendant during delivery and emergency obstetric care (EmOC) in case of complications (UNPF 2003). These efforts are hampered by shortage of funds and poor geographic coverage, resulting in persistent underutilization of and poor quality of care at health facilities (Potts and Hemmerling 2006). Additionally, poor settings are often plagued by electricity outages, lack of transportation or viable roadways to reach higher level facilities, absence of potential trainees for professional clinical positions, and professional migration. The shortage in human resources and necessary infrastructure across the developing world makes these interventions impossible to achieve quickly. In settings where conventional uterotonic are not yet widely available, misoprostol could be beneficial in reducing the overall burden of postpartum hemorrhage. Misoprostol administration by health workers trained in its use for the prevention of PPH can contribute towards achieving universal uterotonic coverage at all deliveries.

Table 8.4 Maternal mortality ratio (MMR), percent births attended by a skilled professional, percent rural population, and contraceptive prevalence by region (Prata et al. 2008)

<table>
<thead>
<tr>
<th>Region</th>
<th>Maternal mortality ratio (a, b) (deaths per 100,000 live births)</th>
<th>% Births with skilled attendants (b)</th>
<th>% rural (b)</th>
<th>Contraceptive prevalence (%) (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>World total</td>
<td>402</td>
<td>62</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>Developed regions</td>
<td>9</td>
<td>99</td>
<td>25</td>
<td>57</td>
</tr>
<tr>
<td>Europe</td>
<td>17</td>
<td>99</td>
<td>28</td>
<td>53</td>
</tr>
<tr>
<td>Africa</td>
<td>824</td>
<td>47</td>
<td>61</td>
<td>21</td>
</tr>
<tr>
<td>Northern Africa</td>
<td>157</td>
<td>70</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>905</td>
<td>53</td>
<td>59</td>
<td>21</td>
</tr>
<tr>
<td>Asia</td>
<td>329</td>
<td>58</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>53</td>
<td>97</td>
<td>54</td>
<td>81</td>
</tr>
<tr>
<td>South-Central Asia</td>
<td>581</td>
<td>39</td>
<td>69</td>
<td>42</td>
</tr>
<tr>
<td>South-Eastern Asia</td>
<td>280</td>
<td>69</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>Western Asia</td>
<td>127</td>
<td>73</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Latin America/Caribbean</td>
<td>132</td>
<td>83</td>
<td>22</td>
<td>63</td>
</tr>
<tr>
<td>Oceania</td>
<td>427</td>
<td>84</td>
<td>29</td>
<td>57</td>
</tr>
</tbody>
</table>

Source: (a) Hill et al. (2007); (b) State of the World’s Population (2007).

9. Treatment details

9.1 Dosage Regimen and duration

For PPH prevention, a single dose of 600 µg (3 tablets of 200 µg) is recommended to be given orally immediately after delivery of the newborn, after confirming that there is no multiple pregnancy, and prior to the expulsion of the placenta (Alfirevic et al. 2007). No special diagnostic or treatment facilities and/or specialized skills are needed for provision of misoprostol for this indication; however providers should take caution to administer the misoprostol after delivery of the second (or third) infant, in the event of multiple pregnancy.
9.2 Reference to Existing WHO and Other Clinical Guidelines

A WHO Technical Consultation on prevention of postpartum hemorrhage made the following recommendation: “In the absence of AMTSL, WHO strongly recommends that a uterotonic drug (oxytocin or misoprostol) should be offered by a health worker trained in its use for prevention of PPH” (Recommendation #7, WHO Recommendations on the Prevention of Postpartum Hemorrhage: WHO 2007).

In a joint statement calling for action to reduce PPH in low-resource settings, the International Federation of Midwives and the International Confederation of Gynaecology and Obstetrics stated: “In situations where no oxytocin is available or birth attendants’ skills are limited, administering misoprostol soon after the birth of the baby reduces the occurrence of haemorrhage.” (Prevention and treatment of post-partum haemorrhage: New advances for low resource settings. Joint Statement by the International Confederation of Midwives and the International Federation of Gynaecology and Obstetrics. 2006).

Misoprostol for Prevention of Postpartum Hemorrhage: An Evidence-Based Review by U.S. Pharmacopeia (USP) (United States Pharmacopeia) lists misoprostol for prevention of PPH as a USP accepted off-label use.

In the 2009 Green-top Guideline, the Royal College of Obstetricians and Gynaecologists notes that while oxytocin is preferable to misoprostol for PPH prevention, in situations where no oxytocin is available or birth attendants’ facilities are limited misoprostol reduces the risk of haemorrhage and that, therefore, it may be used when oxytocin is not available. (Royal College of Obstetricians and Gynaecologists. RCOG Green-top Guideline No. 52. May 2009)

10. Summary of comparative effectiveness in a variety of clinical settings

Active management of the third stage of labor (AMTSL), consisting of the administration of prophylactic uterotonic, controlled cord traction for placental delivery, and uterine massage, is an evidence-based intervention that reduces the rate of PPH by up to 60% (Prendiville et al. 1988). The World Health Organisation, as well as other international agencies, recommends that AMTSL be offered to all women delivering with a skilled birth attendant (ICM/FIGO 2004; WHO 2007; RCOG 2009). Published studies comparing the efficacy and safety of various uterotonics confirm that oxytocin is the preferred drug for actively managing the third stage of labour (Gülmezoglu et al. 2001; Gülmezoglu et al. 2007; Alfirevic et al 2007). The largest hospital-based, multi-center trial comparing pharmacological agents for the prevention of PPH showed that blood loss $\geq$1000 mL occurred among 4% of women given oral misoprostol (600 mcg) compared with 3% given 10 IU of oxytocin prophylactically (Gülmezoglu et al. 2001). Recent systematic reviews of randomized controlled trials comparing misoprostol with injectable uterotonics also confirm oxytocin’s superiority (Gülmezoglu et al. 2007; Alfirevic et al. 2007; Sloan et al 2010). However, oxytocin is not always feasible to administer in resource-poor settings given its cool storage-, sterile equipment-, skilled personnel-, and parenteral administration- requirements (Tsu & Shane 2004). Oxytocin prophylaxis is thus mostly limited to facility-based deliveries and/or those attended by a skilled provider, where the cold chain can
be maintained, leaving the majority of deliveries in community-settings with no uterotonic coverage.

Misoprostol has been explored for preventing PPH in settings where injectable uterotonics are not yet available or feasible to use. Four community-based randomised-controlled trials, where misoprostol was administered at homebirths or at primary health care centres, have demonstrated safe and effective use of misoprostol for PPH prevention (Walraven et al. 2005; Hoj et al. 2005; Derman et al. 2006; Mobeen et al. in press). Two of these studies compared oral misoprostol (600 mcg) to placebo at the community-level (table 10.2) The study conducted in rural India was the first large, randomized, placebo-controlled trial testing the efficacy and safety of a regimen of oral misoprostol (600 mcg) in a community setting where an auxiliary nurse-midwife was in attendance. This study showed that misoprostol reduced PPH ≥500mL by nearly 50% compared with placebo in the absence of controlled cord traction (6% vs. 12%; relative risk 0.53 95% CI 0.39-0.74) (Derman et al. 2006).

More recently, trained birth attendants in Pakistan participated in a large, randomized, placebo-controlled trial also testing post-partum administration of misoprostol versus placebo for PPH prevention at home deliveries. In this study, PPH ≥500mL occurred among 16.5% of women receiving misoprostol compared to 21.9% of women receiving placebo, resulting in a 24% reduction in PPH (Mobeen et al. in press.). Furthermore, a statistically significant difference in drop in Hb > 3 g/dL was observed among 5.1% of women receiving misoprostol compared to 9.6% of women receiving placebo. In addition to confirming the effectiveness of post-partum administration of 600 mcg oral misoprostol in prevention PPH ≥500mL, this study also demonstrated that illiterate birth attendants can be successfully trained to administer misoprostol after delivery and to recognize any side effects that might require additional care.

An earlier study, conducted in the Gambia, compared oral misoprostol (600 mcg) to standard care of 2mg oral ergometrine when administered by traditional birth attendants (TBAs) in home birth settings. This study showed a non-significant trend in reduction of PPH with misoprostol and a statistically significant smaller drop in hemoglobin in the misoprostol arm (Walraven et al. 2005). Controlled cord traction was practiced for about three-quarters of women in both groups in this trial. This community-based trial also highlighted the vital role of TBAs in the prevention of PPH in resource-poor settings and their ability to safely and effectively administer misoprostol in the third stage of labor. Finally, a study testing a sublingual regimen of misoprostol (600 mcg) used by midwives was conducted in Guinea-Bissau in primary-health centers. Hoj et al. (2005) found that sublingual misoprostol (600 mcg) was significantly better than placebo for reduction of severe PPH ≥1000mL (11% misoprostol vs. 17% placebo).

As shown on table 10.3, a number of trials have also tested 400 mcg misoprostol orally for PPH prevention. In addition, some trials have looked at vaginal and rectal administration of misoprostol for this indication (data not shown). For now, available evidence points to the use of a 600 mcg oral regimen for the prevention of PPH. The WHO Recommendations for the Prevention of Postpartum Hemorrhage indicate that 600 mcg oral misoprostol can be used for PPH prevention in settings where AMTSL is not practiced (Strong recommendation, moderate quality evidence) (WHO 2007). Although the data in support of a 600 mcg oral dose is stronger at this time, it is conceivable that future research and meta-analyses may show that a 400 mcg
dose is equally effective in preventing postpartum bleeding. Indeed, a meta-analysis by Hofmeyr and Gülmezoglu (2008) found no evidence of a benefit of 600 mcg over 400 mcg misoprostol in terms of blood loss ≥ 1000 mL (RR 1.02, 95% CI 0.71 – 1.48). As more evidence becomes available on regimens using lower doses (200 mcg or 400 mcg) of misoprostol for post-partum hemorrhage prevention, recommendations on the optimal dose should be re-evaluated.

Table 10.1 Selected randomized controlled studies on 600 micrograms orally or sublingually administered misoprostol

<table>
<thead>
<tr>
<th>First author, year &amp; publication</th>
<th>N in miso arm</th>
<th>Control group</th>
<th>Bld &gt; 1000mL</th>
<th>Additional oxytocics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>miso % (n)</td>
<td>control % (n)</td>
</tr>
<tr>
<td><strong>600 mcg oral administration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India: Derman et al, 2006.</td>
<td>812</td>
<td>placebo</td>
<td>0.2 (2)*</td>
<td>1.2 (10)</td>
</tr>
<tr>
<td>Pakistan: Mobeen et al, BJOG accepted for pub.)</td>
<td>514</td>
<td>placebo</td>
<td>1.9 (10)</td>
<td>3.4 (19)</td>
</tr>
<tr>
<td>Tibet: Miller et al, 2009.</td>
<td>487</td>
<td>Zhi Byed 11</td>
<td>2.1 (10)</td>
<td>3.1 (15)</td>
</tr>
<tr>
<td>Saudia Arabia: Mansouri et al, 2010</td>
<td>309</td>
<td>600 mcg rectal</td>
<td>0.7 (2)</td>
<td>0.3 (1)</td>
</tr>
<tr>
<td>Gambia: Walraven et al, 2005.</td>
<td>630</td>
<td>2mg ergo oral</td>
<td>0.3 (2/629)</td>
<td>0.7 (4/599)</td>
</tr>
<tr>
<td>Nigeria: Oboro et al, 2003.</td>
<td>247</td>
<td>10 IU oxytocin IM</td>
<td>1.2 (3) $^\dagger$</td>
<td>0.0 (1) $^\dagger$</td>
</tr>
<tr>
<td>Multi-center: Gulmezoglu et al, 2001.</td>
<td>9227</td>
<td>10 IU oxytocin IV or IM</td>
<td>4.0 (366)*</td>
<td>3.0 (263)</td>
</tr>
<tr>
<td>Hong Kong: Ng et al, 2001.</td>
<td>1026</td>
<td>1ml synto IM</td>
<td>0.5 (5)</td>
<td>0.4 (4)</td>
</tr>
<tr>
<td>France: Benchimol et al, 2001.</td>
<td>186</td>
<td>2.5 IU oxytocin IV or PBO</td>
<td>8.6</td>
<td>6.1 (oxy)</td>
</tr>
<tr>
<td>Bulgaria: Amant et al, BJOG 1999.</td>
<td>100</td>
<td>200 mcg methyl-ergometrine IV</td>
<td>1.0 (1)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Guinea-Bissau: Hoj et al, 2005.</td>
<td>330</td>
<td>placebo</td>
<td>11.0 (37)*</td>
<td>17.0 (56)</td>
</tr>
</tbody>
</table>

* p<0.05

**Notes from Table 10.1**
- Any maternal deaths in misoprostol arm: Walraven (2); Hoj (1).
- Studies that measured blood loss objectively: Derman, Mobeen, Miller, Walraven, Hoj, Gulmezoglu.
- $^\dagger$ Blood loss >500ml.
Table 10.2 Detailed data from two studies on 600 micrograms misoprostol administered orally compared to placebo at community-level

<table>
<thead>
<tr>
<th></th>
<th>Misoprostol</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mobeen et al, in press.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood loss ≥ 500 ml</td>
<td>85/514 (16.5)</td>
<td>122/558 (21.9)</td>
<td>0.76 (0.59-0.97)</td>
<td>0.016</td>
</tr>
<tr>
<td>Blood loss ≥ 1000 ml</td>
<td>10/514 (1.9)</td>
<td>19/558 (3.4)</td>
<td>0.57 (0.27-1.22)</td>
<td>0.099</td>
</tr>
<tr>
<td>Change in Hb ^</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.0 (0.5, 1.7)</td>
<td>1.2 (0.5, 1.9)</td>
<td>--</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.1 (1.2)</td>
<td>1.3 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drop in Hb (&gt;2 g/dL) ^</td>
<td>88/528 (16.7)</td>
<td>120/572 (21.0)</td>
<td>0.79 (0.62-1.02)</td>
<td>0.040</td>
</tr>
<tr>
<td>Drop in Hb (&gt;3 g/dL) ^</td>
<td>27/528 (5.1)</td>
<td>55/572 (9.6)</td>
<td>0.53 (0.34-0.83)</td>
<td>0.003</td>
</tr>
<tr>
<td>Shivering</td>
<td>50/533 (9.4)</td>
<td>23/583 (3.9)</td>
<td>2.38 (1.47-3.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chills/cold</td>
<td>53/533 (9.9)</td>
<td>29/583 (5.0)</td>
<td>2.00 (1.29-3.10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fever</td>
<td>4/533 (0.8)</td>
<td>7/583 (1.2)</td>
<td>0.63 (0.18-2.12)</td>
<td>0.326</td>
</tr>
<tr>
<td><strong>Derman et al 2006.</strong></td>
<td></td>
<td>(n=818)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood loss ≥ 500 ml</td>
<td>52 (6.4%)</td>
<td>97 (12.0%)</td>
<td>0.53 (0.39-0.74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood loss ≥ 1000 ml</td>
<td>2 (0.2%)</td>
<td>10 (1.2%)</td>
<td>0.20 (0.04-0.91)</td>
<td>0.0218</td>
</tr>
<tr>
<td>Use of additional uterotonic</td>
<td>3 (0.4%)</td>
<td>6 (0.7%)</td>
<td>0.49 (0.12-1.97)</td>
<td>0.3413</td>
</tr>
<tr>
<td>Required transfer</td>
<td>4 (0.5%)</td>
<td>12 (1.5%)</td>
<td>0.33 (0.11-1.02)</td>
<td>0.0475</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>1 (0.1%)</td>
<td>7 (0.9%)</td>
<td>0.14 (0.02-1.14)</td>
<td>0.0382</td>
</tr>
<tr>
<td>Fever</td>
<td>34 (4.2)</td>
<td>9 (1.1)</td>
<td>3.73 (1.80-7.73)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Shivering</td>
<td>419 (52.2)</td>
<td>10 (17.3)</td>
<td>2.96 (2.51-3.49)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Numbers are n (%) unless otherwise specified

**One-tailed p-values are specified
Table 10.3 Selected randomized controlled studies on 400 micrograms orally administered misoprostol

<table>
<thead>
<tr>
<th>First author, year &amp; publication</th>
<th>N in miso arm</th>
<th>Control group</th>
<th>Bld &gt; 1000mL</th>
<th>Additional oxytocics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>miso % (n)</td>
<td>control % (n)</td>
<td>miso % (n)</td>
</tr>
<tr>
<td><strong>400 mcg oral administration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enakpene et al, J Obstet Gynaecol R, 2007</td>
<td>432</td>
<td>500mcg ergometrine IM</td>
<td>1.4 (6) ¶*</td>
<td>9.7 (42) ¶</td>
</tr>
<tr>
<td>Nova Scotia: Baskett et al, 2007.</td>
<td>311</td>
<td>5 U oxytocin IV</td>
<td>4.5 (14)</td>
<td>2.3 (7)</td>
</tr>
<tr>
<td>Hong Kong : Ng et al, 2007.</td>
<td>178</td>
<td>1 ml synto (oxy +ergo) IM</td>
<td>1.1 (2)</td>
<td>0.6 (1)</td>
</tr>
<tr>
<td>India: Zachariah et al, 2006.</td>
<td>730</td>
<td>Arm1: 10 U oxy IM Arm2: 2mg ergo IV</td>
<td>0.1 (1) a1 0.7(4)</td>
<td>a2 0.9(6)</td>
</tr>
<tr>
<td>Zimbabwe: Kundodyiwa et al, 2001.</td>
<td>243</td>
<td>10 IU oxy IM (1ml)</td>
<td>3.7 (9)</td>
<td>2.0 (5)</td>
</tr>
<tr>
<td>Ghana: Walley et al, 2000.</td>
<td>203</td>
<td>10 IU oxy IM (1ml)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Australia: Cook et al, 1999.</td>
<td>424</td>
<td>10 IU oxy IM or 1 ml synto IM</td>
<td>3.1 (13)</td>
<td>1.6 (7)</td>
</tr>
<tr>
<td>South Africa: Hofmeyr et al, 1998.</td>
<td>250</td>
<td>placebo oral</td>
<td>6.0 (15)</td>
<td>9.2 (23)</td>
</tr>
<tr>
<td>Turkey: Caliskan et al, 2003.</td>
<td>388</td>
<td>Arm 3: oxy infusion 10 IU IV</td>
<td>3.6 (14)</td>
<td>3.9 (15)</td>
</tr>
<tr>
<td>India: Verma et al, 2006.</td>
<td>100</td>
<td>200 mcg methyl-ergometrine IM</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>India: Vimala et al, 2004.</td>
<td>60</td>
<td>200 mcg methyl-ergometrine IV</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
</tbody>
</table>

* p<0.05  
¶ Blood loss >500mL.

Notes regarding Table 10.3

Any maternal deaths reported in misoprostol arm: none reported.
Studies that measured blood loss objectively: Enakpene, Verma, Vimala, Caliskan, Hofmeyr, Zachariah, Kundodyiwa, Vimala, Cook
11. Summary of comparative evidence on safety

11.1 Side effects after misoprostol

Women who receive misoprostol during the third stage of labor are at risk for a higher temperature, shivering, nausea and vomiting. The most common side effects associated with the postpartum administration of misoprostol are shivering and pyrexia (Lumbiganon et al 1999). Studies show the rates of shivering and fever to be related, and to be dose- and route-dependent (Lumbiganon et al 1999; Khan et al 2003; Hofmeyr et al 2009). A 2007 Cochrane Review found an increase in the rate of fever following postpartum administration of 600mcg compared with 400 mcg (17% vs. 8%, respectively; relative risk 2.12, 95% CI 1.44 – 3.12) (Gülmezoglu et al. 2007). Compared to placebo, a recent meta-analysis shows that the risk of pyrexia is increased three-fold with 400 mcg misoprostol and six-fold with 600 mcg misoprostol when administered during the third stage of labor (Hofmeyr and Gülmezoglu 2008). Higher rates of shivering and elevated body temperature are also associated with oral and sublingual routes of administration, which achieve a higher and quicker maximum plasma concentration than vaginal or rectal administration (Chong et al. 2004; Tang et al. 2002; Zieman et al. 1997). One trial comparing an oral regimen of misoprostol (600 mcg) versus rectal administration of 600 mcg confirmed that the oral dose resulted in significantly higher rates of shivering (76 versus 54%) and fever (9 versus 1%) (Khan et al 2003). Nevertheless, the reported rates of shivering and fever vary greatly in the literature (Patted et al 2009). For example, rates of shivering and fever following a prophylactic oral dose of 600 micrograms of misoprostol range from 18 to 71% and from 1 to 38%, respectively (Lumbiganon et al 1999; Hofmeyr et al 2001; Gülmezoglu et al 2001). A review of the literature shows that these side effects are not severe and are transient, resolving within 12 hours or less (Gülmezoglu et al 2007; Patted et al 2009; Ng et al 2001; Lumbiganon et al 2002). In the context of childbirth, most agree that the benefits of misoprostol as a potent uterotonic outweigh the risks of experiencing these short-lived side effects (Derman et al. 2006; Durocher et al 2010).

Transient shivering and fever were mostly commonly reported among the three community-based studies that tested a 600 mcg regimen of oral misoprostol. Shivering following misoprostol administration was reported among 52% of women in India, 32% in the Gambia, and 10% in Pakistan (Walraven et al. 2005; Derman et al. 2006; Moeen et al. in press). In comparison, the rates of shivering in the control arms of these studies (placebo in India and Pakistan trials; oral ergometrine in the Gambia) averaged 12%. Reports of fever following misoprostol administration were infrequent in these studies. In the India and Pakistan trials, fever was reported among 4% and 1% of women given misoprostol, respectively. Rates of fever were comparatively low in the control arms and fever was not recorded side effect in the Gambia trial. Misoprostol administration was not associated with increased rates of nausea, vomiting or diarrhea during the third stage of labor in these three trials. Furthermore, there was no evidence of adverse effect on neonates among mothers given misoprostol in India (Derman et al. 2006).

Isolated reports of transient fever above 40 degrees centigrade (104°F) have been documented following misoprostol administration for postpartum hemorrhage prevention. One case in particular – that called the medical community’s attention to this “rare but alarming
complication” – involved a reported peak temperature of 41.9°C following administration of oral misoprostol (800 mcg) given prophylactically (Chong et al. 1997). Other cases of high fever noted in the literature include five of 9198 cases reported from the largest hospital-based clinical trial on the prevention of PPH, in which a prophylactic oral dose of 600 micrograms misoprostol was used (Gulmezoglu et al. 2001). Four cases of 1026 were reported by Ng and colleagues after testing a similar regimen (Ng et al. 2001). In all of these hospital-based reports, the elevated temperatures did not result in further complication. High doses of misoprostol administered sublingually have been associated with fever greater than 40.0°C (104°F) in several PPH treatment studies, with the large majority of cases occurring at one hospital in Ecuador (Winikoff et al 2010). Details on these fevers are reported separately (Durocher et al 2010.) Further research is ongoing to explore why this unexpectedly high rate of high fevers was experienced in this setting (Durocher, Personal communication, 2010).

11.2 Misoprostol and breastfeeding

Misoprostol enters human milk. Newborns of the mothers that take misoprostol could potentially develop the drug’s side effects. However, the maximum concentration in the breast milk (21 pg/mL peaks at 1 hour, followed by a rapid decline in levels) is much lower than ergometrine. Furthermore, after 5 hours of a single oral dose of 600 mcg of misoprostol, the levels in breast milk is unmeasurable. Vogel et al. (2004) estimated that for a nursing volume of 30 mL, the maximum amount of misoprostol delivered in the breast milk is 109 pg, representing approximately $3 \times 10^5$ mg/kg in a 3.5kg newborn ($1/100$ that in the mother). Because the levels of misoprostol in breast milk are so small and decline very rapidly, the risk to the infant is minimal with a single dose. In the study by Derman et al, there were no differences in reports of fever, vomiting or diarrhea between newborns exposed to misoprostol versus placebo (Derman et al 2006). Misoprostol is contraindicated for nursing mothers when used to treat or prevent gastric ulcers¹. When administered for postpartum hemorrhage prevention, misoprostol has no breastfeeding contraindications (Alfirevic et al 2007).

11.3 Misoprostol and maternal mortality

Although postpartum hemorrhage is one of the major contributors to maternal mortality, it is still a relatively rare event and as such, it is difficult to measure in study settings. To date, no studies have been large enough to adequately assess whether or not the possibility of PPH treatment with misoprostol (or any uterotonic) will impact maternal mortality rates. However, several studies suggest that misoprostol may play a role in saving lives given that it could be used at all levels of the health care system (Sutherland et al 2009; Pagel et al 2009). Efforts have been made to discern whether there is an association between misoprostol use for prevention and treatment of post-partum hemorrhage and subsequent maternal death. A review by Hofmeyr and Gülmezoglu (2008) found eleven deaths among more than 40,000 women in forty-seven trials on misoprostol for PPH. Of these 11 deaths, 8 of the women were given misoprostol [RR 2.0, 95% CI 0.68 -

¹ The standard dose for treatment of gastric ulcers dose is 600 mcg (3 tablets), 3 times a day, for 2-3 weeks, depending on need.
The authors theorized that, while misoprostol may reduce post-partum bleeding, it could potentially also have side effects that lead to higher mortality rates overall. As mentioned, these trials sought to study both misoprostol for post-partum hemorrhage prevention and treatment: two of the largest contributors to maternal mortality. Also, they tested a range of doses and routes of administration, including one trial with 3 deaths testing a 1000 mcg misoprostol dose administered orally, sublingually and rectally (Hofmeyr et al. 2004). The recommended dosage in this application is 600 mcg orally, which is much smaller than the dosage tested in the aforementioned trial. In their conclusion of this discussion, the authors note that the wide confidence limits and small total number of deaths makes any firm conclusion about the association between misoprostol and maternal mortality difficult at this point (Hofmeyr and Gülmezoglu 2008) and recommend continued surveillance of future research and programs to monitor this issue. Since the time of this publication (2008), several large randomized controlled trials including misoprostol in at least one of the study arms for PPH prevention have appeared in the literature. No maternal deaths among women given misoprostol during the third stage of labor were reported in recent trials.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

12.1 Range of Costs for the Proposed Medicine

The International Drug Price Indicator Guide, published by Management Sciences for Health (MSH), was used to obtain present prices of misoprostol. The one supplier price listed was USD 0.77 per 200μg tablet of misoprostol (USD 2.31 per dose for prevention). The median price paid by the three buyers listed was USD 0.09 per tablet (range USD 0.07-0.12); or USD 0.27 per dose for prevention. Table 12.1 shows supplier price in USD and Table 12.2 shows buyer costs as listed in the report. As more and more products become available, the price of misoprostol can be expected to drop.

Table 12.1a: Supplier price information (in US$)

<table>
<thead>
<tr>
<th>Source</th>
<th>Package</th>
<th>Package Price</th>
<th>Unit Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDEOR/TZ</td>
<td>28 Tab-cap (Tablets)</td>
<td>$21.82</td>
<td>0.7794/Tab-cap</td>
</tr>
</tbody>
</table>

Table 12.1b Buyer Prices (USD) for 200 μg Misoprostol Tablets

<table>
<thead>
<tr>
<th>Buyer</th>
<th>Package Price (100 tablets)</th>
<th>Unit Price (USD)</th>
<th>Price per Dose (3 Tablets; 600μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organisation of Eastern Caribbean States Pharmaceutical Procurement Service (OECS/PPS)</td>
<td>9.00</td>
<td>.9090</td>
<td>.27</td>
</tr>
<tr>
<td>Malawi</td>
<td>6.94</td>
<td>.0694</td>
<td>.21</td>
</tr>
<tr>
<td>Camerwa</td>
<td>12.04</td>
<td>.1204</td>
<td>.36</td>
</tr>
<tr>
<td>Median Unit Price</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest Unit Price</td>
<td>0.0900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest Unit Price</td>
<td>0.1204</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High/Low Ratio</td>
<td>1.73</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
12.2 Comparative Cost-Effectiveness

One study has examined the cost-effectiveness of misoprostol for PPH prevention and its comparative cost-effectiveness to other PPH prevention methods. Seligman and Xingzhu (2006) assessed the net costs, cost-effectiveness, cost-benefit ratios and net benefits for preventative and curative interventions for PPH in four countries (Argentina, Bangladesh, India, and Nepal). In their analysis, the authors show that, at present, there is considerable variation in the cost per Disability-Adjusted Life Year (DALY) averted due to the diversity of drug prices, labor and delivery patterns, and assumed coverage of each intervention in the four study countries. The variance in the cost per DALY averted in the four countries studied reflects the different cost of misoprostol (at 2006 market price) in each country. This is a result of imperfect market conditions in countries where misoprostol is not yet registered or is sought for other uses.

In the cost-effectiveness study by Sutherland et al 2009, the authors found that misoprostol use after delivery was associated with an incremental cost per life saved of US $1401 (IQR: US $1008–1848) (Sutherland et al 2009). In comparison to US $10,532 which is estimated cost of improve comprehensive emergency obstetric care, misoprostol appears to be a potentially worthwhile intervention. As this study relied in part on previous trial data to generate costing estimates for the model, some costs, such as the cost to train birth attendants to safely administer misoprostol, may have been underestimated. In service delivery programs, the costs of misoprostol introduction for PPH prevention may be higher. Cost-effectiveness in programs will be driven by a number of factors – including the drug price, level of facility used, type of provider and product availability in various jurisdictions. Even if the costs increase in a real world service delivery model, it appears that misoprostol is a promising cost-effective intervention for PPH prevention.

12.3 Comparative Cost-Effectiveness – Summary

In sum, all of the interventions seeking to address PPH although not equally efficacious, can yield a positive return and are thus economically efficient. In terms of cost-benefit ratio, oxytocin in its various forms is the most economically efficient, mainly due to its current lower price. However, in terms of net benefits, misoprostol is superior due to its stability at room temperature and ability to be provided in tablet form to the target population. Misoprostol is currently the only intervention that can be offered in most rural settings given that injectable uterotonicics currently require cold chain, making them inaccessible/unavailable in most remote areas at this time. As more manufacturers begin to produce and market oxytocin in Uniject® and as more inexpensive misoprostol products enter the market, the cost of the full package of interventions for PPH care will likely drop.

13. Summary of regulatory status of the medicine

Many formulations of misoprostol are available (See Appendix 1). Misoprosotol was originally approved in the United States, where it was marketed and distributed as Cytotec® by Searle (now Pfizer). More than a dozen countries have now approved misoprostol for its use in preventing PPH and its global availability is increasing (Fernandez et al, 2009) India’s Drugs Controller General granted the permission for misoprostol use in gynecological conditions like
cervical ripening, prevention of post partum hemorrhage and first trimester abortion with mifepristone in December 2006. Many more countries are now planning to or are in the midst of introducing misoprostol for PPH prevention and several pharmaceutical companies are pursuing dedicated PPH products.

14. Availability of pharmacopoeial standards

Misoprostol (standards available in BAN, USAN, rINN)

U.S. Pharmacopeia conducted a review and made the following conclusion: “Upon review of the studies included in the attached evidence tables on misoprostol, the consensus of the U.S. Pharmacopeia Expert Advisory Panel is that prevention of postpartum hemorrhage should be considered as an Accepted indication in the USP Drug Information (DI) monograph on misoprostol. They recommended misoprostol as an alternative agent in reducing the incidence of postpartum hemorrhage, especially in situations in which oxytocin and other uterotonic drugs are not available” (US Pharmacopeia 2001).

15. Proposed text for the WHO model formulary

SECTION: 22.01.00.00 Oxytocics

FORMULATION (dosage form and strength): Oral tablet: 200 micrograms; ATC Code: A02BB01; Type of List: Complementary List.

DISEASE/INDICATION: Prevention of postpartum hemorrhage.

RATIONALE FOR INCLUSION: Misoprostol offers a low-cost, easy to administer means to prevent postpartum hemorrhage, one of the major contributors to maternal morbidity and mortality worldwide.

GENERAL INFORMATION: Misoprostol is a complementary drug for medical termination of pregnancy of up to 63 days gestation where this is permitted under national law and for induction of labour. The drug is also used for prevention and treatment of postpartum hemorrhage, induction of labor (at smaller doses) and for evacuation of the uterus following incomplete abortion/miscarriage in many jurisdictions.

USES: Prevention of postpartum hemorrhage (used alone).

CONTRAINDICATIONS (for use in PPH prevention): None.

DOSE: Prevention of postpartum hemorrhage, oral administration, ADULT and ADOLESCENT a single dose of 600 micrograms after delivery of the baby.

NOTE: In multiple birth, administration of misoprostol for prevention of postpartum hemorrhage should occur after delivery of the last infant.
ADMINISTRATION: For prevention of postpartum hemorrhage, oral administration of three 200-microgram tablets (600 micrograms total) is recommended.

ADVERSE EFFECTS: fever and shivering.
16. References


Ng PS, Chan AS, Sin WK, Tang LC, Cheung KB, Yuen PM. A multicentre randomized controlled trial of oral misoprostol and i.m. syntometrine in the management of the third stage of labor. Human Reproduction 2001; 16: 31-35.


Royal College of Obstetricians and Gynaecologists. RCOG Green-top Guideline No. 52. May 2009


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Background evidence

Postpartum hemorrhage (PPH) is a major cause of maternal death worldwide. When PPH occurs owing to uterine atony, a number of medical and surgical interventions are used to control the bleeding [1,2]. A crucial aspect of PPH treatment is uterotonic therapy and the gold standard is oxytocin. However, it is often not available in low-resource settings because of parenteral administration and cool storage requirements. Ergometrine is also commonly used for treatment of PPH, but needs to be given by injection and is unstable in heat and light. It is also contraindicated in women with hypertension and cardiac disease. It may not, therefore, be suitable for certain low-resource settings.

Misoprostol, an E1 prostaglandin analogue, has been studied as an alternative to oxytocin because of its low cost, stability at room temperature, and ease of administration. Three randomized controlled trials (RCTs) have assessed the effectiveness of misoprostol for treatment of PPH [3–5]. Two compared 800 μg sublingual misoprostol with 40 IU intravenous oxytocin [3,4]. In the first trial, involving 978 women diagnosed with PPH, oxytocin prophylaxis was not given [3]. Results indicated that intravenous oxytocin was more effective at controlling active bleeding within 20 minutes (96% vs 90% of women) and preventing additional blood loss of 300 mL or greater (17% vs 30%). The second trial involved 809 women diagnosed with PPH, all of whom were given oxytocin prophylaxis (intravenous or intramuscular) [4]. Results indicated misoprostol was non-inferior to oxytocin at controlling active bleeding within 20 minutes (90% vs 89%) and preventing additional blood loss of 300 mL or greater (31% vs 34%). The third RCT compared 800 μg rectal misoprostol with intramuscular Syntometrine plus intravenous Syntocinon, also following receipt of oxytocin prophylaxis [5]. Results suggested that misoprostol may be more effective than Syntometrine/Syntocinon for treatment of PPH. However, this study was single blinded and the outcome was subjective assessment of response, and, therefore, prone to assessment bias.

Four RCTs have assessed the adjunct (simultaneous) use of misoprostol when given in conjunction with conventional uterotonics for treatment of PPH [6–9]. Two trials compared adjunct use of 600 μg sublingual misoprostol with placebo for treatment of PPH [6,7]. Widmer et al. [6] enrolled 1422 women and found no differences between the misoprostol and placebo groups in terms of blood loss of 500 mL or greater, blood loss of 1000 mL or greater, or postpartum hemoglobin changes. However, there was a higher incidence of adverse effects among those given misoprostol [6]; Zuberi et al. [7] enrolled 61 women who had also received uterotonics prophylaxis for management of the third stage. Owing to a lower than expected rate of PPH, the trial was unable to obtain statistical significance in any of the outcomes studied. There were non-significant trends, however, toward reduced postpartum blood loss, smaller drops in postpartum hemoglobin, and need for fewer additional interventions [7]. A third trial by Walraven et al. [8] compared adjunct use of 600 μg misoprostol (200 μg orally plus 400 μg sublingually) with placebo among 160 women who had also received uterotonics prophylaxis. However, this pilot trial was not powered to detect significant differences between misoprostol and placebo [8]. Hofmeyr et al. [9] compared adjunct use of a 1000-μg misoprostol regimen (200 μg oral plus 400 μg sublingually plus 400 μg rectal) with placebo in 238 women with uterotonics prophylaxis, and found no significant differences in blood loss of 500 mL or greater within 1 hour after treatment.

No study has looked at the effectiveness of repeat doses of 800 μg sublingual misoprostol for treatment of PPH and as a result there is insufficient information about the risks and benefits of additional doses. Given documented adverse effects after a single dose of misoprostol for PPH treatment [3–10] and the absence of evidence of effect, repeat doses are not advised.

Regimen

One dose of misoprostol 800 μg sublingually is indicated for treatment of PPH when 40 IU intravenous oxytocin is not immediately available (irrespective of the prophylactic measures). The recommended dose does not change according to the woman’s weight.

Course of treatment

Once PPH is diagnosed, the treatment should be given immediately.

Repeat or consecutive doses

There is insufficient information about the effect of 2 or more consecutive doses of misoprostol for treatment of PPH. In the absence of such information, repeat doses of misoprostol for PPH treatment are not recommended.

If oxytocin is already being provided for treatment of PPH, evidence suggests that adjunct (simultaneous) use of misoprostol has no added benefit.
Since the known adverse effects of misoprostol appear to be dose related, repeat or consecutive doses of misoprostol may increase the incidence of adverse effects.

**Contraindications**

History of allergy to misoprostol or other prostaglandin.

**Precautions**

1. Caution is advised in instances where the woman may have already received misoprostol as prophylaxis for PPH prevention, especially if an initial dose of misoprostol was associated with pyrexia or marked shivering.

2. After provision of uterotonics, the need for other steps to stop the bleeding should be explored, and causes of PPH other than uterine atony should be considered.

**Effects and adverse effects**

Prolonged or serious effects and adverse effects are rare.

The most common known adverse effects associated with misoprostol are:

- **Temperature changes:** Shivering, chills, and/or fever are all commonly associated with use of misoprostol. Shivering has been reported in 37%–47% of women following administration of 800 μg sublingual misoprostol, fever in 22%–44%, and hyperpyrexia (>40 °C) in 1%–14% [3,4,10]. The shivering is self-regulating and even if high temperatures occur, they are transient and settle with reassurance and symptomatic treatment.

- **Gastrointestinal effects:** Nausea occurs in 10%–15% of women given 800 μg sublingual misoprostol and vomiting in about 5% [3,4]. Both should resolve within 2–6 hours. An antiemetic can be used if needed, but in general no action is required except to reassure the woman and her family. Diarrhea may also occur in about 1% of women but should resolve within a day.

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

**References**


## Appendix A – Misoprostol Trade Name List

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<th>Product name</th>
<th>Form</th>
<th>Composition</th>
<th>Company</th>
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