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 acidemia 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 in colostrum 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 \(\mu\)g 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 [\(\text{"}\) Induced\("\)\[Mesh\] OR \(\text{"}\), Induced/adverse effects\[Mesh\] OR \(\text{"}\), 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 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**

**MISO PROSTOL 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
dinoprostone, followed, if needed, by induction with intravenous oxytocin. Misoprostol is considered as alternative where there are not the required facilities for oxytocin use. For both of them, improper dosing, administration, and monitoring may lead to the use of excessive amounts, which can induce hyperstimulation of the uterus and its sequelae.

**Misoprostol versus oxytocin**

A Cochrane systematic review\(^\text{14}\) 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\(^\text{15}\) showed that vaginal misoprostol was associated with more uterine hyperstimulation in comparison to oxytocin for labour induction.

In contrast, a meta-analysis\(^\text{16}\) 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\(^\text{17}\) 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\(^\text{18}\) 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.\(^\text{19}\)

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.\(^\text{20}\)

A randomized controlled trial\(^\text{21}\) 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\(^1\) 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\(^2\) 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\(^3\) 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.\(^4\)

Two randomised clinical trials,\(^5\) with a similar study design, compared efficacy and safety vaginal misoprostol with dinoprostone vaginal insert for labour induction in term pregnant women with unfavorable cervix. 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)\(^6\) 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\(^7\) 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 signification.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 review19 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 review23 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)14 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,42 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)43 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) 44 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.46

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.47 According to Karoshi and Keith,48 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.49 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.50
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 ($P < 0.05$).51

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.52

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 trial53 estimated that one case of PPH (blood loss ≥ 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 analysis54 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)55 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 diarrhoea between the two groups. There were no differences in the incidence of vomiting, diarrhea or fever in the newborns.56

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.49 Nevertheless, the authors of a Cochrane systematic review57 and another review58 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\textsuperscript{59} 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 \(\mu\)g 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,\textsuperscript{40} 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 \(\mu\)g 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\textsuperscript{61} compared the effects of 800 \(\mu\)g 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\textsuperscript{62} compared 800 \(\mu\)g 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%; \( P \leq 0.001 \)).

A double-blind randomised trial (\( n = 622 \))\(^6\) 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 (\( \geq 38 \, ^\circ C \)) 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\(^6\) 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\(^\circ\)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,\(^6\) 300 low-risk women received either 100 \( \mu \)g or 200 \( \mu \)g misoprostol sublingually or 200 \( \mu \)g intramuscular 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\(^\circ\)C. None of the women in the methylergometrine group had either shivering or a recorded temperature of >38\(^\circ\)C. The side effects were mild, reversible and well accepted by the women.

**Misoprostol versus oxytocin plus ergometrine**

A double-blind randomised controlled trial (\( n = 355 \))\(^6\) 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,\(^6\) 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\(^6\) 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\(^6\) 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\(^6\) 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\(^6\) 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 agents 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%. 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. 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. In Derman and colleagues’ trial, 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 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, 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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