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Sublingual Misoprostol for the Treatment of Postpartum Hemorrhage

R. Dabash, I. Dzuba and B. Winikoff

INTRODUCTION

The current gold standard for treating postpartum hemorrhage (PPH) due to atony is intravenous (IV) oxytocin[1]. However, access to this specific drug and the capacity for its timely intravenous administration are lacking in settings with limited resources, especially at lower levels of the health care system.

Misoprostol, a tablet that requires no additional supplies and/or specialized skills to administer, has the potential to play an important role as a first-line treatment for PPH in such settings. Interest in its use for both prevention and treatment of PPH has a decades-long history, and in 2011 misoprostol was added to the World Health Organization's (WHO) Model List of Essential Medicines for PPH prevention[2]. Recent research demonstrates misoprostol's safety and efficacy as compared with oxytocin.

Prior to 2010, the published literature on misoprostol for the treatment of PPH consisted of several small non-randomized trials that examined various doses and routes of administration as either a first-line treatment or an adjunct to standard uterotonics, a handful of case reports (treating 82 women) and one community-based intervention study[3–14]. Although these studies were insufficient to recommend a specific regimen for treatment with misoprostol, they provided a rationale for further investigation. Perhaps of greater import, health care providers worldwide have been using the drug for *ad hoc* treatment of PPH, despite the absence of conclusive evidence and consensus on an optimal regimen.

In 2010, three seminal studies provided evidence on the utility of sublingual misoprostol in the treatment of PPH. Two large multicenter, double-blind, placebo-controlled, randomized trials compared the effectiveness, safety and acceptability of 800 μg sublingual misoprostol with 40 IU intravenous oxytocin[15,16]. Another large multicenter, double-blind, randomized trial assessed 600 μg sublingual misoprostol when used as an adjunctive treatment for PPH (i.e. when given at the same time as the standard uterotonic treatment)[17]. The sublingual route of administration of misoprostol was chosen in all these trials because of its rapid uptake, long-lasting duration of effect and high bioavailability compared with other routes of misoprostol administration[18].

SUBLINGUAL MISOPROSTOL VERSUS OXYTOCIN AS FIRST-LINE TREATMENT OF PPH

Two non-inferiority trials compared treatment of PPH with sublingual misoprostol to intravenous oxytocin[15,16]. These trials were designed as companion studies and were implemented at tertiary and secondary hospitals in five countries. The first trial enrolled women who had received routine oxytocin prophylaxis in the third stage of labor at hospitals in Burkina Faso, Egypt, Turkey and Vietnam. The second trial enrolled only women who had not received oxytocin prophylaxis and was implemented in hospitals in Ecuador, Egypt and Vietnam where the norms did not call for routine oxytocin prophylaxis. The latter study was meant to reflect the clinical context in many lower level facilities where oxytocin is not available or feasible to administer, and where the need for alternative treatment options is greatest.

The dose of 800 μg misoprostol was carefully chosen giving consideration to expert opinion and published reports of elevated body temperatures of 40.0°C or higher following doses ranging from 600 to 1000 μg[10–12]. Expert consensus was that the optimal dose to be tested should be sufficiently high to be effective but with an acceptable side-effects profile. The 800 μg dose had been tested previously in a small randomized controlled trial without reports of excessive side-effects[10].

Over 41,000 women were screened for PPH in these two studies, and 1786 women were randomized to one of two placebo-controlled double-blind treatment arms: 800 μg sublingual misoprostol or 40 IU intravenous oxytocin (Figure 1). Women were enrolled if PPH due to uterine atony was suspected after vaginal delivery either by clinical diagnosis or when blood loss reached 700 ml on a calibrated delivery drape within 1 hour after delivery, whichever occurred first. The primary outcome of interest was cessation of active bleeding within 20 min. Additional outcomes included mean total blood loss after treatment, average time to bleeding cessation, change in

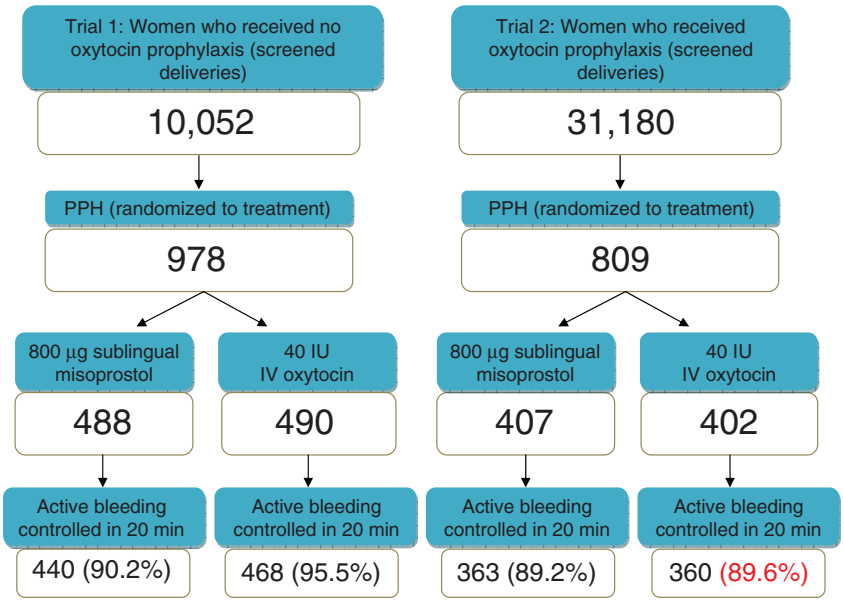

Figure 1 Enrollment and treatment allocation in the two non-inferiority trials of sublingual misoprostol versus intravenous oxytocin for treatment of atonic PPH[15,16]

hemoglobin and recourse to any additional interventions. The frequency and severity of side-effects was also recorded, as was the acceptability to women of each treatment.

Efficacy of treatment

In both trials, median blood loss at time of treatment was 700 ml for women treated. Treatment of PPH with either IV oxytocin or 800 µg sublingual misoprostol successfully controlled bleeding within 20 min of administration in nine out of ten women (Figure 1). Among women who received oxytocin prophylaxis during the third stage of labor and then went on to be diagnosed with PPH, treatment with sublingual misoprostol stopped bleeding as rapidly as IV oxytocin (mean 19 min) and with a similar quantity of additional blood lost (Table 1).

Among women who did not receive a prophylactic uterotonic, both sublingual misoprostol and IV oxytocin were very effective in controlling postpartum bleeding within 20 min, although IV oxytocin was somewhat better (96% vs. 90%; $p = 0.001$), and it stopped active bleeding on average 2 min faster than sublingual misoprostol, resulting in approximately 60 ml less blood loss.

As IV oxytocin is injected directly into the bloodstream, a patient may experience its benefits almost immediately. Pharmacokinetic data on sublingual misoprostol administration show that peak serum concentrations are achieved at around 20 min[18], so there may be a short delay in maximum benefit. In order to avoid treatment delays, study teams made great efforts to administer all medications quickly, which may have diluted the very different logistical burdens of these two treatments. In routine clinical practice, the time from diagnosis to treatment-effect of each of the two drugs may prove to be quite different. This reality may potentially reduce the advantages of oxytocin over misoprostol in the time to bleeding cessation, especially when an intravenous line is not in place and where IV supplies are not readily available.

A cross-study comparison shows that both treatments (sublingual misoprostol or IV oxytocin) performed better and faster in stopping bleeding among women not exposed to oxytocin prophylaxis. This finding suggests that women who develop PPH despite oxytocin prophylaxis have a diminished response to an additional dose of uterotonic for treatment or have worse, more refractory, hemorrhages.

Other indicators of drug efficacy

In the trial of women who had received oxytocin prophylaxis, a similar proportion of women in each treatment group experienced a drop of 2 g/dl or more in hemoglobin concentration. Also, the proportion of women with a drop of 3 g/dl or who received a blood transfusion did not differ by treatment group. Among women in the other trial who had not received prophylactic oxytocin, median hemoglobin changes from pre-delivery to post-treatment (data not shown) were similar in women treated with IV oxytocin and those treated with sublingual misoprostol, as was the proportion of women who had a drop in hemoglobin of 2 g/dl or more (Table 1). However, hemoglobin drops of 3 g/dl or receipt of blood transfusion (40.8 % with sublingual misoprostol vs. 30.2% with IV oxytocin) were significantly more common among women who received sublingual misoprostol than among those who received IV oxytocin.

Recourse to additional interventions is an important indicator of the potential program costs associated with these two uterotonics when used as first-line treatment. In women who had received oxytocin prophylaxis but went on to have PPH, the frequency of

Table 1 Bleeding cessation, blood loss, hemoglobin change and additional intervention outcomes in women treated for PPH with sublingual misoprostol or IV oxytocin in the two non-inferiority trials. Data are expressed as numbers with percentages in parentheses unless otherwise specified

	Women not exposed to oxytocin prophylaxis[16]				*Women who received prophylactic oxytocin*[15]			
	Misoprostol (n = 488)	*Oxytocin (n = 490)*	*RR (95% CI)*	*P value*	*Misoprostol (n = 407)*	*Oxytocin (n = 402)*	*RR (95% CI)*	*P value*
Active bleeding controlled within 20 min of initial uterotonic treatment	440 (90.2%)	468 (95.5%)	0.94 (0.91–0.98)	0.001	363 (89.2%)	360 (89.6%)	0.99 (0.95–1.04)	0.867
Minutes to active bleeding controlled mean (SD)	13.4 (8.2)	11.8 (6.6)	–	0.001	19.3 (15.0)	19.1 (14.6)	–	0.854
Additional blood loss (ml) median (IQR)	200 (110–300)	150 (100–225)	–	<0.0001	200 (100–350)	200 (100–300)	–	0.199
Drop in Hb ≥2 g/dl or blood transfusion	250 (51.2%)	230 (46.9%)	1.09 (0.96–1.24)	0.101	152 (37.6%)	142 (35.7%)	1.06 (0.88–1.27)	0.567
Drop in Hb ≥3 g/dl or blood transfusion	199 (40.8%)	148 (30.2%)	1.35 (1.14–1.60)	<0.0001	104 (25.7%)	90 (22.6%)	1.14 (0.89–1.46)	0.301
Additional uterotonics	61 (12.5%)	31 (6.3%)	1.98 (1.31–2.99)	0.001	40 (9.8%)	46 (11.5%)	0.86 (0.58–1.28)	0.260
Blood transfusion	41 (8.4%)	26 (5.3%)	1.58 (0.98–2.55)	0.036	24 (5.9%)	18 (4.5%)	1.32 (0.73–2.39)	0.229
Hysterectomy/other surgery	0 (0.0)	0 (0.0)	–	–	4 (1.0%)	2 (0.5%)	1.98 (0.36–10.73)	0.350
Maternal death	0 (0.0)	0 (0.0)	–	–	1 (0.2%)	1 (0.2%)	0.99 (0.06–15.74)	0.747

RR, relative risk; Hb, hemoglobin

recourse to additional interventions was similar following initial treatment with oxytocin or misoprostol. The most common intervention was administration of additional uterotonics in approximately 1 in 10 women regardless of treatment group (Table 1).

In women not given prophylaxis before their PPH, additional interventions were more frequently used in the misoprostol group, including administration of additional uterotonics and blood transfusion (Table 1). Women treated with misoprostol were twice as likely to receive additional uterotonic drugs as those in the oxytocin group (12.5% vs. 6.3%; $p = 0.001$, RR 1.98, 95% CI 1.31–2.99; Table 1). As blood loss data suggest, all women in this study bled faster on average than those in the study with routine prophylaxis (mean blood loss within 20 min of 279 ml vs. 249 ml, respectively, in the misoprostol arms and 252 ml vs. 190 ml in the oxytocin arms). This factor, coupled with the slightly slower response time with misoprostol may have contributed to the higher rates of additional uterotonic use in women treated with misoprostol. The availability of additional drugs, as well as preference to use more than one intervention when PPH is diagnosed, may have contributed to provider choices in these hospital settings that were not necessarily based on patient needs; such choices might not be as likely in lower levels of the health care system.

Six hysterectomies (including two deaths) occurred in the study of women who received prophylaxis, while none occurred among women who received no prophylaxis. No differences were present in the rates of these events in the two treatment arms (Table 1). These findings again suggest that women who experience a PPH following prophylaxis may represent a different group of women to those who experience excessive bleeding with no prior prophylaxis. The significant difference in adverse outcomes suggests that women with PPH following prophylaxis failure have a PPH that is more difficult to treat and is less responsive to first-line treatment with additional uterotonics alone. No invasive surgeries, hysterectomies, or deaths were reported in the study of women with no prior prophylaxis.

Side-effects

Women in both studies experienced side-effects regardless of the type of uterotonic treatment received, although fever and shivering were more commonly reported in women treated with sublingual misoprostol. Prior oxytocin prophylaxis did not affect the frequency of side-effects following either treatment. Gastrointestinal side-effects, such as nausea, vomiting and diarrhea, are known effects of misoprostol, but they were also commonly reported in women treated with oxytocin. Of these side-effects, nausea was the most commonly reported, affecting 12.1% of women who took misoprostol and 12.3% of women who received oxytocin. The frequency of vomiting was low, but higher among those women treated with misoprostol (Table 2). In all cases, these side-effects were transient and did not result in any life-threatening complications. The vast majority of study participants reported that the side-effects experienced were tolerable.

The most notable features of the side-effects following treatment with sublingual misoprostol are the rates of fever and shivering. These two side-effects were reported after both oxytocin and misoprostol, but were more likely to occur when women were treated with misoprostol (Table 2). High fever following sublingual administration of misoprostol was infrequent except for in one site in Quito, Ecuador, where a disproportionately high percentage of women receiving misoprostol treatment (35.6%) experienced high fever. In contrast, the rate of high fever in the other hospitals participating in these studies ranged from 0 to 10%[19]. Prior to these two studies, the published literature included four cases (in 146 women) of high fever (≥40°C) following use of misoprostol for treatment of PPH[11,13]. Shivering and fever following misoprostol administration are related events and known to be dose and route dependent[20–22] with higher rates following oral and sublingual administration. Pharmacokinetic research on misoprostol demonstrates a higher plasma concentration and a more rapid rise to peak concentration when it is taken by these routes[18,22,23]. For these reasons, a higher incidence of shivering and fever in studies that employ higher-dose sublingual misoprostol regimens is not unexpected.

Analysis of the reported cases of high fever that occurred in Ecuador showed that they followed a predictable and consistent pattern. They were typically characterized by a sharp increase in temperature within 1 hour of treatment, which peaked 1–2 hours after treatment, and gradually declined over the course of several hours. Average temperatures remained above 40.0°C for less than 2 hours, and measured below 38.0°C approximately 6 hours after receiving misoprostol. Temperature elevation and decline followed the rise and fall of sublingual misoprostol blood plasma concentration (Figure 2). Women with high fever were treated by nurses with oral acetaminophen, cool compresses and IV aspirin, and all women recovered with no sequelae[19].

Table 2 Side-effects following PPH treatment with misoprostol and oxytocin[15,16]. Data are expressed as numbers with percentages in parentheses unless otherwise specified

Side-effect	*Misoprostol (n = 895)*	*Oxytocin (n = 892)*	*Relative risk (95% CI)*
Nausea	108 (12.1)	110 (12.3)	0.98 (0.76–1.27)
Vomiting	43 (4.8)	17 (1.9)	2.52 (1.41–4.57)
Fainting or feeling faint	62 (6.9)	62 (7.0)	1.00 (0.70–1.42)
Diarrhea	7 (0.78)	5 (0.56)	1.40 (0.40–5.03)
Shivering	381 (42.6)	141 (15.8)	2.69 (2.27–3.20)
Fever	305 (34.1)	86 (9.6)	3.54 (2.83–4.44)
Temp ≥40.0°C	71 (7.9)	1 (0.11)	70.76 (9.85–508.21)

It is unclear why some women develop high fever while others do not and why the thermoregulatory response to misoprostol among Ecuadorian women was so notably different from that of participants in other study sites[19]. Despite these uncertainties, the variable responses in some populations raises the question of whether a lower treatment dose (i.e. 600 μg) would be as effective as 800 μg sublingual misoprostol and reduce the incidence of high fever. Currently, the literature does not support a lower dose or other routes of administration for first-line PPH treatment. While it is possible that a lower dose or administration by another route may reduce the occurrence of fevers, it may also reduce efficacy. Given the infrequent nature of this side-effect in most settings and the benign course of these fevers, such a trade-off may not be universally advantageous. Indeed, a rigorous comparative randomized trial to explore the potential of a reduced dose would of necessity be very large and require tremendous time and resources to address a question that may only be relevant to some settings.

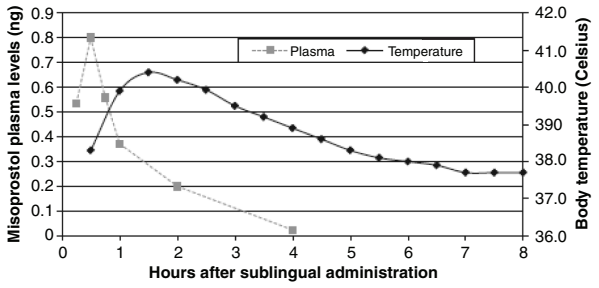

Figure 2 Mean misoprostol plasma concentrations after sublingual administration of misoprostol (800 μg), and mean temperatures over time of 58 cases of high fever following treatment with 800 μg sublingual misoprostol in Quito, Ecuador[24]. Reproduced with permission from Durocher *et al.* High fever following postpartum administration of sublingual misoprostol. BJOG 2010;117:845–52. John Wiley and Sons Ltd

MISOPROSTOL AS AN ADJUNCT TO OXYTOCIN FOR TREATMENT OF PPH

Since providers in many service delivery settings respond to life-threatening PPH with multiple treatment interventions, including more than one uterotonic, practitioners have wondered whether simultaneous administration of both oxytocin and misoprostol confers any additional advantages. A large multicenter, double-blind, placebo-controlled, randomized trial evaluated whether a regimen of 600 μg sublingual misoprostol administered at the same time as routine injectable oxytocin offered any clinical advantage[17]. Secondary outcomes in this trial included additional blood loss, recourse to additional interventions, change in hemoglobin and blood transfusion (Table 3).

The results showed no difference in postpartum blood loss among women who received misoprostol in combination with standard uterotonics and those who received placebo with standard treatment (Table 3). Furthermore, consistent with other reports of side-effects following use of misoprostol, women receiving misoprostol were more likely to experience shivering and fever (Table 3).

This study suggests that the addition of misoprostol to the initial treatment regimen is not more effective than administration of a standard uterotonic alone and is associated with more side-effects. As such, the adjunct use of sublingual misoprostol and conventional uterotonics simultaneously is not recommended. Yet, it remains possible that there could be benefits to the sequential administration of misoprostol following oxytocin or as a last-ditch effort before recourse to more invasive procedures.

PROGRAM IMPLICATIONS AND FUTURE RESEARCH

The results of the two large treatment trials evaluating first-line treatment options for PPH, along with other

Table 3 Outcomes of usual treatment with uterotonic plus concurrent addition of sublingual misoprostol or placebo[17]. Data are expressed as numbers with percentages in parentheses unless otherwise indicated

	Misoprostol + standard uterotonics (n = 705)	*Placebo + standard uterotonics (n = 717)*	*RR (95% CI)*
Blood loss of ≥500 ml within 60 min after randomization	100 (14.2)	100 (13.9)	1.02 (0.79–1.32)
Blood loss of ≥1000 ml within 60 min after randomization	9 (1.3)	9 (1.3)	1.02 (0.41–2.55)
Any uterotonic after randomization	188 (26.7)	203 (28.3)	0.94 (0.79–1.11)
Hemoglobin concentration of <8 g/dl within 24 h postpartum or need for blood transfusion*	121 (17.2)	139 (19.4)	0.89 (0.72–1.11)
Blood transfusion after randomization	103 (14.6)	117 (16.3)	0.89 (0.7–1.14)
Maternal death	2 (0.3)	0 (0)	–
Severe morbidity	8 (1.1)	10 (1.4)	0.81 (0.32–2.00)
Shivering			
Any	455 (64.6)	230 (32.1)	2.01 (1.79–2.27)
Severe	80 (11.4)	7 (1.0)	11.64 (5.41–25.03)
Fever			
≥38°C	303 (43)	107 (14.9)	2.88 (2.37–2.5)
≥40°C	18 (2.6)	3 (0.4)	6.11 (1.81–20.65)

*Data recorded for 691 patients receiving misoprostol and 710 patients receiving placebo; outcomes could not be measured in remaining patients

available literature, suggest that both sublingual misoprostol and IV oxytocin are very effective alone in controlling PPH. The broader implications of these study results depend on the context in which PPH occurs and what treatment options are available (Table 4). For women who receive prophylactic oxytocin in the third stage of labor, 800 μg sublingual misoprostol is clinically equivalent to 40 IU of IV oxytocin for treatment of primary atonic PPH, and either drug can be used to control bleeding. It is also clear that when both misoprostol and oxytocin are available, their simultaneous administration confers no advantages and is only associated with an increase in side-effects.

Where women do not receive any prophylaxis, on the other hand, oxytocin is better than misoprostol as first-line treatment. Unfortunately, the present day realities that limit access to oxytocin prophylaxis are likely also to limit its feasibility for intravenous use for PPH treatment, particularly in limited-resource settings and at the lowest level of the health care system, including the many home births in developing countries[24]. Furthermore, governmental policies commonly limit the authority of certain types of providers to offer on-site treatment. These providers, while expected to be able to diagnose PPH for referral, are infrequently authorized to administer treatment, including injections and intravenous treatments. In these settings, misoprostol appears to be a suitable alternative. Given the evidence, future research should examine the programmatic implications of introducing misoprostol as an on-site treatment option where few or no alternatives currently exist. Community-level research should focus on developing simple models that facilitate diagnosis of PPH based on clinical indicators aside from measured blood loss, which is both costly and difficult to implement.

Sublingual misoprostol and IV oxytocin may prove to be more similar treatments in real-life contexts, especially given the differences in logistical burdens, level of staff able to use the drugs, conditions of storage, etc. In addition, while the studies described above compared sublingual misoprostol to the highest recommended dose of IV oxytocin (40 IU), many country protocols and supplies only allow for lower doses, such as 5 or 10 IU of oxytocin[1]. To complicate matters, in many settings oxytocin may only be available in intramuscular (IM) administration. While the efficacy of IV oxytocin is clear, information about treatment of PPH with IM oxytocin is not yet available. Future research is critical to understanding how the current data on efficacy of misoprostol and oxytocin translate into programmatic effectiveness when service delivery realities come into play.

Table 4 Implications of research evidence on first-line treatment options for PPH in different service delivery contexts

	No prophylactic oxytocin	*Prophylactic oxytocin*
IV Oxytocin feasible	Oxytocin preferred	Either drug
IV Oxytocin not feasible	Misoprostol	Misoprostol

As misoprostol is increasingly being used for PPH prophylaxis at the community level, it is also important to understand how such prophylaxis interacts with the efficacy and safety of misoprostol for treatment. Decisions about resource allocation would benefit from information about the relative advantages of universal prophylaxis or implementation of more targeted strategies, such as treatment as needed. For example, new comparative studies are underway to assess the programmatic effectiveness of secondary prevention models, whereby the treatment dose of 800 μg sublingual misoprostol is selectively administered to women who bleed slightly more than average (around 350 ml). Novel approaches that medicate fewer women, reduce costs and still achieve comparable outcomes might be developed using new hybrid service delivery strategies

CONCLUSION

At least, two-thirds of PPH occurs in women with no known risk factors[25]. The largely unpredictable nature of PPH makes it a challenge to service delivery, especially in low-resource or remote areas. While universal prophylaxis significantly reduces the incidence of PPH, it does not eliminate the need to treat some women. In many settings, treatment only occurs after referral to higher levels of care, which can take hours to days. Since hemorrhage from uterine atony can cause death in 2 hours or less, the availability of simple treatment options where women deliver is critical.

Evidence suggests sublingual misoprostol should be used for treatment whenever oxytocin is not available. It can also be used as the first choice treatment for hemorrhages occurring after women have received oxytocin as prophylaxis. Misoprostol is an important weapon in the arsenal of methods to combat PPH in sites that for the most part have oxytocin but face logistical challenges to its IV use, for example, no stock, loss of refrigeration, or absence of a provider trained/confident in IV administration. Moreover, misoprostol may prove to be most useful in settings where few if any alternatives exist. Given the very small differences in efficacy between sublingual misoprostol and IV oxytocin, it is clear why misoprostol is being promoted for use by less skilled attendants and at lower levels of the health care system. Data on program effectiveness will be critical in better understanding the health impact of these technologies and interventions when used on a wide scale.

References

1. Mousa HA, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev 2007;(1): CD003249
2. WHO. Unedited Report of the 18th Expert Committee on the Selection and Use of Essential Medicines. Accra, Ghana: WHO, 2011:1–211
3. O'Brien P, El-Refaey H, Gordon A, Geary M, Rodeck CH. Rectally administered misoprostol for the treatment of

postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. Obstet Gynecol 1998;92:212–4
4. Ozan H, Bilgin T, Ozsaraç N, Ozerkan K, Cengiz C. Misoprostol in uterine atony: A report of 2 cases. Clin Exp Obstet Gynecol 2000;27:221–2
5. Abdel-Aleem H, El-Nashar I, Abdel-Aleem A. Management of severe postpartum hemorrhage with misoprostol. Int J Gynecol Obstet 2001;72:75–6
6. Shojai, R., Piéchon L, d'Ercole C, Boubli L, Pontiès JE. [Rectal administration of misoprostol for delivery induced hemorrhage. Preliminary study]. J Gynécol Obstét Biol Reprod 2001;30:572–5
7. Adekanmi O, Purmessur S, Edwards G, Barrington JW. Intrauterine misoprostol for the treatment of severe recurrent atonic secondary postpartum haemorrhage. BJOG 2001;108: 541–2
8. Oboro V, Tabowei T, Bosah J. Intrauterine misoprostol for refractory postpartum hemorrhage. Int J Gynecol Obstet 2003;80:67–8
9. Shojai R, Desbrière R, Dhifallah S, et al. [Rectal misoprostol for postpartum hemorrhage]. Gynécol Obstét Fertil 2004;32: 703–7
10. Lokugamage AU, Sullivan KR, Niculescu I, et al. A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. Acta Obstet Gynecol Scand 2001;80:835–9
11. Hofmeyr GJ, Ferreira S, Nikodem VC, et al. Misoprostol for treating postpartum haemorrhage: a randomized controlled trial. BioMed Central Pregnancy and Childbirth 2004;4:1–7
12. Walraven G, Dampha Y, Bittaye B, Sowe M, Hofmeyr J. Misoprostol in the treatment of postpartum haemorrhage in addition to routine management: a placebo randomised controlled trial. BJOG 2004;111:1014–7
13. Zuberi NF, Durocher J, Sikander R, Baber N, Blum J, Walraven G. Misoprostol in addition to routine treatment of postpartum hemorrhage: a hospital-based randomized-controlled trial in Karachi, Pakistan. BMC Pregnancy Childbirth 2008;8:40
14. Prata N, Mbaruku G, Campbell M, Potts M, Vahidnia F. Controlling postpartum hemorrhage after home births in Tanzania. Int J Gynaecol Obstet 2005;90:51–5
15. Blum J, Winikoff B, Raghavan S, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. Lancet 2010; 375:217–23
16. Winikoff B, Dabash R, Durocher J, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. Lancet 2010;375:210–6
17. Widmer M, Blum J, Hofmeyr GJ, et al. Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial. Lancet 2010;375:1808–13
18. Tang OS, Schweer H, Seyberth HW, Lee SW, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. Hum Reprod 2002;17:332–6
19. Durocher J, Bynum J, León W, Barrera G, Winikoff B. High fever following postpartum administration of sublingual misoprostol. BJOG 2010;117:845–52
20. Hofmeyr GJ, Gülmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bull World Health Organ 2009;87:666–77
21. Lumbiganon P, Hofmeyr J, Gülmezoglu AM, Pinol A, Villar J. Misoprostol dose-related shivering and pryexia in the third stage of labour. BJOG 1999;106:304–8
22. Khan RU, El-Refaey H. Pharmacokinetics and adverse-effect profile of rectally administered misoprostol in the third stage of labor. Obstet Gynecol 2003;101:968–74
23. Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997;90:88–92
24. WHO. Coverage of Maternity Care: A Listing of the Available Information, 4th edn. Geneva, WHO, 1997:1–71
25. Mousa HA, Cording V, Alfirevic Z. Risk factors and interventions associated with major primary postpartum hemorrhage unresponsive to first-line conventional therapy. Acta Obstet Gynecol Scand 2008;87:652–61