Expert Opinion

Misoprostol for the prevention and treatment of postpartum hemorrhage

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Introduction: Uterotonic drugs are recommended for the prevention and treatment of postpartum hemorrhage (PPH), and oxytocin is considered the gold standard for both indications due to its established efficacy and safety. Unfortunately, access to oxytocin is still limited in many low-resource settings due to the need for cool storage, sterile equipment and administration by skilled personnel. Misoprostol, an E1 prostaglandin analog, has therefore been explored as an alternative for such settings due to its proven ability to induce uterine contractions, low cost, stability at room temperature and ease of administration.

Areas covered: This review covers evidence from 51 randomized controlled trials for both prevention and treatment of PPH. It discusses efficacy and side effects in the context of the various doses that have been studied using oral, sublingual or rectal routes of administration for both indications.

Expert opinion: There is now a solid body of evidence to justify the use of misoprostol for postpartum hemorrhage indications in many settings. The evidence supports use of 600 μg orally for the prevention of PPH and 800 μg sublingually for the treatment of PPH. There is no evidence to support the adjunct use of misoprostol following administration of conventional uterotonics for prevention or treatment purposes.

Keywords: misoprostol, postpartum hemorrhage, prevention, treatment

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1. Introduction

Postpartum hemorrhage (PPH) is the leading source of maternal mortality in low-resource settings and accounts for close to one-third of maternal deaths in Africa and Asia [1]. The problem is most acute in low-resource countries, where 60% of births still occur outside of health facilities with no skilled birth attendants present [2]. In such settings, access to conventional uterotonics for the prevention and/or management of PPH is often limited, recognition of excess bleeding is often delayed and geographic isolation frequently prevents timely receipt of needed medical care.

These problems are compounded by the unpredictability of PPH, with two-thirds of cases occurring in women with no known risk factors [3,4]. Given that the average time to death from onset of PPH is 2 h [5], treatments for PPH need to be available at lower levels of the health-care system. Oxytocin is considered the gold standard for the prevention and treatment of PPH [6-9]. However, its routine use is limited by the need for cool storage, sterile equipment and administration by skilled personnel [10]. As a result, provision of oxytocin, particularly its intravenous administration for PPH treatment, is largely confined to facility-based deliveries, thus leaving most births in low-resource communities without adequate uterotonic coverage.

Misoprostol, an E1 prostaglandin analog, was originally developed for use in the prevention of gastric ulcers (**Box 1**). However, it has long been considered a

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Box 1. Drug summary.

Drug name	Misoprostol
Phase	iv
Indication	Prevention and/or treatment of postpartum hemorrhage
Pharmacology description	Synthetic prostaglandin E1 analog
Route of administration	Oral (prevention), sublingual (treatment)
Chemical name	15-deoxy-16-hydroxy-16-methyl PGE1
Pivotal trial(s)	*For prevention of PPH:*[6,50,52] *For treatment of PPH:*[69,70,72]

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promising alternative for the prevention and treatment of PPH due to its proven ability to induce uterine contractions. Unlike other prostaglandins, misoprostol is also relatively inexpensive, remains stable at room temperature and can be administered via several routes. As a result, the drug has entered clinical practice where providers use it in an ad hoc manner to stop or slow postpartum bleeding. These practices have been justified by a growing body of evidence related to the efficacy and safety of misoprostol for both prevention and treatment of PPH.

This review covers the evidence from randomized controlled trials of vaginal deliveries testing the use of misoprostol for both PPH indications. It discusses efficacy and safety in the context of the various doses and routes of administration that have been studied. We included results pertaining to the primary outcomes of each trial as well as any secondary outcomes relating to postpartum blood loss or hemoglobin concentrations. We used PubMed, Medline and Cochrane reviews to identify all randomized controlled trials of vaginal deliveries that compared oral, sublingual or rectal misoprostol with other uterotonics or with placebo for either prevention or treatment of PPH. We identified a total of 51 such trials, 44 related to prevention and 7 related to treatment of PPH (**Box 2**).

2. Misoprostol for the prevention of PPH

2.1 Introduction

Active management of the third stage of labor (AMTSL) is recommended for the prevention of PPH and includes administration of a uterotonic agent immediately following delivery of the baby [11-13]. Oxytocin is considered the first-choice uterotonic due to its superior efficacy and lower incidence of side effects [6,7,14,15] and is believed to reduce the risk of PPH due to uterine atony by 50% [14]. However, for reasons already cited, a safe and effective alternative to oxytocin could expand uterotonic coverage for prevention of PPH in resource-constrained settings. In order to assess the feasibility of misoprostol for this purpose, a large number of good-quality studies have been conducted since the late 1990s. A variety of doses and routes of administration have been tested using control regimens that have included conventional and nonconventional uterotonics, as well as placebo (**Table 1**).

2.2 Misoprostol versus conventional uterotonics for the prevention of PPH

Thirty-one trials were included in this review that compared the effectiveness of misoprostol with conventional uterotonics such as oxytocin, Syntometrine or ergometrine. Twelve used a dose of 600 µg misoprostol, administered either orally (8), sublingually (2) or rectally (2). The largest of these was a hospital-based, multicenter trial that enrolled more than 18,000 women and found that blood loss ≥ 1000 ml occurred among 4% of those given misoprostol, as compared with 3% of those given 10 IU oxytocin either intravenously or intramuscularly (RR 1.39, 95% CI 1.19 – 1.63) [6]. This same study also found that misoprostol was associated with a 40% increase in the likelihood of receiving additional uterotonics ($p < 0.001$). Thus, the authors concluded that oxytocin was superior to misoprostol for the prevention of PPH. Two other studies, both involving approximately 1600 participants and four study groups, found provision of 600 µg oral or rectal misoprostol to be less effective than 10 IU oxytocin intravenously, either alone or in combination with other uterotonics [16,17].

Eight of the trials testing 600 µg misoprostol found no significant differences between misoprostol and conventional uterotonics in terms of blood loss ≥ 500 ml, mean or median blood loss and/or the need for additional uterotonics [18-25]. One of these was a community-based study conducted in the Gambia that involved trained traditional birth attendants administering misoprostol or 2 mg oral ergometrine to more than 1200 women during at home births [18]. Results showed nonsignificant trends suggesting lower blood loss ≥ 500 ml (RR 0.91 95% CI 0.67 – 1.24) and postpartum Hb < 8 g/dl (RR 0.84 95% CI 0.67 – 1.05) in the misoprostol arm, but significantly lower risk of pre- to postpartum hemoglobin drop ≥ 2 g/dl (RR 0.77 95% CI 0.60 – 0.98). However, six of the eight studies did not use oxytocin as the conventional uterotonic, and among the two that did use oxytocin, one had only 200 participants. Lastly, one trial found that misoprostol was associated with reduced median blood loss as compared with either Methergine (0.125 mg oral or 0.2 mg intramuscular) or, in a few cases,

Box 2. Current recommendations.

For PPH prevention, a single dose of 600 μg (3 tablets of 200 μg) misoprostol orally is recommended. For safety reasons, the drug should be administered after delivery of the baby [8]

In 2010, WHO added misoprostol for the prevention of PPH to the Model List of Essential Medicines [76]

For PPH treatment, a single dose of 800 μg (4 tablets of 200 μg) misoprostol sublingually, administered on diagnosis of excessive postpartum bleeding suspected to be due to uterine atony, is recommended based on evidence from clinical trials available at this time [69,70]

There is no evidence to support adjunct use of misoprostol with conventional uterotonics for the prevention or treatment of PPH [59,60,72]

The sublingual route is recommended for PPH treatment because it is the only evidence-based regimen studied in randomized controlled trials [69,70]. Furthermore, its rapid uptake, prolonged duration and greater bioavailability when administered sublingually (as opposed to other routes of administration) enhance its efficiency when used to treat a PPH [77]

Intravenous oxytocin should be used when available, but misoprostol could be an effective first-line treatment alternative in instances oxytocin i.v. is not feasible

Clinical experience and trials on the use of misoprostol for PPH, as well as other reproductive health indications, have shown side effects to be tolerable and short in duration with a range of doses and routes of administration

spontaneous placental expulsion (100 vs 200 ml, $p < 0.001$) [26]. Of note, with exception of the two Çalişkan trials in which three doses of misoprostol (oral or rectal) were administered 4 h apart (first 400 μg, then two doses of 100 μg each), all other trials tested a single dose of 600 μg oral, sublingual or rectal misoprostol.

Fourteen studies compared a dose of 400 μg misoprostol with conventional uterotonics using oral (eight), sublingual (three) or rectal (three) administration. Among these, 11 found misoprostol to be similarly effective to conventional uterotonics in terms of blood loss ≥ 500 or 1000 ml, median or mean blood loss, the need for additional uterotonics and/or pre- and postpartum hemoglobin or hematocrit changes [27-37]. Two trials found misoprostol to be less effective than conventional uterotonics: one compared oral misoprostol with 10 IU intramuscular oxytocin or Syntometrine and found misoprostol was not as effective at reducing postpartum blood loss, the need for additional uterotonics and pre- to postpartum hemoglobin changes [38]; while the other compared rectal misoprostol with 20 IU intravenous oxytocin and found it less effective at reducing the need for additional uterotonics [39]. One last trial involving more than 800 participants found oral misoprostol to be more effective in terms of reducing postpartum blood loss, duration of the third stage, need for additional oxytocics and peripartal hematocrit changes when compared with 500 μg intramuscular Methylergometrine [40]

Five studies compared alternate doses and routes of misoprostol (50 μg sublingual, 500 μg oral, 800 μg oral or rectal, and 200 or 400 μg rectal) with conventional uterotonics. In two of the trials, there were no significant differences in blood loss or hemoglobin outcomes between study arms [41,42], while in three others, misoprostol was associated with reduced postpartum blood loss [43-45]. One of these was a study with 75 participants that tested 50 μg sublingual misoprostol versus 16 mIU/min oxytocin i.v. or 0.2 mg Methylergometrine i.m., while another had 450 participants and compared 800 μg oral misoprostol with 10 IU intramuscular oxytocin, and the last had 140 participants and compared 200 or 400 μg rectal misoprostol with 5 IU oxytocin i.m. plus 0.2 mg ergometrine i.m..

The bulk of the evidence comparing misoprostol with conventional uterotonics suggests that the differences in efficacy are clinically negligible. Because of the small differences involved, many of these trials were underpowered to detect such a difference between groups, and there were also methodological discrepancies that make cross-study comparisons difficult. Furthermore, systematic reviews of all misoprostol trials for PPH prevention have concluded that injectable uterotonics are overall more effective than misoprostol at preventing severe PPH [7,46].

2.3 Misoprostol versus other uterotonics for the prevention of PPH

Two trials have compared 600 μg oral misoprostol with other, nonconventional uterotonics. One study, conducted in a Tibetan hospital, enrolled more than 900 women and compared misoprostol with a traditional medication, Zhi Byed 11 [47]. Findings indicated that misoprostol significantly reduced the frequency of blood loss ≥ 500 ml, as compared with the traditional medication (RR 0.80 95% CI 0.65 – 0.98). The second study, involving 120 participants, compared 400 μg rectal misoprostol with 15-methyl prostaglandin F2α and found no differences between groups in terms of blood loss or any other outcomes studied [48].

2.4 Misoprostol versus placebo for the prevention of PPH

When compared with placebo, misoprostol prophylaxis has been shown to reduce PPH risk significantly [7,8,46,49]. Nine trials were included in this review that compared oral (six), sublingual (one) or rectal (two) misoprostol with placebo. The three largest trials, which were all community-based and involved provision of 600 μg misoprostol, have provided the most important evidence-to-date of the benefits of misoprostol in low-resource settings. One was conducted in rural India and enrolled more than 1600 women in a community home birth and subcenter setting [50]. Oral misoprostol 600 μg was associated with a nearly 50% reduction in the

Table 1. Summary of RCTs involving oral, sublingual or rectal misoprostol for the prevention of postpartum hemorrhage.

Misoprostol regimen	Control regimen(s)	N	Primary outcome(s) + other blood loss or Hb outcomes	Summary of results	Ref.
Misoprostol vs conventional uterotonics					
600 μg oral	0.2 mg Methergine i.m. or 0.125 mg Methergine oral or spontaneous placental expulsion	1200	Median blood loss	100 vs 200 ml, $p < 0.001$	[26] (Chandhiok 2006)
600 μg oral	2 mg Ergometrine oral	1229	Blood loss ≥ 500 ml Postpartum Hb < 8 g/dl Δ in Hb ≥ 2 g/dl (pre- vs postpartum)	11 vs 12%, RR 0.91 (0.67 – 1.24) 19.4 vs 33.1%, RR 0.84 (0.67 – 1.05) 16.4 vs 21.2%, RR 0.77 (0.60 – 0.98)	[18] (Walraven 2005)
600 μg oral	0.2 mg Methylergometrine i.v.	200	Mean blood loss Blood loss ≥ 500 ml Use of additional oxytocics	124.1 vs 124.1 ml, $p = 0.455$ 8.0 vs 6.0%, $p = 0.593$ 10.0 vs 7.0%, $p = 0.447$	[19] (Garg 2005)
600 μg oral	10 IU Oxytocin i.m.	496	Blood loss ≥ 500 ml	1.2 vs 0.4%, RR 3.02 (0.32 – 28.9)	[20] (Oboro 2003)
Group 1: 10 IU Oxytocin i.v. + 400 μg oral misoprostol + 2 doses 100 μg oral misoprostol, 4 h apart Group 2: 400 μg oral misoprostol + 2 doses 100 μg oral misoprostol 4 h apart Group 3: 10 IU Oxytocin i.v. Group 4: 10 IU Oxytocin i.v.+ 0.2 mg Methergine i.m.		1574	Blood loss ≥ 500 ml Drop in Hb (pre- vs 24 h postpartum)	3.2 vs 9.0 vs 7.3 vs 3.5%, $p < 0.01$ (group 2 vs 3) and $p = 0.01$ (group 2 vs group 4) 1.4 vs 1.4 vs 1.4 vs 1.5 g/dl, NS across any groups	[16] (Çalişkan 2003)
600 μg oral	1 ml Syntometrine i.m.	2058	Blood loss ≥ 500 ml Mean blood loss Drop in Hb (pre- vs 48 h postpartum)	5.8 vs 4.3%, RR 1.37 (0.94 – 2.00) 296 vs 254 ml, NS 1.34 vs 1.34 g/dl	[21] (Ng 2001)
600 μg oral	10 IU Oxytocin i.v. or i.m.	18530	Blood loss ≥ 1000 ml Use of additional uterotonics	4 vs 3%, RR 1.39 (1.19 – 1.63) 15 vs 11% RR 1.40 (1.29 – 1.51)	[6] (Gülmezoglu 2001)
600 μg oral	200 μg Methylergometrine i.v.	200	Blood loss > 500 ml Use of additional oxytocics Mean Hb 3 days postpartum	8.3 vs 4.3%, $p = 0.57$ 12.8 vs 4.4%, $p = 0.065$ 11.2 vs 11.0 g/dl, $p = 0.39$	[22] (Amant 1999)
600 μg sublingual 800 μg sublingual 1000 μg sublingual	0.2 mg Methylergometrine i.m.	1200	Mean blood loss Drop in Hb (pre- vs 24 h postpartum)	143, 131, 128 and 149 ml $p = 0.508$ (600 μg vs control) $p = 0.03$ (800 μg vs control) $p = 0.006$ (1000 μg vs control) 0.4, 0.4, 0.3 and 0.5 g/dl $p = 0.06$ (600 μg vs control) $p = 0.02$ (800 μg vs control) $p = 0.01$ (1000 μg vs control)	[23] (Soltan 2007)
600 μg sublingual	1 ml Syntometrine i.v.	60	Median blood loss Drop in Hb (pre- vs postpartum)	280 vs 226 ml, NS 0.50 vs 0.85 g/dl, NS	[24] (Lam 2004)

Results for relative risk are presented RR (95% CI).

Hb: Hemoglobin; IU: International units; i.m.: Intramuscular; i.v.: Intravenous; ml: Milliliters; dl: Deciliters; NS: Not significant; RR: Relative risk.

Table 1. Summary of RCTs involving oral, sublingual or rectal misoprostol for the prevention of postpartum hemorrhage (continued).

Misoprostol regimen	Control regimen(s)	N	Primary outcome(s) + other blood loss or Hb outcomes	Summary of results	Ref.
600 μg rectal	10 IU Oxytocin i.m.	200	Mean estimated blood loss Drop in Hb (pre- vs postpartum) Use of additional oxytocics	161.67 vs 150.97 ml, p = 0.302 0.253 vs 0.23 g/dl, p = 0.159 5.0 vs 1.0%, p = 0.212	[25] (Gupta 2006)
Group 1: 10 IU Oxytocin i.v. + 400 μg rectal misoprostol +2 doses 100 μg rectal misoprostol, 4 h apart Group 2: 400 μg rectal misoprostol + 2 doses 100 μg rectal misoprostol 4 h apart Group 3: 10 IU Oxytocin i.v. Group 4: 10 IU Oxytocin i.v. + 1 ml Methylergometrine i.m.		1606	Blood loss ≥ 500 ml Drop in Hb (pre- vs 24 h postpartum)	6.6 vs 9.8 vs, 8.1 vs 3.5% p < 0.001 (group 2 vs 4), All other differences NS 1.5 vs 1.5 vs 1.4 vs 1.5 g/dl, NS across any groups	[17] (Çalişkan 2002)
400 μg oral	10 IU Oxytocin i.m.	200	Blood loss ≥ 500 ml Drop in Hb (pre- vs 48 h postpartum)	0 vs 0%, NS 0.3 vs 0.4 g/dl, p = 0.49	[27] (Afolabi 2010)
400 μg oral	500 μg Methylergometrine i.m.	864	Mean blood loss Blood loss ≥ 500 ml Mean duration of third stage Peripartal hematocrit Δ > 10% Use of additional oxytocics	191.6 vs 246.0 ml, p < 0.0001 1.4 vs 9.7%, p < 0.0001 19.6 vs 9.4 min, p < 0.0001 1.2 vs 8.8%, p < 0.0001 7.6 vs 18.5%, p < 0.0001	[40] (Enakpene 2007)
400 μg oral	5 IU Oxytocin i.v.	622	Hematocrit drop ≥ 10% during first 24 h Hb drop ≥ 30 mg/l Blood loss > 1000 ml	3.7 vs 3.4%, p = 0.98 10.2 vs 8.9%, p = 0.70 4.5 vs 2.3%, p = 0.18	[28] (Baskett 2007)
400 μg oral	1 ml Syntometrine i.m.	355	Drop in Hb (pre- vs 48 h postpartum) Use of additional oxytocics Blood loss ≥ 500 ml	1.7 vs 1.6 g/dl, NS 23.0 vs 13.6%, RR 1.56 (0.98 – 2.50) 10.1 vs 5.1%, RR 1.90 (0.87 – 4.11)	[29] (Ng 2007)
400 μg oral	10 IU Oxytocin i.m. or 2 mg Ergometrine i.v.	2023	Mean blood loss Use of additional oxytocics Blood loss > 500 ml Blood loss > 1000 ml	193 vs 183 vs 188, NS 8.6 vs 6.2 vs 7.5%, p = 0.234 2.6 vs 2.1 vs 3.0%, p = 0.623 0.1 vs 0.7 vs 0.9%, p = 0.146	[30] (Zachariah 2006)
400 μg oral	10 IU Oxytocin i.m.	499	Blood loss > 500 ml Blood loss > 1000 ml Use of additional uterotonics	15.2 vs 13.3%, RR 0.92 (0.72 – 1.2) 3.7 vs 2.0%, RR 0.75 (0.50 – 1.12) 5.3 vs 2.7%, RR 0.74 (0.53 – 1.03)	[31] (Kundodyiwa 2001)
400 μg oral	10 IU Oxytocin i.m.	401	Drop in Hb (pre- vs 12 h postpartum) Blood loss > 500 ml	0.60 vs 0.55 g/dl, p = 0.54 0 vs 1%, p = 0.24	[32] (Walley 2000)

Results for relative risk are presented RR (95% CI).

Hb: Hemoglobin; IU: International units; i.m.: Intramuscular; i.v.: Intravenous; ml: Milliliters; dl: Deciliters; NS: Not significant; RR: Relative risk.

Table 1. Summary of RCTs involving oral, sublingual or rectal misoprostol for the prevention of postpartum hemorrhage (continued).

Misoprostol regimen	Control regimen(s)	N	Primary outcome(s) + other blood loss or Hb outcomes	Summary of results	Ref.
400 μg oral	10 IU Oxytocin i.m. or Syntometrine i.m.	863	Mean blood loss Blood loss ≥ 500 ml Use of additional uterotonics Drop in Hb (pre- vs postpartum)	279 vs 209 ml, $p < 0.001$ 15 vs 6%, RR 2.72 (1.73 – 4.27) 22 vs 8%, RR 2.89 (2.00 – 4.18) 6.9 vs 4.0 g/dl, $p = 0.015$	[38] (Cook 1999)
400 μg sublingual	0.2 mg Methylergometrine i.m. 125 μg 15-methyl PGFα i.m.	200	Blood loss ≥ 500 ml Use of additional oxytocics Drop in Hb (pre- vs postpartum)	12.1 vs 17.9 vs 19.4%, $p = 0.490$ 13.6 vs 20.9 vs 13.4%, $p = 0.407$ 4.5 vs 5.4 vs 5.4 g/dl, NS	[33] (Vaid 2009)
400 μg sublingual	200 μg Methylergometrine i.m.	200	Mean blood loss Blood loss ≥ 500 ml Drop in Hb Use of additional oxytocics	137.6 vs 125.8 ml, $p = 0.254$ 1.0 vs 0.0%, $p = 1.000$ 0.31 vs 0.25 g/dl, $p = 0.124$ 4.0 vs 2.0%, $p = 0.683$	[34] (Verma 2006)
400 μg sublingual	200 μg Methylergometrine i.v.	120	Blood loss > 500 ml Use of additional oxytocics Drop in Hb (pre- vs postpartum)	3.1 vs 0.0%, $p > 0.05$ 8.3 vs 5.0%, $p > 0.05$ 0.76 vs 0.8 g/dl, $p > 0.05$	[35] (Vimala 2004)
400 μg rectal	10 IU Oxytocin i.m.	663	Mean blood loss Use of additional oxytocics Drop in Hb (pre- vs postpartum)	155.0 vs 157.3 ml, NS 2.2 vs 2.1%, NS 0.9 vs 0.7 g/dl	[36] (Bugalho 2001)
400 μg rectal	1 ampoule Syntometrine i.m.	491	Mean estimated blood loss Blood loss > 500 ml Postpartum Hb	187 vs 183 ml, $p = 0.70$ 0.9 vs 0.4%, RR 2.02 (0.18 – 22.0) 11.7 vs 11.7 g/dl, $p = 0.90$	[37] (Bamigboye 1998)
400 μg rectal	20 IU Oxytocin i.v.	325	Blood loss ≥ 800 ml Use of additional uterotonics	17 vs 18%, $p = 0.79$ 23 vs 11%, $p = 0.004$	[39] (Gerstenfeld 2001)
50 μg sublingual	16 mUI/min Oxytocin i.v. 0.2 mg Methylergometrine i.m.	75	Blood loss 1 h postpartum	389 vs 467 vs 547 ml, $p < 0.01$	[43] (Peñaranda 2002)
500 μg oral	Oxytocin or Ergometrine or Oxytocin + Ergometrine	1000	Blood loss ≥ 500 ml Blood loss ≥ 1000 ml	12 vs 11%, RR 1.10 (0.79 – 1.55) 2 vs 2%, RR 0.89 (0.37 – 2.19)	[41] (El-Refaey 2000)
800 μg oral	10 IU Oxytocin i.m.	450	Drop in Hb (pre- vs postpartum) Blood loss > 500 ml	1.07 vs 1.00 g/dl, $p = 0.54$ 0.0 vs 2.2%, RR 0.20 (0.01 – 7.27)	[44] (Parsons 2006)
800 μg rectal	5 IU Oxytocin i.v.	514	Blood loss > 500 ml Hemoglobin 24 h postdelivery	6.6 vs 4.7%, NS 9.8 vs 10.0 g/dl, NS	[42] (Nasr 2009)
200 μg rectal or 400 μg rectal	5 IU Oxytocin i.m. + 0.2 mg Ergometrine i.m.	140	Mean blood loss Blood loss ≥ 500 ml Use of additional oxytocics Drop in Hb (pre- vs 48 h postpartum)	234 vs 273 ml, $p < 0.01$ 2.9 vs 4.3%, NS 5.7 vs 21.4%, $p < 0.01$ 0.8 vs 1.3 g/dl, $p < 0.01$	[45] (Diab 1999)

Results for relative risk are presented RR (95% CI).

Hb: Hemoglobin; IU: International units; i.m.: Intramuscular; i.v.: Intravenous; ml: Milliliters; dl: Deciliters; NS: Not significant; RR: Relative risk.

Table 1. Summary of RCTs involving oral, sublingual or rectal misoprostol for the prevention of postpartum hemorrhage (continued).

Misoprostol regimen	Control regimen(s)	N	Primary outcome(s) + other blood loss or Hb outcomes	Summary of results	Ref.
Misoprostol vs other uterotonics					
600 μg oral	Zhi Byed 11 oral	967	Rate of maternal death, blood loss ≥ 500 ml and/or administration of uterotonic within 1 h after delivery Blood loss ≥ 500 ml	16.1 vs 21.8%, RR 0.82 (0.68 – 0.98) 12.4 vs 17.4%, RR 0.80 (0.65 – 0.98)	[47] (Miller 2009)
400 μg rectal	15-Methyl prostaglandin F2α	120	Blood loss ≥ 500 ml Use of additional oxytocics Drop in Hb (pre- vs postpartum	6.5 vs 5.0%, NS 16.6 vs 303%, NS 0.58 vs 0.62 g/dl, NS	[48] (Nellore 2006)
Misoprostol vs placebo					
600 μg oral	Placebo	1119	Blood loss ≥ 500 ml Drop in Hb > 2 g/dl (pre- vs postpartum) Drop in Hb > 3 g/dl (pre- vs postpartum)	16.5 vs 21.9%, RR 0.76 (0.59 – 0.97) 16.7 vs 21.0%, RR 0.79 (0.62 – 1.02) 5.1 vs 9.6%, RR 0.53 (0.34 – 0.83)	[52] (Mobeen 2010)
600 μg oral	Placebo	1620	Blood loss ≥ 500 ml Blood loss ≥ 1000 ml Mean blood loss	6.4 vs 12.0%, RR 0.53 (0.39 – 0.74) 0.2 vs 1.2%, RR 0.20 (0.04 – 0.91) 214.3 vs 262.3 ml, p < 0.0001	[50] (Derman 2006)
600 μg oral	2.5 IU Oxytocin i.v. Placebo	602	Blood loss > 500 ml Blood loss > 1000 ml	28.0 vs 14.8 vs 27.3%, group 1 vs 3, NS 8.6 vs 6.1 vs 5.9%, NS	[53] (Benchimol 2001)
600 μg oral	Placebo	599	Blood loss ≥ 1000 ml	9.0 vs 9.7%, RR 0.93 (0.56 – 1.53)	[54] (Hofmeyr 2001)
600 μg oral	Placebo	65	Mean blood loss Blood loss ≥ 500 ml Drop in hematocrit (pre- vs 48 h postpartum) Drop in hemoglobin (pre- vs 48 h postpartum)	345 vs 417 ml, p = 0.031 7 vs 15%, NS 4.5 vs 7.9%, p = 0.014 1.6 vs 2.6%, p = 0.015	[55] (Surbek 1999)
600 μg sublingual	Placebo	661	Blood loss ≥ 500 ml Blood loss ≥ 1000 ml Hb drop ≥ 10% (pre- vs 24 h postpartum)	45 vs 51%, RR 0.89 (0.76 – 1.04) 11 vs 17%, RR 0.66 (0.45 – 0.98) 32 vs 35%, RR 0.92 (0.74 – 1.14)	[51] (Høj 2005)
400 μg oral	Placebo	500	Blood loss ≥ 1000 ml Use of additional oxytocics	6.0 vs 9.2%, RR 0.65 (0.35 – 1.22) 4.8 vs 5.2%, RR 0.64 (0.38 – 1.07)	[56] (Hofmeyr 1998)

Results for relative risk are presented RR (95% CI).

Hb: Hemoglobin; IU: International units; i.m.: Intramuscular; i.v.: Intravenous; ml: Milliliters; dl: Deciliters; NS: Not significant; RR: Relative risk.

Table 1. Summary of RCTs involving oral, sublingual or rectal misoprostol for the prevention of postpartum hemorrhage (continued).

Misoprostol regimen	Control regimen(s)	N	Primary outcome(s) + other blood loss or Hb outcomes	Summary of results	Ref.
400 µg rectal 400 µg vaginal	Placebo	150	Mean blood loss Drop in hemoglobin (pre- vs 24 h postpartum) Drop in hematocrit (pre- vs 24 h postpartum)	171.4 vs 206.1 vs 171.1 ml, NS 1.2 vs 1.0 vs 1.0 g/dl, NS 2.1 vs 2.1 vs 2.0%, NS	[57] (Ozkaya 2005)
400 µg rectal	Placebo	550	Blood loss ≥ 1000 ml Use of additional oxytocics	4.8 vs 7.0%, RR 0.69 (0.35 – 1.37) 1.8 vs 4.4%, RR 0.42 (0.15 – 1.18)	[58] (Bamigboye 1998)
Adjunct use of misoprostol					
400 µg sublingual	Placebo	1103	Blood loss ≥ 500 ml Blood loss ≥ 1000 ml	4.0 vs 6.3%, RR 0.64 (0.38 – 1.37) 0.9 vs 0.2%, RR 3.70 (0.61 – 22.38)	[59] (Hofmeyr 2011)
400 µg sublingual	Placebo	1345	Blood loss ≥ 500 ml Blood loss ≥ 1000 ml Hb < 6 g/dl 24 h postpartum	6.1 vs 6.4%, RR 0.96 (0.63 – 1.45) 0.6 vs 1.2%, RR 0.50 (0.15 – 1.66) 0.6 vs 0.8%, RR 0.80 (0.22 – 2.98)	[60] (Fawole 2011)

Results for relative risk are presented RR (95% CI).
Hb: Hemoglobin; IU: International units; i.m.: Intramuscular; i.v.: Intravenous; ml: Milliliters; dl: Deciliters; NS: Not significant; RR: Relative risk.

risk of blood loss ≥ 500 ml (RR 0.53 95% CI 0.39 – 0.74) and an even greater reduction in the risk of blood loss ≥ 1000 ml (RR 0.20 95% CI 0.04 – 0.90). A second trial conducted in primary-health centers in Guinea-Bissau and involving a total of 661 women tested a 600 µg regimen of sublingual misoprostol that was administered by midwives [51]. Findings indicated that misoprostol was substantially better than placebo in preventing severe PPH (RR 0.66 95% CI 0.45 – 0.98). The third study was conducted in rural Pakistan and involved more than 1100 women [52]. Administration of 600 µg oral misoprostol by trained traditional birth attendants during at-home births significantly reduced the risk of blood loss ≥ 500 ml (RR 0.76, 95% CI 0.59 – 0.97). There were no measurable differences between study groups for severe PPH, but significantly fewer women receiving misoprostol experienced a drop in hemoglobin > 3 g/dl, as compared with placebo (RR 0.53, 95% CI 0.34 – 0.83).

Among the six other studies that compared misoprostol with placebo, all were carried out in hospital settings and involved between 65 and 602 participants. Three administered a dose of 600 µg orally [53-55], while the remaining three used a lower, 400-µg dose either orally (one) or rectally (two) [56-58]. There were no significant differences between the misoprostol and placebo groups in the five largest studies in terms of blood loss ≥ 500 ml, blood loss ≥ 1000 ml or the use of additional oxytocics. In the smallest study involving just 65 participants, misoprostol was associated with a significant reduction in mean blood loss as compared with the placebo group (345 ml misoprostol vs 417 ml placebo, p = 0.031), as well as changes in pre- to postpartum hematocrit and hemoglobin levels [55].

While the hospital-based trials did not, for the most part, find misoprostol to be any more effective than placebo, all three of the large, community-based studies that used a 600-µg dose consistently found that prophylactic administration of oral misoprostol significantly reduced PPH risk. These studies are important because they represent the settings in which misoprostol may be most useful for PPH prevention.

2.5 Adjunct use of Misoprostol

Two large, randomized placebo-controlled trials have assessed the adjunct use of misoprostol to augment conventional uterotonics for the prevention of PPH [59,60]. Both studies tested the sublingual administration of 400 µg misoprostol among women who all received standard AMTSL with either intravenous or intramuscular administration of oxytocin or ergometrine. In both cases, there were no significant differences in the risk of blood loss ≥ 500 or ≥ 1000 ml.

2.6 Side effects

Shivering and pyrexia are the most common side effects associated with the postpartum administration of misoprostol and are known to be dose and route dependent [9,61]. Results from a recent meta-analysis indicated that when compared with placebo, the risk of pyrexia increased threefold with 400 µg misoprostol and sixfold with 600 µg misoprostol when

administered during the third stage of labor [49]. Higher rates of shivering and pyrexia are also associated with oral and sublingual routes of administration, as compared with rectal administration [62-64]. In the largest multicenter trial involving more than 18,000 women and comparing 600 µg oral misoprostol with 10 IU oxytocin, misoprostol was associated with higher incidence of shivering and fever > 38°C [6]. Similarly, there was a higher incidence of both side effects in the three community-based trials that compared 600 µg oral misoprostol with placebo [50-52].

Prior studies of the prophylactic use of misoprostol for the prevention of PPH have found wide variation in the incidence of shivering and fever. For instance, following administration of 600-µg oral prophylaxis, the incidence of shivering has ranged from 18 to 71%, while that of fever has ranged from 1 to 38% [65]. And despite one known case from the 1990s of a previously healthy woman who developed severe hyperthermia following prophylactic administration of 800 µg oral misoprostol [66], there is now a large body of evidence confirming that for the vast majority of women, these side effects are short lived and not life threatening [7,21,65,67,68].

2.7 Recommended dose and route of administration

Of the 44 trials included in this review for the prevention of PPH, 25 administered misoprostol orally, 9 sublingually and 10 rectally. As noted previously, the largest of these compared 600 µg of oral misoprostol with 10 IU oxytocin, and while findings indicated oxytocin was superior to misoprostol, the rate of severe hemorrhage among misoprostol recipients was only 4%, as compared with 3% among oxytocin recipients. Furthermore, the two largest studies that compared misoprostol with placebo also tested a 600 µg dose of oral misoprostol and, in both cases, found misoprostol to be significantly more effective than placebo at reducing postpartum blood loss.

Among the 14 trials that tested a 400-µg dose of misoprostol, there was wide variation in both the types and the regimens of uterotonics used for control groups, and findings were inconsistent. Given that the side effects associated with the higher, 600-µg dose are benign, our review suggests that in settings where oxytocin is unavailable, 600-µg misoprostol should be administered orally for the prevention of PPH.

3. Misoprostol for the treatment of PPH

3.1 Introduction

Treatment of PPH suspected to be due to uterine atony typically includes administration of a uterotonic drug (generally oxytocin and/or ergometrine), uterine massage and bimanual compression. Uterotonic management of PPH due to uterine atony is critical because, when successful, it avoids recourse to other more invasive interventions, including administration of intravenous fluids, additional drug therapy, blood transfusion and/or surgical intervention. Currently, oxytocin is the gold standard for the treatment of PPH because it is safe and highly effective and free of the side effects and contraindications associated with ergometrine [9]. Nonetheless, there is a role for alternatives to oxytocin for the management of PPH in low-resource settings, and misoprostol has been explored for this purpose.

Since 2004, there have been seven randomized controlled trials of postpartum administration of misoprostol for the treatment of PPH that met the inclusion criteria for this review [69-75]. Only one of these has compared misoprostol with standard uterotonics in the absence of uterotonic prophylaxis, two have compared misoprostol with standard uterotonics following provision of uterotonic prophylaxis and the remaining four have assessed the adjunct effect of various regimens of misoprostol for PPH treatment when combined with standard uterotonics (**Table 2**).

3.2 Misoprostol for the treatment of PPH in the absence of oxytocin prophylaxis

In 2010, Winikoff *et al.* published results from the only trial to compare the effect of misoprostol with standard uterotonics in the absence of oxytocin prophylaxis [69]. In this study, 978 women were treated for PPH at four hospitals in Ecuador, Egypt and Vietnam. Participants were randomly assigned to either 800-µg sublingual misoprostol (n = 488) or 40 IU i.v. oxytocin (n = 490). Active bleeding was controlled within 20 min with study treatment alone for 440 (90%) women given misoprostol and 468 (96%) of those given oxytocin (p = 0.001). Although misoprostol was less effective than oxytocin, it did stop active bleeding for 90% of women (essentially the same proportion of women for whom active bleeding is stopped with either misoprostol or oxytocin within 20 min after oxytocin prophylaxis, see Blum *et al.* 2010). As a result, the authors concluded that it was sufficiently effective to be considered a suitable first-line treatment for PPH in settings where oxytocin remains inaccessible.

3.3 Misoprostol for the treatment of PPH following oxytocin prophylaxis

Blum *et al.* (2010) presented data from one of two trials to compare the effect of misoprostol with standard uterotonics following administration of 10 IU oxytocin prophylaxis [70]. A total of 807 women were treated for PPH at five hospitals in Burkina Faso, Egypt, Turkey and Vietnam. Participants were randomly assigned to either 800 µg sublingual misoprostol (n = 407) or 40 IU i.v. oxytocin (n = 402). Active bleeding was controlled within 20 min after the initial treatment for 363 (89%) women given misoprostol and 360 (90%) of those given oxytocin (p = 0.867). The authors concluded that among women who have received oxytocin prophylaxis during the third stage of labor, misoprostol is clinically equivalent to oxytocin when used for the management of PPH due to uterine atony.

In 2001, Lokugamage *et al.* published findings from a study examining the effect of misoprostol following oxytocin prophylaxis. They reported that 800 µg rectal misoprostol conferred a significant advantage over a combination of

Table 2. Summary of RCTs involving oral, sublingual or rectal misoprostol for treatment of postpartum hemorrhage.

Misoprostol regimen	Control regimen	N	Primary outcome(s)	Summary of results	Ref.
Misoprostol in absence of uterotonic prophylaxis					
800 μg sublingual	40 IU Oxytocin i.v.	978	Active bleeding controlled within 20 min	90 vs 96%, RR 0.94 (0.91 – 0.98)	[69] (Winikoff 2010)
			Additional blood loss ≥ 300 ml	30 vs 17%, RR 1.78 (1.40 – 2.26)	
Misoprostol following oxytocin prophylaxis					
800 μg sublingual	40 IU Oxytocin i.v.	807	Active bleeding controlled within 20 min	89 vs 90%, RR 0.99 (0.95 – 1.04)	[70] (Blum 2010)
			Additional blood loss ≥ 300 ml	34 vs 31%, RR 1.12 (0.92 – 1.37)	
800 μg rectal	Syntometrine i.m. (5 IU oxytocin + 500 μg ergometrine) + Syntocinon i.v. (10 IU oxytocin)	64	Active bleeding controlled within 20 min	94 vs 66%, p = 0.01	[71] (Lokugamage 2001)
Adjunct use of misoprostol					
600 μg sublingual	Placebo	1422	Blood loss ≥ 500 ml within 60 min following treatment	14 vs 14%, RR 1.02 (79 – 1.32)	[72] (Widmer 2010)
			Blood loss ≥ 1000 ml within 60 min following treatment	1 vs 1%, RR 1.02 (0.41 – 2.55)	
			Blood loss ≥ 500 ml within 90 min following treatment	21 vs 23%, RR 0.93 (0.77 – 1.14)	
			Blood loss ≥ 1000 ml within 90 min following treatment	2 vs 3%, RR 0.78 (0.42 – 1.47)	
			Hb < 80 g/l within 24 h	18 vs 20%, RR 0.89 (0.72 – 1.11)	
600 μg sublingual	Placebo	61	Blood loss post-treatment Blood loss ≥ 500 ml Drop in Hb	175 vs 187 ml, p = 0.809 7.4 vs 12.5%, RR 0.59 (0.12 – 2.99) 2.0 vs 2.2 g/dl, p = 0.614	[73] (Zuberi 2008)
600 μg (400 μg sublingual + 200 μg oral)	Placebo	160	Mean blood loss	325 vs 410 ml, NS	[74] (Walraven 2004)
1000 μg (200 μg oral + 400 μg sublingual + 400 μg rectal)	Placebo	238	Blood loss ≥ 500 ml within 60 min following treatment	5.1 vs 9.2%, RR 0.56 (0.21 – 1.46)	[75] Hofmeyr 2004)

Results for relative risk are presented RR (95% CI).

dl: Deciliters; Hb: Hemoglobin; IU: International units; i.m.: Intramuscular; i.v.: Intravenous; ml: Milliliters; NS: Not significant; RR: Relative risk.

Syntometrine i.m. plus Syntocinon i.v. for PPH treatment when administered to 64 women experiencing PPH [71]. There was a 28.1% difference in the rate of bleeding cessation within 20 min in favor of misoprostol ($p = 0.01$). Unfortunately, this study was not blinded and blood loss was assessed visually, which may have led to investigator bias.

3.4 Adjunct use of misoprostol for the treatment of PPH

Four trials have assessed the effectiveness of misoprostol as an adjunct to standard PPH treatments [72-75]. All compared the effectiveness of misoprostol with placebo. Two used a dose of 600 µg that was administered sublingually [72,73], one used a dose of 600 µg that was administered sublingually (400 µg) and orally (200 µg) [74] and the fourth used a higher dose of 1000 µg with multiple routes of administration (200 µg orally, 400 µg sublingually and 400 µg rectally [75]. There were no significant differences in blood loss or hemoglobin-related outcomes between the misoprostol and placebo groups in any of the four studies.

These findings demonstrate that the addition of 600-µg sublingual misoprostol to conventional injectable uterotonics for PPH treatment confers no clinical advantage. The early trials, which enrolled a collective total of 459 participants, were not adequately powered to detect differences between the misoprostol and placebo arms though all showed favorable trends in blood loss reduction in the misoprostol arms [73-75]. The larger, adequately powered trial involving more than 1400 participants provided a more definitive assessment of the role of misoprostol as adjunct care for PPH [72].

3.5 Side effects

Shivering and fever are common side effects following misoprostol's use as a first-line treatment and as an adjunct therapy for PPH. In the studies reviewed here, the incidence of shivering ranged from 5.4 to 64.6%, and the occurrence of pyrexia ranged from 9.6 to 44.5%. The two studies testing an 800-µg dose of sublingual misoprostol as first-line PPH treatment documented rates of shivering that ranged from 37 to 47%, compared with 15 – 17% among women given i.v. oxytocin [69,70]. In these same studies, rates of fever after treatment were also more common in the misoprostol group (22 – 44% vs 6 – 15% with i.v. oxytocin). Two other studies testing a 600-µg regimen of sublingual misoprostol versus placebo as an adjuvant therapy also reported significantly higher rates of shivering and fever among women randomized to misoprostol [72,73]. Lower rates of shivering and fever were documented in one study testing 600 µg (400 µg sublingual plus 200 µg oral) among 160 women randomized to receive either misoprostol plus standard uterotonics or placebo plus standard uterotonics (shivering 29 vs 10%; fever 20 vs 10%) [74].

In several PPH treatment studies, misoprostol has been associated with fever greater than 40.0°C (104°F). In Pakistan, a single case of high fever (out of 29) following adjunct treatment with a sublingual dose of 600 µg was reported [73] while the largest multicountry trial investigating this dose as adjunct PPH treatment also documented a 7% rate of high fever above 40.0°C (48 women out of 704), compared with 1% among women who received standard uterotonics plus placebo as PPH treatment [72]. The two multicenter studies testing an 800-µg regimen of sublingual misoprostol as first-line treatment for PPH reported a higher-than-expected rate of fever above 40.0°C at one participating hospital located in Quito, Ecuador (36%), while rates in the remaining eight participating hospitals located in Burkina Faso, Egypt, Turkey and Vietnam were much lower, ranging from 0 to 9% [65,69,70]. There were no complications associated with elevated temperatures reported in any of these trials.

3.6 Recommended dose and route

The two largest trials that compared the effect of misoprostol with conventional uterotonics used a regimen of 800 µg sublingually [69,70]. Although there have been more side effects associated with this higher dose, it was found to be safe and effective both with and without the receipt of oxytocin prophylaxis.

4. Conclusions

Misoprostol is a suitable uterotonic for the management of PPH. For both PPH prevention and treatment, its use in health-care systems, particularly at the lowest levels, can fill a gap in service delivery.

5. Expert review

All the clinical trials that have been conducted have been too small to answer questions about the overall effect of misoprostol on maternal mortality [61]. It is nevertheless clear that misoprostol is an effective means for reducing postpartum blood loss. Due to the fact that misoprostol, unlike most drugs, was not originally developed and registered by any pharmaceutical company for the indications for which is most commonly prescribed (women's reproductive health), there has been a proliferation of doses, routes and regimens for each of the purposes for which it is used. Since the women for whom it is prescribed have very different needs and situations (e.g., women with normal deliveries seeking to prevent a hemorrhage, women in the midst of a PPH, women with botched abortions, women seeking pregnancy termination, women with late-term intrauterine fetal death, women needing induction of labor), various ways of using the drug have been proposed, and use for these different indications is quite frequently completely idiosyncratic.

Fortunately, with respect to indications for use in the prevention and treatment of PPH, the last few years have seen a rich expansion of the scientific literature, with an abundance of good-quality studies. Thus, our recommendations for use of misoprostol can now rest on more secure scientific fact – as well as years more experience using the drug on the ground. Indeed, almost all technical agencies have now

come to agree that use of misoprostol for PPH indications is justified where access to oxytocin is not possible or would result in delays of treatment for women who are bleeding heavily postpartum.

There has been a convergence of information and consensus about the use of misoprostol for the prevention of PPH in settings where oxytocin is unavailable or not feasible. In 2011, the WHO added misoprostol for the prevention of PPH to the Model List of Essential Medicines [76], thus solidifying recommendations for its use, including dose and route of administration. The current international consensus is that 600 µg administered orally is optimal in terms of efficacy and has an excellent safety profile. While some researchers assert that 400 µg of misoprostol would also work, studies testing this lower dose have obtained conflicting results and lacked consistency in the routes of administration used, thus making it difficult to draw any conclusions or to recommend this dose. In addition, since the safety profile of 600-µg oral misoprostol is so excellent, there is little pressure to lower the dose. A study to test whether 400 µg performs as well as 600 µg for program purposes would be enormous and prohibitively expensive. The likelihood is that the 600-µg oral dose will remain the standard for prevention of PPH for the foreseeable future.

For the treatment of PPH, the only well-studied effective dose is 800-µg sublingual misoprostol. Although there have been more side effects with this dose (especially in certain specific populations) than with some lower doses or routes, there has been no safety rationale to avoid using the full tested dose. At the moment, the only evidence-based recommendation is to use 800 µg sublingual misoprostol when i.v. oxytocin is not available. When oxytocin prophylaxis has been used, misoprostol and oxytocin i.v. work equally well as treatments. When oxytocin is available only intramuscularly, misoprostol should be regarded as the preferred agent for the treatment of PPH, both with and without oxytocin prophylaxis, since the use of oxytocin i.m. for treatment purposes has not yet been sufficiently studied.

On the other hand, we cannot recommend treating PPH with both oxytocin and misoprostol simultaneously. Doing so does not enhance the response or lower blood loss but only increases side effects. Even where both oxytocin and misoprostol are available, initial therapy for PPH should be carried out with one drug: where feasible, oxytocin i.v. for women who have not had oxytocin prophylaxis, either oxytocin i.v. or misoprostol when women have had oxytocin prophylaxis and misoprostol where oxytocin i.v. is not feasible. Use of misoprostol for the treatment of PPH following provision of misoprostol prophylaxis has not yet been studied, but if oxytocin is unavailable, there is no reason to withhold misoprostol treatment if bleeding poses a risk to life.

The major advances in understanding the role and regimens of misoprostol in PPH are heartening. The availability of solid new information raises another challenge, however. Now, the new information needs to be incorporated into standards of practice, into programs and into provider education. The task for the next years is to reduce the amount of medical 'ad hockery' in routes, dosages and regimens, and to base more guidance and practice on the evidence we now have.

Declaration of interest

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