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Overview of Misoprostol Studies in Postpartum Hemorrhage

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INTRODUCTION

A series of tables of peer-reviewed misoprostol studies have been compiled to provide the reader with a set of comprehensive references since 1997 to the use of misoprostol for both prevention and treatment of postpartum hemorrhage (PPH). The tables include both randomized and non-randomized trials, and they represent a diversity of situations.

Table 1 provides an overview of 52 studies on the prevention of PPH (including number of participants, dosage and route of administration, and control agents). Table 2 gives an overview of 11 studies on the treatment of PPH (including number of participants, dosage and route of administration, and control agents). Table 3 lists nine reviews and meta-analyses published on the topic.

SUMMARY

Misoprostol greatly reduces severe PPH[1], but is less effective than injectable oxytocin for the prevention and treatment of PPH[2,3].

Although the use of injectable uterotonics is preferred in hospital settings, misoprostol has effectively been used in community and home settings[3–8] (see Chapter 42).

For prevention of PPH, misoprostol should be administered during the third stage of labor at any point after the anterior shoulder is delivered[9]. Currently the dose most commonly used for PPH is 600 μg of oral or sublingual misoprostol. Rectal administration may offer similar benefits, and causes fewer side-effects[9]. Newer studies show that a dose of 400 μg of oral misoprostol is as effective as 600 μg, but with fewer side-effects[10,11].

Existing evidence continues to grow regarding the use of misoprostol in treatment of PPH. A single dose of 600 μg oral or 800 μg sublingual misoprostol is recommended in instances when other treatments have either failed to work or are not available[12–14]. A Cochrane review found no significant reduction in mortality or decreased need for further blood transfusion and use of more uterotonics when comparing misoprostol with a combination of injectable uterotonics (oxytocin and ergometrine)[15].

Administering misoprostol in addition to the normal regimen with injectable uterotonics showed no added benefit[16–18].

Pyrexia and shivering were more common side-effects with misoprostol than with injectable uterotonics, and seem to be dose related[1,2,7,11,15,18,19]. Although frequently mentioned as a limitation associated with use of misoprostol, neither is life threatening or bothersome for an inordinate period of time.

In the event of continued hemorrhage, a minimum of 2 hours waiting period is recommended before the application of a second dose. In case of pyrexia or marked shivering, at least 6 h should pass[3,20].

Table 1 Misoprostol for prevention of postpartum hemorrhage (PPH)

Author	*Site(s)*	*Study title*	*Journal*	*Total number of participants*	*Participants in misoprostol group(s)*	*Dosage of misoprostol* (μg)	*Route of administration*	*Participants in control group(s)*	*Control agent(s)*
Hashima-E-Nasreen	Bangladesh	Oral misoprostol for preventing postpartum haemorrhage in home births in rural Bangladesh: how effective is it?	*Glob Health Action* 2011; Epub 2011 Aug 10	2017	1009	400 μg	Oral	1008	Placebo
Mobeen *et al.*	Pakistan	Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: a randomised placebo-controlled trial.	*BJOG* 2011;118:353–61	1119	534	600 μg	Oral	585	Placebo
Hofmeyr *et al.*	South Africa, Nigeria, Uganda	Administration of 400 μg of misoprostol to augment routine active management of the third stage of labor	*Int J Gynaecol Obstet* 2011;112:98–102	1103	547	400 μg [plus 10 IU oxytocin I.M. or 0.2–0.5 mg ergometrine I.M. as routine AMTSL]	Subligual	556	Placebo. All participants received 10 IU oxytocin I.M. or 0.2–0.5 mg ergometrine I.M. as routine AMTSL
Fawole *et al.*	Nigeria	A double-blind, randomized, placebo-controlled trial of misoprostol and routine uterotonics for the prevention of postpartum hemorrhage	*Int J Gynaecol Obstet* 2011;112:107–11	1345	672	400 μg [plus 10 IU oxytocin I.M. or 0.2–0.5 mg ergometrine I.M. as routine AMTSL]	Subligual	673	Placebo. All participants received 10 IU oxytocin I.M. or 0.2–0.5 mg ergometrine I.M. as routine AMTSL
Mansouri *et al.*	Saudi Arabia	Rectal versus oral misoprostol for active management of third stage of labor: a randomized controlled trial	*Arch Gynecol Obstet* 2011;283;935–9	658	[1] 331 [2] 327	600	[1] Oral [2] Rectal		
Sanghvi *et al.*	Afghanistan	Prevention of postpartum hemorrhage at home birth in Afghanistan	*Int J Gynaecol Obstet* 2010;108:276–81	3187	1421	600	Oral	1148	Placebo
Afolabi *et al.*	Nigeria	Oral misoprostol versus intramuscular oxytocin in the active management of the third stage of labour	*Singapore Med J* 2010; 51:207	200	100	400	Oral	100	10 IU oxytocin I.M.
Singh *et al.*	India	Comparison of sublingual misoprostol, intravenous oxytocin, and intravenous methylergometrine in active management of the third stage of labour	*Int J Gynaecol Obstet* 2009;107:130–4	300	[1] 75 [2] 75	[1] 400 [2] 600	Sublingual	[3] 75 [4] 75	[3] 5 IU oxytocin I.V. [4] 0.2 mg methylergometrine I.V.
Vaid *et al.*	India	A randomized controlled trial of prophylactic sublingual misoprostol versus intramuscular methyl-ergometrine versus intramuscular 15-methyl PGF2-Alpha in active management of third stage of labor	*Arch Gynecol Obstet* 2009;280:893–987	200	66	400	Sublingual	[1] 67 [2] 67	[1] 0.2 mg methylergometrine I.M. [2] 125 μg 15-methyl PGF2-Alpha I.M.
Nasr *et al.*	Egypt	Rectal misoprostol versus intravenous oxytocin for prevention of postpartum hemorrhage	*Int J Gynaecol Obstet* 2009;105:244–7	514	257	800	Rectal	257	5 IU oxytocin I.V.
Harriott *et al.*	Jamaica	A randomized comparison of rectal misoprostol with syntometrine on blood loss in the third stage of labour	*West Indian Med J* 2009;58:201–6	140		400	Rectal		Syntometrine I.M. (10 IU syntocinone and 0.5 mg ergometrine)
Haque *et al.*	Bangladesh	Comparative study between rectally administered misoprostol as a prophylaxis versus conventional intramuscular oxytocin in post partum hemorrhage	*Mymensigh Med J* 2009;18(1 Suppl): S40–4	200	100	600	Rectal	100	10 IU oxytocin I.M.

Al-Harazi *et al.*	Yemen	Sublingual misoprostol for the prevention of postpartum hemorrhage	*Saudi Med J* 2009;30: 912–6	215	[1] 118 [2] 97	600	[1] Sublingual [2] Rectal		
Prata *et al.*	Ethiopia	Prevention of postpartum hemorrhage: options for homebirths in rural Ethiopia	*Afr J Reprod Health* 2009;13:87–95	966	485	600	Oral	481	Current AMTSL practices
Enakpene *et al.*	Nigeria	Oral misoprostol for the prevention of primary post-partum hemorrhage during third stage of labor	*J Obstet Gynaecol Res* 2007;33:810–7	864	432	400	Oral	432	0.5 mg methylergometrine I.M.
Ng *et al.*	China	A double-blind randomized controlled trial of oral misoprostol and intramuscular syntometrine in the management of the third stage of labor	*Gynecol Obstet Invest* 2007;63:55–60	355	178	400	Oral	177	1 ml syntometrine I.M. (5 IU syntocinone and 0.5 mg ergometrine)
Baskett *et al.*	Canada	Misoprostol versus oxytocin for the reduction of postpartum blood loss	*Int J Gynaecol Obstet* 2007;97:2–5	622	311	400	Oral	311	5 IU oxytocin I.V.
Parsons *et al.*	Ghana	Rectal misoprostol versus oxytocin in the management of the third stage of labour	*J Obstet Gynaecol Can* 2007;29):711–8	450		800	Rectal		10 IU oxytocin I.M.
Parsons *et al.*	Ghana	Oral misoprostol versus oxytocin in the management of the third stage of labour	*J Obstet Gynaecol Can* 2006;28:20–6	450		800	Oral		10 IU oxytocin I.M.
Derman *et al.*	India	Use of oral misoprostol in the prevention of PPH	*Lancet* 2006;368:1248–53	1620	812	600	Oral	808	Placebo
Prata *et al.*	Egypt	Misoprostol and active management of the third stage of labor	*Int J Gynaecol Obstet* 2006;94:149-–55	2532	1189	600	Oral	1343	Current AMTSL practices
Nellore *et al.*	India	Rectal misoprostol vs. 15-methyl prostaglandin F2(alpha) for the prevention of postpartum hemorrhage	*Int J Gynaecol Obstet* 2006;94:45–6	120	60	400	Rectal	60	125 μg 15-methyl prostaglandin F2α I.M.
Chandhiok *et al.*	India	Oral misoprostol for prevention of postpartum hemorrhage by paramedical workers in India	*Int J Gynaecol Obstet* 2006;92:170–5	1200	600	600	Oral	600	Current government guidelines for PPH prevention
Zachariah *et al.*	India	Oral misoprostol in the third stage of labor	*Int J Gynaecol Obstet* 2006;92:23–6	2023	730	400	Oral	[1] 617 [2] 676	[1] 10 IU oxytocin I.M. [2] 2 mg ergometrine I.V.
Garg *et al.*	India	Oral misoprostol versus injectable methylergometrine in management of the third stage of labor	*Int J Gynaecol Obstet* 2005;91:160–1	200	100	600	Oral	100	0.2 mg methylergometrine I.V.
Ozkaya *et al.*	Turkey	Placebo-controlled randomized comparison of vaginal with rectal misoprostol in the prevention of postpartum hemorrhage	*J Obstet Gynaecol Res* 2005;31:389–93	150	[1] 50 [2] 50	400	[1] Rectal [2] Oral	50	Placebo
Hoj *et al.*	Guinea-Bissau	Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomised double blind clinical trial	*BMJ* 2005;331:723	661	330	600	Sublingual	331	Placebo
Walraven *et al.*	The Gambia	Misoprostol in the management of the third stage of labour in the home delivery setting in rural Gambia: a randomised controlled trial	*BJOG* 2005;112: 1277–83	1229	630	600	Oral	599	2 mg ergometrine oral

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Table 1 *Continued*

Author	*Site(s)*	*Study title*	*Journal*	*Total number of participants*	*Participants in misoprostol group(s)*	*Dosage of misoprostol* (μg)	*Route of administration*	*Participants in control group(s)*	*Control agent(s)*
Vimala *et al.*	India	Sublingual misoprostol versus methylergometrine for active management of the third stage of labor	*Int J Gynaecol Obstet 2004;87:1–5*	120	60	400	Sublingual	60	0.2 mg methylergometrine I.V.
Lam *et al.*	China	A pilot-randomized comparison of sublingual misoprostol with syntometrine on the blood loss in 3rd stage of labor	*Acta Obstet Gynecol Scand* 2004;83:647–50	60	30	600	Sublingual	30	1 ml syntometrine I.V. (5 IU syntocinone and 0.5 mg ergometrine)
Caliskan *et al.*	Turkey	Oral misoprostol for the 3rd stage of labor: a randomized controlled trial	*Obstet Gynecol* 2003; 101:921–8	1574	388	600	Oral	[1] 404 [2] 384 [3] 398	[1] 600 μg misoprostol plus 10 IU oxytocin I.V. [2] 10 IU oxytocin I.V.[3] 10 IU oxytocin I.V. plus 0.2 mg methylergonovine
Oboro *et al.*	Nigeria	A randomised controlled trial of misoprostol versus oxytocin in the active management of the third stage of labour	*Obstet Gynaecol* 2003; 23:13–6	496	247	600	Oral	249	10 IU oxytocin I.M.
Lumbiganon *et al.*	Thailand	Side effects of oral misoprostol during the first 24 hours after administration in the third stage of labour	*BJOG* 2002;109: 1222–6	1686	843	600	Oral	843	10 IU oxytocin I.M. or I.V.
Quiroga Diaz *et al.*	Mexico	Vaginal misoprostol in the prevention of PPH	*Ginecol Obstet Mex* 2002;70:572–5	400	208	800	Vaginal	192	Current AMTSL practices
Caliskan *et al.*	Turkey	Is rectal misoprostol really effective in the treatment of third stage of labor? A randomized controlled trial	*Am J Obstet Gynecol* 2002;187:1038–45	1606	396	600	Rectal	[1] 401 [2] 407 [3] 402	[1] 10 IU oxytocin I.V. plus 600 μg misoprostol rectal [2] 10 IU oxytocin I.V. [3] 10 IU oxytocin I.V. plus 1 ml methylergometrine I.M.
Karkanis *et al.*	Canada	Randomized controlled trial of rectal misoprostol versus oxytocin in third stage management	*J Obstet Gynaecol Can* 2002;24:149–54	214	110	400	Rectal	113	5 IU oxytocin I.V. or 10 IU oxytocin I.M.
Kundodyiwa *et al.*	Zimbabwe	Misoprostol versus oxytocin in the third stage of labor	*Int J Gynaecol Obstet* 2001;75:235–41	499	243	400	Oral	256	10 IU oxytocin I.M.
Benchimol *et al.*	France	Role of misoprostol in the delivery outcome	*J Gynecol Obstet Biol Reprod* 2001;30:576–83	600	200	600	Oral	[1] 200 [2] 200	[1] 2.5 IU oxytocin I.V. [2] placebo
Gerstenfeld *et al.*	USA	Rectal misoprostol versus intravenous oxytocin for the prevention of PPH after vaginal delivery	*Am J Obstet Gynecol* 2001;185:878–82	325	159	400	Rectal	166	20 IU oxytocin I.V.

Gulmezoglu *et al.*	Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand, Vietnam	WHO multicentre randomised trial of misoprostol in the management of the third stage of labour	*Lancet* 2001;358: 689–95	18530	9264	600	Oral	9266	10 IU oxytocin I.M. or I.V.
Hofmeyr *et al.*	South Africa	Side-effects of oral misoprostol in the third stage of labour – a randomised placebo-controlled trial	*S Afr Med J* 2001;91: 432–5	600	300	600	Oral	300	placebo
Bugalho *et al.*	Mozambique	Misoprostol for prevention of PPH	*Int J Gynaecol Obstet* 2001;73:1–6	663	324	400	Rectal	339	10 IU oxytocin I.M.
Ng *et al.*	China	A multicentre randomized controlled trial of oral misoprostol and I.m syntometrine in the management of the third stage of labour	*Hum Reprod* 2001;16:31–5	2058	1026	600	Oral	1032	1 ml syntometrine I.V. (5 IU syntocinone and 0.5 mg ergometrine)
Walley *et al.*	Canada	A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour	*BJOG* 2000;107: 1111–5	401	203	400	Oral	198	10 IU oxytocin I.M.
El-Refaey *et al.*	UK	The misoprostol third stage of labour study: a randomised controlled comparison between orally administered misoprostol and standard management	*BJOG* 2000;107: 1104–10	1000	501	500	Oral	499	Standard oxytocic regimens (10 IU oxytocin or 0.5 mg ergometrine or 1 ml syntometrine)
Cook *et al.*	Australia	A randomized clinical trial comparing oral misoprostol with synthetic oxytocin or syntometrine in the third stage of labour	*Aust NZ J Obstet Gynaecol* 1999;39: 414–9	863	424	400	Oral	439	Standard oxytocic regimens (10 IU oxytocin I.M. or 1 ml syntometrine I.M.)
Amant *et al.*	Belgium	Misoprostol compared with methylergometrine for the prevention of postpartum haemorrhage: a double-blind randomised trial	*Br J Obstet Gynaecol* 1999;106:1066–70	200	100	600	Oral	100	0.2 mg methylergometrine I.V.
Surbek *et al.*	Switzerland	Oral misoprostol for the 3rd stage of labor: a randomized placebo-controlled trial	*Obstet Gynecol* 1999;94:255–8	65	31	600	Oral	34	Placebo
Bamigboye *et al.*	South Africa	Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial	*Am J Obstet Gynecol* 1998;179:1043–6	546	271	400	Rectal	275	Placebo
Hofmeyr *et al.*	South Africa	A randomised placebo controlled trial of oral misoprostol in the third stage of labour	*Br J Obstet Gynaecol* 1998;105:971–5	500	250	400	Oral	250	Placebo
Bamigboye *et al.*	South Africa	Randomized comparison of rectal misoprostol with Syntometrine for management of third stage of labor	*Acta Obstet Gynecol Scand* 1998;77:178–81	491	241	400	Rectal	250	1 ml syntometrine I.M. (5 IU syntocinone and 0.5 mg ergometrine)
El-Refaey *et al.*	UK	Use of oral misoprostol in the prevention of PPH	*BJOG* 1997;104:336–9	237	237	600	Oral	0	–

Table 2 Misoprostol for treatment of postpartum hemorrhage (PPH)

Authors	*Site(s)*	*Study title*	*Journal*	*Total participants*	*Participants in misoprostol group*	*Dosage of misoprostol*	*Route of administration*	*Participants in control group*	*Control agent(s)*
Widmer A *et al.*	Argentina, Egypt, South Africa, Thailand, Vietnam	Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial	*Lancet* 2010;375: 1808–13	1422	705	600 μg [+ standard uterotonic regimen of 10 IU oxytocin I.V. or I.M.]	Sublingual	717	Placebo [+ standard uterotonic regimen of 10 IU oxytocin I.V. or I.M.]
Winikoff B *et al.*	Ecuador, Egypt, Vietnam	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	978	440	800 μg	Sublingual	490	40 IU oxytocin I.V.
Blum J *et al.*	Burkina Faso, Egypt, Turkey, Vietnam	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	809	407	800 μg	Sublingual	402	40 IU oxytocin I.V.
Zuberi N *et al.*	Pakistan	Misoprostol in addition to routine treatment of postpartum hemorrhage: A hospital-based radomized-controlled trial in Karachi, Pakistan	*BMC Pregnancy Childbirth* 2008;8:40	61	29	600 μg [+ standard uterotonic regimen]	Sublingual	32	Placebo [+ standard uterotonic regimen of 15–110 IU oxytocin I.V. and 0.2–0.4 mg methylergometrine I.V.]
Prata N *et al.*	Tanzania	Controlling PPH after home births in Tanzania.	*Int J Gynaecol Obstet* 2005;90:51–5	849	454	1000 μg	Rectal	395	Current practices
Walraven G *et al.*	The Gambia	Misoprostol in the treatment of PPH in addition to routine management: a placebo randomised controlled trial.	*BJOG* 2004;111: 1014–7	160	79	600 μg	200 μg oral and 400 μg sublingual	81	Placebo
Hofmeyr GJ *et al.*	South Africa	Misoprostol for treating postpartum haemorrhage: a randomized controlled trial	*BMC Pregnancy Childbirth* 2004;4:16	238	117	1000 μg	200 μg oral and 400 μg sublingual and 400 μg rectal	121	Placebo
Shojai R *et al.*	France	[Rectal misoprostol for postpartum hemorrhage]	*Gynecol Obstet Fertil* 2004;32:703–7	41	41	1000 μg	Rectal	0	–
Lokugamage AU *et al.*	UK	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	64	32	800 μg	Rectal	32	1 ml syntometrine I.M. (5 IU syntocinone and 0.5 mg ergometrine) plus 10 IU oxytocin I.V.
Abdel-Aleem H *et al.*	Egypt	Management of severe postpartum hemorrhage with misoprostol	*Int J Gynaecol Obstet* 2001;72:75–6	18	18	600 μg or 1000 μg	Rectal	0	–
O'Brien P *et al.*	UK	Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study	*Obstet Gynecol* 1998;92:212–4	14	14	1000 μg	Rectal	0	–

Table 3 Reviews of misoprostol use in postpartum hemorrhage (PPH)

Author	*Institution*	*Study title*	*Journal*
Sloan *et al*.	Gynuity New York, USA	What measured blood loss tells us about postpartum bleeding: a systematic review	*BJOG* 2010;117:788–800
Rajan *et al*.	University of California, Irvine, USA	Postpartum hemorrhage: evidence-based medical interventions for prevention and treatment	*Clin Obstet Gynecol* 2010;53:165–81
Hofmeyr *et al*.	University of Witwatersrand, South Africa	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
Elati *et al*.	University of Liverpool, UK	The use of misoprostol in obstetrics and gynaecology	*BJOG* 2009;116(Suppl 1):61–9
Hofmeyr *et al*.	University of Witwatersrand, South Africa	Misoprostol for the prevention and treatment of postpartum haemorrhage	*Best Pract Res Clin Obstet Gynaecol* 2008;22:1025–41
Alfirevic *et al*.	University of Liverpool, UK	Prevention of postpartum hemorrhage with misoprostol	*Int J Gynaecol* Obstet 2007;99:S198–201
Blum *et al*.	Gynuity New York, USA	Treatment of postpartum hemorrhage with misoprostol	*Int J Gynaecol* Obstet 2007;99:S202–5
Mousa *et al*.	University of Nottingham, UK	Treatment for primary postpartum haemorrhage	*Cochrane Database Syst Rev* 2007;(1):CD003249
Gulmezoglu *et al*.	WHO Geneva, Switzerland	Prostaglandins for preventing postpartum haemorrhage	*Cochrane Database Syst Rev* 2007;(3):CD000494

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