Misoprostol
for
Prevention of Postpartum Hemorrhage:

An Evidence-based Review
by the United States Pharmacopeia

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Background

The third stage of labor is potentially the most dangerous part for the mother, and active management is necessary. The main risk is the occurrence of postpartum hemorrhage, defined as bleeding from the genital tract of 500 mL or more in the first 24 hours following delivery of the baby. (1) The primary cause of postpartum hemorrhage is uterine atony. Postpartum hemorrhage is an important cause of maternal morbidity and mortality worldwide, accounting for at least 150,000 maternal deaths every year. (2, 46, 60) The World Health Organization (WHO) estimates that 20 million morbidities every year result from postpartum hemorrhage. (5)

Postpartum hemorrhage in developing countries

The decreased prevalence of postpartum hemorrhage in most developed parts of the world probably is due to better management of the third stage of labor. (65) However, this is not true in developing countries where postpartum hemorrhage is estimated to be responsible for about 28% of maternal deaths. (3, 46) It is prevalent in those countries where high multiparity, prolonged labor, fibroids, and severe anemia (probably caused by close spacing of pregnancies, poor diet, or parasitic infections) are common (4), although most cases of postpartum hemorrhage occur without such predisposing factors. (65) The risk of dying from postpartum hemorrhage depends on the amount and rate of blood loss and also on the health status of the mother. (46) When women already are compromised by severe anemia and intercurrent illnesses, maternal blood loss of as little as 250 mL may be fatal. (47)

Active management of the third stage of labor

Active management of the third stage of labor, consisting of administration of oxytocics, early cord clamping and cutting, and delivery of placenta by controlled traction of the umbilical cord has been shown to lower the rate of postpartum hemorrhage. (6, 7, 14) Use of prophylactic oxytocics resulted in about a 40% reduction in the risk of postpartum hemorrhage based on analysis of nine controlled trials comparing uterotonic drugs with a placebo or no routine prophylaxis. (8) Other measures to reduce postpartum hemorrhage such as suckling and nipple stimulation in order to stimulate the release of oxytocin have been investigated. However, more studies are warranted, as these small preliminary trials yielded variable results. (48, 63, 64)

Oxytocic agents

Conventional oxytocic agents used include oxytocin, the ergot alkaloids ergonovine (ergometrine) and methylergonovine (methylergometrine), syntometrine (which consists of 5 IU oxytocin [*Syntocinon*] + 0.5 mg ergometrine), and prostaglandins such as carboprost.

Oxytocin, the ergot alkaloids, and syntometrine are equally effective in reducing the risk of postpartum hemorrhage when used in the active management of labor. (13, 14, 17, 50, 57) Oxytocin, which has been used routinely for many years, is considered the drug of choice for preventing postpartum hemorrhage because it produces the fewest side effects. (6, 58) The ergot alkaloids, which have strong uterotonic properties, can be used as second-line agents. (15, 57, 58)

Syntometrine, which combines the rapid onset of action of oxytocin and the prolonged action of ergometrine, is an alternative. (16, 17, 50) Prostaglandins (e.g., carboprost, sulprostone) are strong uterotonic third-line agents used in intractable postpartum hemorrhage when fundal massage and use of other oxytocics fail. (1, 4, 58)

Several drawbacks are associated with use of these oxytocics. (9, 10) Gastrointestinal side effects may occur. In one comparative study, oxytocin and syntometrine caused nausea and vomiting in 1% of patients. (17) In another study, syntometrine was associated with vomiting in as many as 12% of patients following its administration. (49) Syntometrine is contraindicated in women with hypertension in pregnancy because it can precipitate a rise in blood pressure (in 1.2 to 13% of patients). (9, 39, 50) Further, syntometrine has been reported to cause cardiac arrest (51) and intracerebral hemorrhage, and these may be attributed to the ergonovine (ergometrine) component. (18, 67) A recent report associated the ergot alkaloid with acute myocardial infarction. (56) Administration of methylergonovine to 50 patients resulted in the following side effects: cramping (78%), headache (27%), hypertension (22%), dizziness (20%), bradycardia (10%), tachycardia (8%), and some mild gastrointestinal side effects. (52) The prostaglandins, which are expensive agents, generally do not cause hypertension. Carboprost has been reported to cause nausea, vomiting, and diarrhea in 9% of patients. It also has been associated with occasional hypertensive episodes and bronchospasm. (19, 20, 21, 53, 55)

None of these oxytocics are stable in light or in high ambient temperatures and therefore require refrigeration for maintenance of the “cold chain." They also should be protected from freezing. (11, 12, 54) Further, these agents require parenteral administration. (4)

Misoprostol

Misoprostol, a prostaglandin E_1 analog, is used orally for the prevention and treatment of gastric/duodenal ulcer caused by the use of nonsteroidal anti-inflammatory agents (NSAIDs). Its safety for this indication has been established over several years. (22) Oral absorption is rapid (23, 24) and its side effects are usually mild and infrequent. (25)

Misoprostol has been shown to be a potent uterotonic agent selectively binding to EP_2 or EP_3 prostanoid receptors. (26) Its effect on the early pregnant uterus has been shown to be rapid. (27) It has been investigated in the induction of labor (28, 29), cervical priming (30), and induction of abortion, either alone or in combination with mifepristone. (31, 32)

Misoprostol also has been investigated in the prevention of postpartum hemorrhage, using either the oral or rectal route of administration, and compared with placebo or other oxytocics (s*ee attached evidence tables*). (33, 34, 35, 36, 37, 38, 39, 40, 41, 60, 61, 62, 68, 69) Results of most of these studies show a trend toward less postpartum hemorrhage with misoprostol, suggesting that it might be effective for this indication without causing serious side effects. These studies, however, failed to reveal a significant statistical difference regarding blood loss. Recent studies indicated misoprostol is comparable to standard oxytocics. (61, 68, 69) Some experts (42) argue that failure when the rectal route was used probably was due to a pharmacokinetic problem, since rate of absorption of misoprostol from the rectum is yet to be determined. They suggest that further research on the pharmacokinetic properties and transmucosal absorption of misoprostol is warranted. (43)

Misoprostol produces less serious side effects. Gastrointestinal disturbances are infrequent. Vomiting (8%) and diarrhea (3%) have been reported in an uncontrolled study. (40) The oral route has been associated with dose-related shivering (19 to 62%) and pyrexia (temperature >38

°C) (2 to 34%). (33, 34, 38, 40, 59) Some experts believe the rectal route may prove advantageous because it could lessen the gastrointestinal side effects. With this route, misoprostol can be administered to patients who are vomiting or unable to take oral medications, those who are under general anesthesia, or those with heavy vaginal bleeding. (36, 37, 43)

USP Expert Advisory Panel consensus and recommendation

Upon review of the studies included in the attached evidence tables on misoprostol, the consensus of the U.S. Pharmacopeia Expert Advisory Panel is that prevention of postpartum hemorrhage should be considered as an *Accepted* indication in the *USP Drug Information (DI)* monograph on misoprostol. They recommended misoprostol as an alternative agent in reducing the incidence of postpartum hemorrhage, especially in situations in which oxytocin and other uterotonic drugs are not available. The suggested single dose is 400 to 600 micrograms given either orally or rectally immediately following delivery of the child. (66)

Implications for developing countries

In developing countries where there is a high incidence of severe anemia during pregnancy because of nutritional, genetic, or environmental factors, even a relatively small reduction in postpartum blood loss could be clinically relevant. Simple route of administration and use of stable, inexpensive drugs are needed because many deliveries take place away from hospitals or medical facilities and are supervised only by birth attendants (who may not be qualified to administer parenteral oxytocics) (4, 33) or most often, not supervised at all. (54) Re-use of needles for parenteral administration is common practice, thus posing a major risk of the spread of blood-borne infections such as hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection. Further, there is lack of availability of safe blood transfusion services and prior knowledge of blood pressure often is not available. (4)

Misoprostol is an inexpensive drug and easily available. It is easy to use and does not require special storage conditions (i.e., can be stored easily at room temperature; is thermostable and light stable; does not require specific conditions for transfer) and has a shelf life of several years. (44, 45) These advantages make it a useful drug in reducing the incidence of postpartum hemorrhage in developing countries. (65)

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TABLE 1. Misoprostol for Prevention of Postpartum Hemorrhage

Note: The following is not intended to be an in-depth review of each article. Instead, it is a brief overview/review of the studies, assuming readers are already familiar with the cited references.

Evidence Ratings (ranked in descending order of strength):

I Evidence from randomized, controlled trials or meta-analyses of a group of randomized, controlled trials

II Evidence from well-designed, internally controlled clinical trials without randomization, from cohort or case-controlled analytic studies, preferably from more than one center, from multiple time series, or from dramatic results in uncontrolled experiments

III Evidence from clinical trials with low power, preliminary reports of trials in progress, opinions of respected authorities on the basis of clinical experience, descriptive studies such as case reports or series, or reports of expert committees

AUTHOR/YEAR/ REFERENCE # / SPONSOR(S)/ EVIDENCE RATING OR TYPE OF STUDY	DESIGN/ METHODS/ GOAL	DOSE/ DURATION OF THERAPY/ N	RESULTS/ CONCLUSIONS	LIMITATIONS OF STUDY/STAFF COMMENTS
Surbek DV, Fehr PM, Hosli I, et al. Oral misoprostol for third stage of labor; a randomized placebo-controlled trial. Obstet Gynecol 1999; 94(2): 255-8. (A) *Sponsor(s)*: None *Affiliation(s) of the researchers:* Dept of OB-GYN University of Basel, Switzerland *Study protocol approved by:* University of Basel Hospital institutional review board	*Design:* Randomized, double-blind, placebo-controlled trial *Methods*: • Inclusion: - Women at low risk of postpartum hemorrhage undergoing vaginal deliveries • Exclusion: –multiple pregnancy –pre-eclampsia –history of postpartum hemorrhage or –antepartum hemorrhage –planned cesarean delivery • Assessments: –Primary end points: Postpartum blood loss ≥ 500 mL, hematocrit values (prenatally, 24 and 48 hours	*Dose/Duration*: • Misoprostol 600 mcg (n = 31) or placebo (n = 34), one single dose orally, immediately after cord clamping N = 65	*Results*: • Outcomes #1: –Mean (± standard error of the mean) estimated blood loss (345 ± 19.5 mL vs 417 ± 25.9 mL, *P* = 0.31) and hematocrit difference (4.5 ± 0.9% vs 7.9 ± 1.2%, *P* = 0.014) in women who received misoprostol and placebo, respectively. The rate of postpartum hemorrhage, 7% versus 15% in misoprostol and placebo group respectively, was not statistically significant (*P* = 0.43) • Outcomes #2: –Length of 3rd stage of labor: 8 ± 0.9 minutes in misoprostol group vs 9 ± 1 minutes in the placebo group –Need for additional oxytocics: 16% in the misoprostol group vs 38% in the placebo group (*P* = 0.47) –Side effects (nausea, vomiting,	*Limitations/Comments*: • Baseline variables were similar in both groups • Except for the intervention, both groups were treated similarly • Excellent follow-up; all patients were accounted for • Small sample • Although there was less postpartum hemorrhage observed in the misoprostol group than in the placebo group, the study failed to show a statistically significant difference. There were fewer women in the misoprostol group who required additional oxytocics and this was nonstatistically significant • Authors acknowledged a weak point in the study in that blood loss was estimated and not measured and that visual estimates, although acceptable, have been shown to underestimate actual blood loss by 30 to 50%; objective estimate by

Evidence rating: I	postpartum) –Secondary end points: Length of 3rd stage of labor, need for additional oxytocics, side effects including nausea, vomiting, shivering, hypotension, and pain (using visual analog scale) –Other intervention: If IV oxytocin was used during the 2nd stage of labor, it was stopped immediately after delivery. If uterine bleeding was more than normal, and if placental separation did not occur until 30 minutes after delivery, additional oxytocin was administered intravenously in boluses of 5 IU, repeated as necessary –A sample size of 60 was calculated to detect a 20% difference in estimated blood loss between groups with a power of 80%, at a significance level of 0.05 –Statistic tests: Chi-square test or Fisher's exact test and Mann-Whitney test. A two-tailed $P < 0.05$ was considered statistically significant *Goal*: • To investigate whether orally administered misoprostol during 3rd stage of labor is efficient in reducing postpartum blood loss		diarrhea, or hypotension) were not different between the two groups. Shivering occurred in 22% of patients in the misoprostol group vs 3% in the placebo group ($P = 0.023$). Pain was similar between the misoprostol and placebo groups (mean 3.7 vs 3.4, respectively [$P = 0.665$]). –Fetal outcome was favorable in all women *Conclusions*: • Oral misoprostol administered in the third stage of labor reduced postpartum blood loss and might be effective in reducing incidence of postpartum hemorrhage	hemoglobin/hematocrit determinations was done and showed a significant difference • Another source of bias was the use of additional oxytocic by some women to prevent excessive bleeding • Shivering occurred in 22% of the misoprostol group which was significant
Amant F, Spitz B, Timmerman D, et al.	*Design:* Randomized, double-blind,	*Dose/Duration:* • Misoprostol 600	*Results*: • Outcome #1:	*Limitations/Comments*: • Both groups received active

Misoprostol compared with methylergometrine for the prevention of postpartum hemorrhage: a double-blind randomized trial. Br J Obstet Gynecol 1999; 106: 1066-70. (B) *Sponsor(s)*: None *Affiliation(s) of the researchers:* Dept of OB-GYN University Hospital Leuven, Belgium *Study protocol approved by:* Local ethics committee **Evidence rating: I**	controlled trial *Methods*: • Inclusion: –Women who anticipated vaginal delivery • Exclusion: –cesarean section –hypertensive disorders –gestational age < 32 weeks –intrauterine death –uterine malformations –allergy to prostaglandins or alkaloids –inflammatory bowel disease –obliterative vascular and –coronary disease –sepsis • Assessment: –Primary end points: Rate of postpartum hemorrhage, need for therapeutic oxytocic drugs, side effects –Other end points: Length of 3rd stage of labor, need for manual removal of placenta, need for blood transfusion (hemoglobin and hematocrit levels were measured on admission and on the 3rd day postpartum; temperature and BP values were recorded) –A sample size of 60 women in each group was required to obtain a power of 90%; a sample size of 100 was chosen in order to be well above this limit –Statistic tests: Two-sample *t*	mcg (n = 100) or placebo, orally; and methylergometrine 200 mcg (n = 100) or placebo, injected intravenously, after delivery N = 213 enrolled, minus 13 who were excluded because a cesarean section was performed after randomization (n = 3), or because no pre-partum (n = 3) or postpartum (n = 7, short hospital stay) blood sample was taken, resulting in 200 who completed the study	–Estimated blood loss (>500 mL): 4.3% in the methylergometrine group vs 8.3% in the misoprostol group ($P = 0.57$); 1% in the misoprostol group had blood loss > 1000 mL and none in the methylergometrine group –Need for additional oxytocics: 12.8% in the misoprostol group vs 4.4% in the methylergometrine group ($P = 0.065$) –Side effects: Shivering occurred in the misoprostol group (42%) more than in the methylergometrine group (8.5%) ($P = 0.0001$), which was statistically significant. There was no difference between both groups in the occurrence of other side effects such as nausea, vomiting, diarrhea, hot flush, headache, or vertigo • Other outcomes: –Need for manual removal of placenta was similar in both groups (3% in the methylergometrine group vs 4% in the misoprostol group [$P = 1$, Fisher exact test]) –1 woman in each group needed a blood transfusion –The median length of labor was similar for both groups ($P = 0.88$). –Temperature, one hour after delivery: A significant rise in temperature (≥ 38 °C) occurred in 34% in the misoprostol group and 3% in the methylergometrine group ($P = 0.0001$). A rise in temperature (≥ 39 °C) occurred	management of the third stage equally • Demographic characteristics and labor variables were similar • The misoprostol group had increased need for therapeutic oxytocics compared with the methylergometrine group, although this was not statistically significant • Less blood loss occurred in the methylergometrine group than in the misoprostol group, although this was not statistically significant • Incomplete data in some cases as in the recording of side effects and need for additional oxytocics • The authors stated that the oral absorption of misoprostol delayed the effects on hemorrhage during the first hour after delivery, requiring more oxytocics for those patients, whereas parenteral injection of methylergometrine was effective immediately. The authors suggested use of combined prophylaxis consisting of a parenteral uterotonic such as methylergometrine to prevent uterine bleeding immediately after delivery and oral misoprostol to reduce blood loss in the hours following delivery • Blood loss was visually estimated (subjective); hemoglobin/hematocrit determinations were done (objective) • Significant side effects observed in the misoprostol group were shivering and pyrexia

	test, chi-square test, and Wilcoxon rank sum test *Goal*: • To compare the efficacy and side effects of misoprostol in the prevention of postpartum hemorrhage with those of methylergometrine		only in the misoprostol group (8%) –No difference in systolic and diastolic blood pressure or in hemoglobin and hematocrit values *Conclusions*: • This study suggests that although protection from postpartum hemorrhage using parenteral methylergometrine and oral misoprostol is nearly equal, misoprostol is associated with more side effects	
Diab KM , Ramy AR, Yehia MA. The use of rectal misoprostol as active pharmacological management of the third stage of labor. J Obstet Gynaecol Res 1999; 25(5): 327-32. (C) *Sponsor(s)*: None *Affiliation(s) of the researchers:* Dept of OB-GYN Ain Shams University Cairo, Egypt **Evidence rating: II**	*Design:* Comparative study *Methods*: • Inclusion: –Women at low risk for vaginal delivery • Exclusion: –grandmultiparity (parity ≥ 5) –under anticoagulant therapy –placenta previa –antepartum hemorrhage –polyhydramnios –intrauterine fetal death –previous postpartum hemorrhage –uterine scar –prolonged (≥ 24 hours) or rapid (≤ 2 hours) –under epidural anesthesia –contraindications such as hypertension or cardiac diseases • Assessments:	*Dose and duration:* • Misoprostol 200 mcg (n = 25) or 400 mcg (n = 45) rectally, or oxytocin 5 Units plus ergometrine 0.2 mg IM (n = 70) N =140	*Results*: • Outcomes: Estimated blood loss: mean – 234 ± 11 in misoprostol group vs 273 ± 12 in the oxytocin/ergometrine group; need for additional oxytocics: 4 in misoprostol group vs 15 in oxytocin/ergometrine group; side effects: nausea, vomiting, and diarrhea occurred in 8 patients in the misoprostol group and none in the other group; shivering occurred in 5 patients in the misoprostol group and none in the other group; postpartum systolic hypertension: less in the misoprostol group (112 ± 1.4 in the misoprostol group vs 122 ± 1.6 in the oxytocin/ergometrine group); postpartum diastolic hypertension: less in the misoprostol group (73 ± 1.1 in the misoprostol group vs 78 ± 1.8 in the oxytocin/ergometrine group); duration of the 3rd stage was similar in both groups (mean: 2.97 ± 0.14 in the misoprostol group vs 3.1 ± 0.13 in the oxytocin/ergometrine	*Limitations/Comments*: • No mention of randomized concealed allocation • Both groups received similar active management of the 3rd stage • Nonblind • Baseline characteristics were similar in both groups • All patients were accounted for • Blood loss visually estimated (subjective); hemoglobin/hematocrit determinations were done (objective) • There was less blood loss (significant at $P = < 0.01$) and need for additional oxytocics in the misoprostol group than in the oxytocin/ergometrine group • Mild gastrointestinal side effects occurred more in the misoprostol group. However, hypertension occurred more in the oxytocin/ergometrine group

	–End points: Duration of 3rd stage of labor (prolonged if ≥ 30 min), amount of blood loss (≥ 500 mL), need for additional therapeutic oxytocics, perineal trauma (episiotomy/tear), side effects such as nausea, vomiting, shivering, hypertension (systolic BP ≥ 150 mm Hg, or diastolic BP ≥ 100 mm Hg), neonatal outcome; pre- and postpartum hemoglobin and hematocrit determinations –After delivery of the fetus, any oxytocin infusion used for labor augmentation was stopped and plain 5% glucose was administered. In the event of excessive bleeding, additional therapeutic uterotonic agents were administered consisting of 0.2 mg ergometrine IM plus 30 Units oxytocin by IV infusion in 500 mL glucose 5%. –Statistic tests: Student's *t* test, Fisher's exact test *Goal:* • To determine the safety and efficacy of administration of misoprostol rectally, compared to combined intramuscular administration of oxytocin and ergometrine as uterotonic agents in the		group); none needed manual removal of placenta, none needed blood transfusion; postpartum hemoglobin and hematocrit levels were significantly decreased in the oxytocin/ergometrine group *Conclusions*: • Rectal misoprostol may be used safely as an active pharmacological management in the 3rd stage of labor. Further studies are needed to explore the exact dose to be used rectally	

	active management of the 3rd stage of labor			
Bamigboye AA, Hofmeyer GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. Am J Obstet Gynecol, 1998; 179: 1043-6 (D) *Sponsor(s)*: None *Affiliation(s) of the researchers:* Dept of OB-GYN Coronation Hospital Natalspruit Hospital University of Witwatersrand Johannesburg, South Africa *Study protocol approved by:* Committee for Research on Human Subjects of the University of Witwatersrand **Evidence rating: I**	*Design:* Randomized, placebo-controlled study *Methods*: • Inclusion: –Pregnant women at low risk in labor • Assessment: –Primary end points: Excessive bleeding/blood loss measured, need for additional oxytocic agents, need for oxytocin infusion –Secondary end points: Spontaneous delivery of placenta, duration of 3rd stage of labor, side effects, especially shivering –Other intervention: IM administration of 1 ampul syntometrine (ergometrine 0.5 mg/oxytocin 5 IU) for signs of excessive blood loss and if bleeding persisted, infusion of oxytocin 20 Units in 1 L lactated Ringer's solution –Sample size of 550 was calculated to give an 80% chance of detecting a reduction in blood loss >1000 mL from 12.5 to 5%, determined from data from 2 previous randomized trials showing estimated postpartum hemorrhage of 13.5% w/ physiologic	*Dose/Duration*: • Misoprostol, rectal, 400 mcg (n = 271), or placebo (n = 275) within 1 minute after normal vaginal delivery and clamping of the cord N = 550 enrolled minus 4 (records untraced) = 546 analyzed	*Results*: • Outcomes #1: –Blood loss of ≥1000 mL in 4.8% in the misoprostol group and in 7% in the placebo group (RR 0.69 [95% CI, 0.35–1.37]) (P = 0.37); additional oxytocic agent needed by 3.3% in misoprostol group and 4.7% in the placebo group (RR 0.70 [95% CI, 0.31–1.62]) (P = 0.54); oxytocin infusion required by 1.8 and 4.4%, respectively (RR 0.42 [95% CI, 0.15–1.18]) (P = 0.15) • Outcomes #2: –The mean duration of the third stage of labor was 6.6 minutes in the misoprostol group and 6.4 minutes in the placebo group –Vomiting reported in 1 woman in each group –Shivering reported in 1 woman in the misoprostol group and 4 women in the placebo group (7.1%) *Conclusions*: • Postpartum use of 400 mcg of rectal misoprostol was well tolerated and associated w/ a nonsignificant trend toward less postpartum hemorrhage. Low side effect profile when compared to oral route of administration. Potential benefit of misoprostol may be greater in an environment in which	*Limitations/Comments:* • Double-blinding was not achieved due to inability to obtain identical-looking placebo tablets from manufacturer • Potential to demonstrate a difference in the rate of excessive blood loss between the misoprostol & placebo groups was limited by the need to administer oxytocic agents as soon as blood loss appeared excessive • Incidence of postpartum hemorrhage in the control group (7%) was lower than that on which the power calculations were based (12.5%) • No mention of exclusion criteria • Baseline variables were similar for both groups • Except for the intervention, both groups were treated in the same manner • Clinical estimate of blood loss was done with detailed description of how blood loss was collected and measured (e.g., pan collection and blood-soiled linen, etc. weighed); no hemoglobin/hematocrit determinations were done • Good follow-up • Although there was less postpartum hemorrhage observed in the misoprostol group than in the placebo group, the study failed to reveal a significant statistical difference regarding blood loss between the two groups. (Power analysis was done at the start of the trial.) Also, there was less need for further oxytocics postpartum in the misoprostol group than in placebo group, but the difference was

	management of the 3rd stage compared w/ 4.1% w/ active management –Statistic tests: Fisher's exact test, Mann-Whitney test *Goal*: • To investigate the use of rectal misoprostol compared with placebo in preventing postpartum hemorrhage		oxytocic agents are not available	nonsignificant • Side effects observed were mild
O'Brien P, El-Refaey H, Gordon AAA, et al. Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. Obstet Gynecol 1998; 92(2): 212-4. (E) *Sponsor(s)*: None *Affiliation(s) of the researchers:* Dept of OB-GYN University College Hospital London, UK **Evidence rating: III**	*Design:* Descriptive study *Methods*: • Inclusion: –Women with postpartum hemorrhage unresponsive to oxytocin & ergometrine (n = 10) or when ergometrine was contraindicated, oxytocin alone (n = 4) • Assessment: –Blood loss –Labor complications –Other intervention: Oxytocin IV infusion (40 Units in 500 mL normal saline over 15 minutes and bolus (10 to 20 Units), ergometrine (0.5 to 1 mg IM or IV), or carboprost *Goal*: • To investigate whether rectally administered misoprostol is an effective treatment for postpartum hemorrhage unresponsive to conventional first-line management	*Dose/Duration*: • Misoprostol 1000 mcg (five tablets) rectally, while awaiting carboprost. If carboprost was ready for administration before misoprostol, the woman was excluded from the study and carboprost was administered according to hospital policy N = 14	*Results*: • Blood loss: –Hemorrhage was controlled in all 14 women & sustained uterine contraction was produced w/in 3 minutes following administration of misoprostol. No woman required any further uterotonic treatment –Median estimated blood loss was 1000 mL; 9 women (64%) had blood loss of 1000 mL or more; 11 women (79%) required a blood transfusion, with 2 patients requiring overnight stay in intensive care unit. All 14 women made full recovery –Some of the complications that developed were preeclampsia and DIC *Conclusions*: • Rectally administered misoprostol is an effective treatment for postpartum hemorrhage unresponsive to oxytocin & ergometrine & may be an alternative to parenteral prostaglandins. The authors	*Limitations/Comments:* • Authors stated that the possibility cannot be ruled out that these women responded to the previously administered oxytocics or to the combined effects of the oxytocics and misoprostol, rather than to the misoprostol alone. However, they added that IV oxytocics have a rapid onset of action and that an appropriate therapeutic interval had passed; any effect on hemorrhage may have occurred by the time misoprostol was administered • Small sample • Uncontrolled study and, therefore, would be difficult to conclude that the resolution of postpartum bleeding was due to misoprostol. The observed effect could be due to the previously administered oxytocics or a combination of these drugs with misoprostol • Ten of the 14 women included in the study were high risk as evidenced by the complications reported (preeclampsia, DIC, breech, etc.); almost all required blood transfusion • No mention of side effects. Use of a higher dose (1000 mcg) did not result in shivering

			suggested that absorption of misoprostol is mucous-membrane dependent & rectal absorption might be just as effective as vaginal or oral absorption • Rectal administration appears to be ideal, given that women under general anesthesia cannot be given oral medication & that vaginal administration is unlikely to be effective in the presence of heavy vaginal bleeding • Misoprostol is inexpensive & stable & has considerable potential to reduce maternal mortality in developing countries. Authors suggested the need for further investigation, both for developed and developing countries	
Hofmeyr GJ, Nikodem VC, De Jager M, et al. A randomized placebo-controlled trial of oral misoprostol in the third stage of labor. Br J Obstet Gynaecol 1998; 105(9): 971-5. (F) *Sponsor(s)*: South African Medical Research Council *Affiliation(s) of the researchers:* Dept of OB-GYN Coronation Hospital University of	*Design:* Randomized, double-blind, placebo-controlled trial *Methods*: • Inclusion: –Low-risk women expected to deliver vaginally • Exclusion: –women in labor with oxytocin infusion in progress at the time of delivery –hypertension –diabetes –previous cesarean section • Assessment: –Primary end points:	*Dose/Duration*: • Misoprostol 400 mcg (n = 250), orally, or placebo (n = 250), after delivery N=500	*Results*: • Outcomes #1: –Blood loss of > 1000 mL: 6% in the misoprostol group vs. 9.2% in the placebo group (RR 0.65 [95% CI, 0.35–1.22]) (*P* = 0.18) –Need for additional oxytocics: 8.4% in the misoprostol group vs 13% in the placebo group (RR 0.64 [95% CI, 0.38–1.07]) (*P* = 0.08); oxytocin infusion was required by 2.8% in the misoprostol group and 8.4% in the placebo group (RR 0.33 [CI 0.14–0.77]) (*P* = 0.006) w/c is statistically significant • Outcomes #2:	*Limitations/Comments:* • Authors stated that the actual difference between the two groups may have been limited by the policy of early conventional oxytocic management the moment bleeding appeared to be more than usual • Double-blinding was achieved in spite of the use of unidentical-looking placebo tablets • Baseline variables were similar for both groups • Clinical estimate of blood loss with well-described method of how blood loss was collected and measured (e.g., pan collection and blood-soiled linen, etc. weighed); hemoglobin/hematocrit determinations were not done

Witwatersrand Johannesburg, South Africa **Evidence rating: I**	Measured blood loss ≥1000 mL and need for conventional oxytocics –Secondary end points: Duration of 3rd stage, manual removal of placenta, blood transfusion, side effects –Cointervention: Conventional oxytocics (Syntometrine [1 ampul] IM or oxytocin [10 IU] or for severe bleeding, an IV infusion of oxytocin [20 IU in 100 mL saline]) were not given routinely unless necessary –A sample size of 496 was calculated to detect a reduction in the incidence of measured blood loss of ≥ 1000 mL from 12.5 to 5% with 80% power at the 5% level of certainty –Statistic tests: Chi-square test or Fisher's exact test *Goal*: • To compare the effectiveness of misoprostol, 400 mcg, administered orally, with placebo in the routine management of the 3rd stage of labor		–Side effects results were statistically significant, occurring in 22% in the misoprostol group and 10% in the placebo group (RR 2.08 [95% CI 1.35–3.20]) (P = 0.001) with shivering more common in misoprostol group (19%) vs placebo group (5.2%) (RR 3.69 [95% CI 2.05–6.64]) (P= < 0.0001). Other secondary outcomes were nonsignificant Blood loss of > 800 mL (not a predefined end point in this study but was used to compare with the results from a recent Swedish trial using this as end point): 11.2% for misoprostol and 17.2% for placebo (RR 0.65 [95% CI 0.42–1.01] (P = 0.055) *Conclusions*: • Misoprostol shows promise as a method of reducing the risk of postpartum hemorrhage. Shivering is a common side effect. Further research to determine misoprostol's efficacy with certainty is needed	• Except for the intervention, both groups were treated in the same manner • Complete follow-up • Although there was less postpartum hemorrhage observed in the misoprostol group than in the placebo group, the study failed to reveal a significant statistical difference regarding blood loss between the two groups. (Power analysis was done at the start of the trial.) The misoprostol group had less need for further oxytocics postpartum, but the difference was nonsignificant • Mild side effects; shivering significantly occurred in the misoprostol group
Bamigboye AA, Merrell DA, Hofmeyer GJ, et al. Randomized comparison of rectal misoprostol with syntometrine for the	*Design:* Randomized, comparative study *Methods*: • Inclusion:	*Dose/Duration*: • Misoprostol (n = 250) 400 mcg rectally, or syntometrine (n =	*Results*: • Outcomes: –Blood loss > 500 mL: 0.9% in the misoprostol group vs 0.4% in the syntometrine group (RR	*Limitations/Comments*: • Recording of trial data was incomplete in several cases • Bias may have been introduced that probably favored the syntometrine

management of the third stage of labor. Acta Obstet Gynecol Scand 1998; 77(2): 178-81. (G) *Sponsor(s)*: South African Medical Research Council *Affiliation(s) of the researchers:* Dept of OB-GYN Natalspruit Hospital Coronation Hospital University of Witwatersrand Johannesburg, South Africa **Evidence rating: I**	–Low risk women in labor • Hypertension (contraindication) detected after enrollment excluded some women from syntometrine group • Assessments: –End points: Estimated blood loss, blood pressure, hemoglobin level, duration of 3rd stage of labor –Statistic tests: Chi square test or Fisher's exact test, Mann-Whitney test *Goal*: • To compare the effectiveness of rectal misoprostol (400 mcg) with syntometrine (1 ampul) in the management of the 3rd stage of labor	241) 1 ampul IM, after delivery N = 491	2.02% [95% CI 0.18–22] *P* = 0.6) –BP systolic > 140 mm Hg: 15% in the misoprostol group vs 19% in the syntometrine group (RR 0.79% [95% CI 0.53-1.2] *P* = 0.3) –BP diastolic > 90 mm Hg: 4.6% in the misoprostol group vs 13% in the syntometrine group (RR 0.37% [95% CI 0.19–0.72] *P* = 0.004) –Hemoglobin <10%: 14% in the misoprostol group vs 17% in the syntometrine group (RR 0.82% [95% CI 0.49–1.39] *P* = 0.6) –Duration of 3rd stage was almost identical between the two groups (6.7 min in misoprostol group vs 6.8 min in syntometrine group) – Additional oxytocic management was given to 4 women in the misoprostol group vs 1 woman in the syntometrine group because of inadequate uterine contraction –No side effects were noted *Conclusions*: • No evidence of greater blood loss in the misoprostol group. Authors suggest further randomized trials of sufficient sample size comparing misoprostol with conventional oxytocics; further research is required to determine the optimal dose and route of administration	group by excluding high-risk women (with hypertension) from the syntometrine group after enrollment (nonprotocol exclusion). To evaluate the possible bias, reanalysis of the data was done after excluding all women w/systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg during labor (45 in the misoprostol group and 39 in the syntometrine group) and authors reported that the results were essentially the same as for the whole data set • Another potential bias was the use of additional oxytocics in some of the women enrolled • Authors considered the sample size (491) insufficient to compare incidence of postpartum hemorrhage • No mention of blinding • No mention of exclusion criteria at start of study • Baseline variables were similar for both groups • Blood loss was visually estimated (subjective); however, hemoglobin determination also was done (objective) • The study did not result in a significant statistical difference regarding blood loss between the two groups. There was no mention of power analysis done at the start of the trial • No mention of side effects other than postpartum diastolic hypertension that occurred more in the syntometrine group (13%) • In terms of cost, misoprostol is cheaper than syntometrine. Authors stated that cost ratio of misoprostol 400 mcg to syntometrine + injection supplies = 1 to 3.4 (cost of refrigeration of

				syntometrine not included)
El-Refaey H, O'Brien P, Morafa W, et al. Use of misoprostol in the prevention of postpartum hemorrhage. Br J Obstet Gynaecol 1997; 104(3): 336-9. (H) *Sponsor(s)*: None *Affiliation(s) of the researchers:* Dept of OB-GYN University College Hospital London, UK **Evidence rating: III**	*Design:* Prospective, observational study *Methods*: • Inclusion: –Women undergoing vaginal delivery • Exclusion: –placenta previa –multiple pregnancy –intrauterine death –gestational age < 32 weeks –history of postpartum hemorrhage –in the 6th pregnancy or more –cesarean section –pre-eclampsia Assessments: –Primary end point: Postpartum blood loss ≥ 500 mL –Secondary end points: Severe postpartum blood loss (> 1000 mL), secondary postpartum hemorrhage, need for blood transfusion, and need for further oxytocics –Other end points: Length of 3rd stage, rate of manual removal of placenta, need for subsequent evacuation of the uterus, hemoglobin concentration and packed cell volume, side effects such as vomiting, diarrhea, shivering, and hypertension (defined as a diastolic BP	*Dose/Duration:* • Misoprostol 600 mcg, orally, immediately after delivery N = 237	*Results*: • Outcome #1: –Blood loss ≥ 500 mL occurred in 6% of patients • Outcome #2: –None had blood loss ≥ 1000 mL –No secondary postpartum hemorrhage was reported –1% required blood transfusion –5% needed further oxytocic drug • Outcome #3: –Median length of 3rd stage of labor was 5 minutes –2% required manual removal of placenta –None required surgical evacuation of uterus –2% had postpartum hemoglobin < 9 grams/dL –Side effects: vomiting (8%), diarrhea (3%), shivering (62%) –No differences found in systolic/diastolic BP pre- and postpartum –Temperature significantly increased by 0.5 ºC (P = 0.001) *Conclusions*: • Misoprostol may be effective in the prevention of postpartum hemorrhage & has few side effects • The rate of postpartum hemorrhage with misoprostol (6%), need for further therapeutic oxytocics (5%), and the length of the 3rd stage are lower than those reported when	*Limitations/Comments* • Uncontrolled study and therefore, would be difficult to conclude that the resolution of postpartum hemorrhage was due to misoprostol • Shivering as a side effect occurred in 62% of patients

	≥100 mm Hg or a systolic BP ≥150 mm Hg) –Cointervention: Syntometrine IM when necessary –Statistical tests: paired *t* test, chi-square test *Goal*: • To investigate the use of oral prostaglandin E_1 analog, misoprostol, in the prevention of postpartum hemorrhage; ascertain the rate of postpartum hemorrhage		3rd stage is managed physiologically. Results are also comparable with those of syntometrine. (Reviews of prophylactic administration of oxytocics in the 3rd stage of labor showed a decrease in the rate of postpartum hemorrhage from 18% to 5%; the need for therapeutic oxytocics is reduced from 30% to 6%; and the length of the 3rd stage reduced from 15 minutes to 5 minutes.) • A double-blind randomized trial of oral misoprostol & IM syntometrine is required	
El-Refaey H, O'Brien P, Morafa W, et al. Misoprostol for the third stage of labor. Lancet 1996 [letter]; 347(9010): 1257. (I) *Affiliation(s) of the researchers:* Dept of OB-GYN University College Hospital London, UK **Evidence rating: III**	*Design:* Observational *Methods*: • Inclusion: –Women in labor with mean age of 27.7 years • Assessment: –Primary end point: Incidence of postpartum hemorrhage (estimated blood loss of 500 mL or more) –Other end points such as side effects (vomiting, diarrhea, shivering, hypertension) –Cointervention: Syntometrine, if there was clinical indication *Goal*: To investigate whether active management of the 3rd stage of labor can be carried out	*Dose & Duration:* • Misoprostol 600 mcg (three tablets) orally immediately after delivery and clamping and cutting of the cord N = 100	*Results*: • Outcome #1: –An estimated blood loss of 500 mL occurred in 3 patients –Blood loss of > 500 mL occurred in 3 patients –No patient had blood loss of 1000 mL or more –Median blood loss for the study population was 200 mL • Other outcomes: –Mild gastrointestinal side effects were infrequent with loose stools reported by 3 patients; shivering occurred in 68 patients, and a mean reduction of 1 mm Hg in systolic and 1.2 mm Hg in diastolic BP was observed w/c were statistically nonsignificant –Manual removal of the placenta was required by 2 patients –Blood transfusion was required by	*Limitations/Comments:* • This brief report (preliminary observation) is a letter to the editor and does not include description of detailed methodology. Although this study showed less postpartum blood loss, reliability of data is in question because of incomplete nature of evidence • Shivering was noted in 68 patients

	safely with misoprostol		1 patient w/ broad ligament hematoma that was managed conservatively –Syntometrine was used in 6 patients –Mean duration of labor was 5 minutes *Conclusions*: • Misoprostol can be used in the management of the third stage of labor. The frequency of postpartum hemorrhage (6%), need for further therapeutic oxytocics (6%), and the length of the 3rd stage of labor (median 5 minutes) in this study are considerably lower than those reported when the 3rd stage is managed physiologically and similar to results with the use of syntometrine	
Walley RL, Wilson JB, Crane JMG, et al. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. Br J Obstet Gynaecol 2000; 107: 1111-5. (J) *Sponsors:* MaterCare Intl, Canadian Intl Development Agency *Affiliation(s) of the researchers:*	*Design:* Randomized, double-blind, placebo-controlled trial *Methods:* • Inclusion: -Women in labor • Exclusion: -grand multiparity (> gravida 5) -multiple gestation -gestation < 32 weeks -gestational hypertension with the HEELP (hemolysis, elevated liver enzymes, low platelets) syndrome -hydramnios, previous PPH -cesarean delivery -coagulation abnormalities	*Dose/Duration:* With delivery of anterior shoulder • Misoprostol 400 mcg in powdered form (in 50 mL of water) orally and 1 mL normal saline (placebo) IM (n = 203) • Powdered lactose placebo (in 50 mL of water) and 1 mL oxytocin 10 IU IM (n = 198) N = 401 women enrolled, of whom 392 had pre- and post-	*Results:* • Primary outcome: -No significant difference between the 2 groups in drop in hemoglobin concentrations (from a mean 11.1 [SD 1.3] to 10.5 [1.3] in the misoprostol group and 10.9 [1.2] to 10.4 [1.3] in the oxytocin group, RR (95% CI) was 1.5% [–1.0 to 4.0%], $P = 0.25$). Other measures of postpartum hemoglobin concentrations were not different between the 2 groups • Secondary outcomes include estimated blood loss, length of the 3rd stage, and use of additional oxytocics were similar between the groups • Shivering occurred more frequently	*Limitations/Comments:* • Demographic variables were similar in both groups • Outstanding follow-up • Equal treatment for both groups with the exception of the intervention; active management of 3rd stage with controlled cord traction until delivery of placenta with IV oxytocin when necessary for blood loss > 1000 mL • Authors stated the following reasons why they chose change in hemoglobin concentration as primary outcome: First, the incidence of PPH is such that a very large study would be required to evaluate a significant change in PPH as the primary outcome and such a study would need to be multicentered and may require undue time to completion; second, excessive blood

Dept of OB-GYN and Nursing Memorial University of Newfoundland, Canada; University Dept of OB-GYN University of Ghana Medical School, Accra, Ghana *Study protocol approved by:* Human Investigation Committee of the Faculty of Medicine, Memorial University of Newfoundland and Korle Bu Teaching Hospital **Evidence rating: I**	-precipitous labor (< 3 hours) -chorioamnionitis -oxytocin induction or augmentation of labor -known hypersensitivity to prostaglandins -hemoglobin concentration of < 8 grams/dL • Assessments: -Primary end point: A drop in hemoglobin concentration. A chart review of 50 women found a standard deviation in the drop of hemoglobin concentration of 0.3 grams/dL. A difference of drop >0.1 grams/dL between the misoprostol and oxytocin group was considered clinically important. Hemoglobin determination was done pre- and post-delivery (12 hours [± 4 hours]) -Secondary end points: Estimated blood loss, length of the 3rd stage, use of additional oxytocics, side effects including nausea, vomiting, diarrhea, shivering, and elevated temperature (within 1 hour of delivery) -Other intervention: IV oxytocin as standard hospital management when estimated blood loss was > 1000 mL -Sample size was calculated using a two tailed $\alpha = 0.05$ and $\beta = 0.10$, finding 191 women required per group Statistic tests used: Parametric and nonparametric in analyzing	delivery hemoglobin results (200 in the misoprostol group and 192 in the oxytocin group)	in women who received misoprostol and this was statistically significant (22.2% in the misoprostol group vs 5.7% in the oxytocin group, RR 4.73 [95% CI 2.31–9.68], $P = < 0.0001$); temperature ≥ 37.5 °C was present in the misoprostol group but was not statistically significant (7.4% vs 3.3% in the misoprostol and oxytocin groups, respectively, RR 2.35 [95% CI 0.84–6.58], $P = 0.11$) • There were no differences between the 2 groups with regard to other side effects such as nausea,vomiting, and diarrhea *Conclusion* : • Oral misoprostol appears to be as effective as intramuscular oxytocin in minimizing blood loss in low-risk women in the 3rd stage of labor; it has great potential for use in the 3rd stage of labor in developing countries	loss may be difficult to define clinically, especially if it is based on subjective observations; blood loss based on clinical assessment often is underestimated. Hemoglobin or hematocrit determination is more objective measure. Authors recognized that the objective laboratory measurement is serving only as proxy for the clinical outcome of excessive blood loss • Mild side effects; there was a trend toward elevated temperature postpartum in the misoprostol group but this was not statistically significant; shivering probably was related to a prostaglandin E_1 effect on central thermoregulatory centers

	the data on an intent-to-treat basis; primary outcome measure was assessed by Student's *t* test and significant at $P < 0.05$; secondary outcomes was at $P < 0.01$ to account for multiple testing (Bonferroni correction) *Goal:* • To compare in a blinded fashion the effectiveness of misoprostol 400 mcg administered orally with oxytocin 19 IU administered intramuscularly, routinely in the 3rd stage of labor to minimize blood loss			
Abdel-Aleem H, El-Nashar I, Abdel-Aleem A. Management of severe postpartum hemorrhage with misoprostol. Intl J Gynecol Obstet 2001; 72: 75-6. (K) *Sponsor(s):* None *Affiliation(s) of the researchers:* Dept of OB-GYN, Assiut University, Egypt *Study protocol approved by:* Ethical committee of Dept of OB-GYN, Assiut University **Evidence rating: III**	*Design:* Descriptive prospective study *Methods:* • Inclusion: Women with severe postpartum hemorrhage not responding to oxytocin, methylergometrine, and enzaprost (a prostaglandin $F_{2\alpha}$); mean age was 28.2 years, mean parity was 3.8; fourteen had hospital delivery, 4 had community delivery of whom 2 had acute inversion of the uterus in addition to atonic postpartum hemorrhage; thirteen delivered vaginally, 5 by CS; 12 showed risk factors for postpartum hemorrhage • Assessment: -Outcome: Cessation of bleeding	*Dose/Duration:* • Misoprostol 1000 mcg rectally for continuous bleeding given a few minutes after other uterotonics were administered (n =14); 600 mcg (n = 4) N = 18	*Results:* • 16 patients (88.2%) responded promptly to misoprostol; bleeding stopped within 30 seconds to 3 minutes (mean = 1.4 minutes) • 2 patients failed to respond and were subjected to subtotal hysterectomy *Conclusion:* • Rectal misoprostol is an effective line of treatment in cases of atonic postpartum hemorrhage refractory to other uterotonic drugs, particularly where other prostaglandins are not available or affordable	*Limitations/Comments* • Authors stated that on the basis of their data, it is difficult to exclude with certainty the possibility that cessation of bleeding was due to the previously administered oxytocic or to the combination of oxytocic and misoprostol, rather than to misoprostol alone • Authors agreed with other investigators' opinions (Ramsey et al.) on the importance of characterizing the absorption and pharmacokinetics of transrectal misoprostol and the need for a properly designed randomized trial • Small sample • Uncontrolled study and therefore, would be difficult to conclude that the resolution of postpartum bleeding was due to misoprostol

	-Other interventions: • Oxytocin IV (bolus 10 to 20 IU and infusion 20 IU in 500 mL saline) and methylergometrine up to 0.4 mg IV as first aid measures in all patients • enzaprost was used in cases unresponsive to the previous uterotonics on six patients; however, enzaprost was not available for the rest of the patients • Surgery (ligation of the uterine and/or internal iliac arteries or hysterectomy) as a last resort for cases not responding to rectal misoprostol -All patients were managed according to hospital protocol which included resuscitation of the patient, exclusion of traumatic bleeding, and massage of the uterus/bimanual compression *Goal:* • To explore the use of rectal misoprostol in the treatment of severe cases of atonic postpartum hemorrhage not responding to oxytocin and methergine			
El-Refaey H, Nooh R, O'Brien P, et al. The	*Design:* Randomized, controlled, open trial	*Dose/Duration:* • Misoprostol 500	*Results:* • Primary end point:	*Limitations/Comments:* • Baseline characteristics were similar in both

misoprostol third stage of labour study: a randomised controlled comparison between orally administered misoprostol and standard management. Br J Obstet Gynaecol 2000; 107: 1104-10. (L) *Sponsor(s):* None *Affiliation(s) of the researchers:* Dept of OB-GYN, University College Hospital, London School of Hygiene and Tropical Medicine, London, UK *Study protocol approved by:* Local research ethics committee **Evidence rating: I**	*Methods:* • Inclusion: -vaginal delivery • Exclusion: -cesarean section -history of severe asthma (requiring hospital admission and steroids) -water birth • Assessments: -Primary end point: Postpartum blood loss (PPH defined as estimated blood loss ≥ 500 mL, and severe PPH as estimated blood loss > 1000 mL -Secondary end points: Incidence and severity of side effects (nausea, vomiting, abdominal pain, diarrhea, hot flushes, headache, tiredness, dizziness, shivering) -Other end points were: Need for blood transfusion, use of other oxytocic drugs, length of the 3rd stage of labor, manual removal of the placenta, hemoglobin concentration and hematocrit pre- and post delivery, management of the umbilical cord, blood pressure, temperature, vomiting, analgesia for 'after pains' -This study was based on a sample size of 1000 women allowing investigators to detect a difference in the incidence of PPH (from 5 to 10%) with a power of 80% at a two-sided significance level of 5% -Statistic tests used : chi-square	mcg orally immediately after birth of the baby and clamping and division of the umbilical cord (n = 501) • Other oxytocics (either syntometrine IM, except in women with pregnancy-induced hypertension or with cardiac disease who were given syntocinon 10 Units IM instead, or ergometrine 500 mg IM for women at high risk of atonic PPH) given after the delivery of the anterior shoulder (n = 499) N = 1000	Incidence of PPH was 12% in the misoprostol group, compared with 11% with other oxytocics Incidence of severe PPH (blood loss > 1000 mL) was 2% in both groups • Secondary end points: Nausea, headache, dizziness, and tiredness were reported more often in the other oxytocics group; there were no differences in the incidence of vomiting, abdominal pain, diarrhea, and hot flushes; shivering occurred more often in the misoprostol group (72%) vs other oxytocics group (37%) • Other end points: -Manual removal of the placenta, need for blood transfusion, and length of the 3rd stage of labor were similar in both groups -Need for further oxytocics was slightly higher in the misoprostol group (14 vs 10%) but this was not statistically significant ($P = 0.08$) -Hemoglobin and hematocrit levels and blood pressure were similar in both groups -Increase in temperature was significantly greater in the misoprostol group (mean 0.59 vs 0.25; $P < 0.001$) -Management of the umbilical cord and need for analgesia for 'after pains' were similar in both groups *Conclusion:* • Oral misoprostol for the prevention	groups • Authors acknowledged the trial was not large enough to establish equivalence between misoprostol and standard oxytocics in the prevention of PPH. They estimated that the incidence of PPH would be 5% with standard oxytocics and that an increase to 6% with misoprostol would be unacceptable. This would require more than 16,000 participants in a randomized trial ($\alpha = 0.05$; $1-\beta = 0.80$). The incidence of severe PPH (which may be life-threatening) with standard oxytocics in this trial was 2% and authors considered an increase in the incidence to 2.5% as unacceptable ($\alpha = 0.05$; $1-\beta = 0.80$). Authors claimed this trial was large enough to exclude doubling of all PPH and a tripling of severe PPH with misoprostol. A larger trial or the results of smaller trials combined is required to establish equivalence of misoprostol with standard oxytocics • Good follow-up • Blood loss was estimated subjectively by the midwife although objective determinations (hemoglobin and hematocrit) were also done and values were similar in both groups • Nonblind, which might have influenced the midwives in their ascertainment of PPH, as suggested by the high rate of PPH in women receiving standard oxytocics (11%), which is more than double the rate used to estimate number of women required for the trial • Response bias. There were more questionnaires on side effects returned by women who received misoprostol; authors argue it is unlikely that this bias could account for the sizeable differences in the incidence of some of the side effects, such as headache and shivering

	test, Student's *t* test, Mann-Whitney *U* test *Goals:* • To ascertain whether 500 mcg of oral misoprostol could replace the standard oxytocic drugs without an increase in the incidence of postpartum hemorrhage • To assess the incidence and severity of the side effects of both drug regimens		of postpartum hemorrhage was comparable to standard oxytocics. Many side effects were less common with misoprostol but shivering and pyrexia were more common	• Shivering and an increase in temperature occurred more in the misoprostol group and there was a clear association between these side effects
Cook CM, Spurrett B, Murray H. 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: 4: 414-19. (M) *Sponsor(s):* None *Affiliation(s) of the researchers:* Dept of OB-GYN, University of Sydney at Nepean Hospital Penrith, New South Wales *Study protocol approved by:* Hospital's Ethics Committee (Nepean) **Evidence rating: I**	*Design:* Multicenter, blocked, randomized, controlled, open trial *Methods:* • Inclusion: -vaginal delivery, with or without the need for episiotomy • Exclusion: -cesarean section -history of severe asthma -known blood coagulation disorders -heart disease -severe renal disease -epilepsy -hypertension significant enough to contraindicate the use of ergometrine • Assessments: -Primary end points: Postpartum blood loss, need for uterine massage, need for additional oxytocics (infusion of synthetic oxytocin or IM or IV ergometrine/oxytocin) in the	*Dose/Duration:* • Misoprostol 400 mcg (2 tablets) orally immediately after delivery of the fetal anterior shoulder (n = 455) • Other oxytocics, either 1 ampul of syntometrine (0.5 mg ergometrine + 5 Units of oxytocin) or synthetic oxytocin (10 Units) IM after delivery of the anterior fetal shoulder (n = 475) N = 1024 recruited, of whom 94 were excluded prior to randomization, 930 randomized, 65 excluded after randomization and prior to treatment	*Results:* • Primary outcomes: -Postpartum blood loss: significantly greater overall in the misoprostol group than in the standard oxytocic group (mean ± SD is 279 ± 14.6 in the misoprostol group vs 209 ± 9.0; $P = < 0.001$) -Need for uterine massage was greater in the misoprostol group (37% in the misoprostol group vs 17%; RR 2.18 [95% CI 1.71–2.78]) -Need for additional oxytocics was greater in the misoprostol group (22% in the misoprostol group vs 8%; RR 2.89 [95% CI 2.00–4.18]) -Need for blood transfusion was similar in both groups • Secondary outcomes: -Temperature was increased in the misoprostol group (15% in the misoprostol group vs 10%) -There was no difference in blood pressure between the 2 groups -Hemoglobin level was lower in the misoprostol group (mean ± SD is	*Limitations/Comments:* • Baseline variables were similar in both groups • Method to determine blood loss was well described; blood loss was determined both subjectively and objectively • Good follow-up • One center had women with high antepartum levels of anemia and women with hemoglobin of < 90 grams per liter were routinely treated with iron up to and including during labor; this potentially had an impact on the postpartum hemoglobin in this center; however, authors stated that its effect on outcome in the study was minimized through the block randomization • Authors chose not to blind the study because the use of placebo treatment would have increased the cost of the trial and also because recruitment would have been more difficult as women would have had to receive 2 modalities of treatment (IM injection and oral tablets); also there was an ethical concern regarding the use of a drug in a research context that had not been investigated properly for a condition with a

	3rd stage of labor, need for blood transfusion -Secondary end points: Temperature, blood pressure, hemoglobin pre/post delivery, side effects such as vomiting, diarrhea, and shivering -Blood loss was determined by combining the 'estimated' and 'measured' amounts following the standard clinical practice at each center (use of calibrated measuring jug, weighing of blood-stained undersheets and pads and subtracting their dry weight) -Power calculations based on a PPH rate (≥ 500 mL) of 8% in the current treatment ranging up to 12% with the test treatment indicated 1862 women were required for a power of 80% with a confidence level of 95% -Statistic tests used : chi-square test, Student's *t* test *Goals:* • To compare efficacy of oral misoprostol with traditional uterotonic agents used prophylactically in the 3rd stage of labor	due to need for cesarean section and development of hypertension, 865 received treatment of whom 2 were excluded in the analysis as no record was made of the primary outcome of blood loss, resulting in 863 who completed the study	108 ± 16 in the misoprostol group vs 111 ± 17; *P* = < 0.01) and the change from pre- to post-delivery was also greater in the misoprostol group (mean ± SD is –69 ± 17.5 in the misoprostol group vs –4.0 ± 16.7; *P* = < 0.015) -There was no difference in side effects such as vomiting and diarrhea; however, shivering occurred more in the misoprostol group (19 vs 7%) *Conclusion:* • Misoprostol was not as effective as the conventional treatments and its oral use for PPH could not be recommended in doses of 400 mcg administered orally after delivery of the fetus	potential for life-threatening blood loss; the need for an earlier interim analysis indicated by concerns of an apparently higher PPH rate in the misoprostol group vindicated this decision • Conclusion was drawn by the authors based on the fact that the PPH rate in women receiving misoprostol was 15%, which is more than double the 6% rate for women receiving standard injectable oxytocics; the 6% rate was lower than the 8% in their power calculations, which did not take into account the low PPH in one center • All cases of shivering were reported to be mild to moderate and required minimal treatment • Study was immediately stopped following the adverse findings of the interim analysis
Ng PS, Chan ASM, Sin WK, et al. A multicenter randomized controlled trial of oral misoprostol and i.m. syntometrine in the management of the third stage of labor. Hum Reprod 2001; 16(1): 31-5.	*Design:* Prospective, multicenter, randomized, controlled, single-blind trial *Methods:* • Inclusion:	*Dose/Duration:* • Misoprostol 600 mcg (three 200 mcg tablets) orally immediately after delivery of the baby (n = 1026)	*Results:* • Primary outcome: -Amount of blood loss during delivery and occurrence of PPH: no significant difference (≥ 500 mL is 5.8% in misoprostol group and 4.3% in syntometrine group, RR 1.37	*Limitations/Comments:* • Baseline variables were similar in both groups • Excellent follow-up • Not double-blind and therefore potential bias in assessment of blood loss and the use of additional oxytocics could not be

(N) *Sponsor(s):* None *Affiliation(s) of the researchers:* Dept of OB-GYN, The Chinese University of Hong Kong Prince of Wales Hospital, Shatin, New Territories, Hong Kong *Study protocol approved by:* Clinical Research Ethics Committee of the Faculty of Medicine of the Chinese University of Hong Kong **Evidence rating: I**	-singleton pregnancy -vaginal delivery • Exclusion: -pre-eclampsia -cardiac disease -asthma -presence of conditions requiring prophylactic oxytocin infusion after delivery such as grand multiparity (parity ≥ 4) or presence of uterine fibroids; however, those who had oxytocin infusion during the first stage were included -presence of any other contraindications for the use of misoprostol or syntometrine • Assessments: -Primary end point: Amount of blood loss during delivery and occurrence of PPH, defined as blood loss of 500 mL or more -Secondary end points: Blood pressure, pulse, temperature, duration of 3rd stage, incidence of prolonged 3rd stage (longer than 30 minutes), need for manual removal of the placenta, use of additional IM syntometrine, side effects including nausea, vomiting, headache, chest pain, fever, shivering -Blood loss was assessed by clinical estimation and hemoglobin determination pre- and post-delivery -3rd stage was managed by awaiting signs of placental separation and placenta	• Syntometrine (0.5 mg ergometrine + 5 Units of oxytocin) 1 mL IM at delivery of anterior shoulder of the baby (n = 1032) N = 2058 recruited and randomized	[95% CI 0.94 – 2.00]; ≥ 1000 mL is 0.5% in misoprostol group and 0.4% in syntometrine group, RR 1.26 [95% CI 0.34 – 4.67]) -There was no difference in the mean fall in hemoglobin concentration after delivery (decreased by 10 to 20% in both groups) • Secondary outcomes: -Blood pressure: Significantly lower in the misoprostol group than in syntometrine group 30 min and 60 min post delivery (29.2% in the misoprostol group vs 47.5%, RR 0.62 [95% CI 0.39 – 0.96] $P < 0.05$ and 2.1% in the misoprostol group vs 3.9%, RR 0.55 [95%CI 0.33 – 0.92] $P < 0.05$) -Temperature (≥ 38 °C): Significantly higher in the misoprostol group than in syntometrine group (8.5% in the misoprostol group vs 1.3%, RR 6.73 [95% CI 3.78 – 11.98] $P < 0.05$) -There was no significant difference in the incidence of delayed hemorrhage within the first 24 hours. Incidence of prolonged 3rd stage (longer than 30 minutes) and incidence of blood transfusion were similar -Need for manual removal of the placenta was significantly lower in the misoprostol group (0.4% in the misoprostol group vs 1.4%, RR 0.29 [95% CI 0.09 – 0.87] $P < 0.05$) -Need for additional oxytocic was significantly higher in the misoprostol group (22.6% in the misoprostol group vs 14%, RR 1.62	eliminated; however, this was minimized in all cases by having the randomization, preparation, and administration of the medication carried out by independent nursing staff not involved in the management of the patient except for the drug administration; authors stated that the consistent results among the 3 participating hospitals and a similar overall result compared with that reported in the literature suggested that the results were unlikely to be due to bias • Amount of blood loss was assessed subjectively (clinical estimate) and objectively (hemoglobin concentration). Authors stated that clinical estimation of blood loss has been shown to underestimate the true blood loss. They acknowledged that this is how PPH is diagnosed and managed in actual day-to-day clinical practice. Clinical estimation is also one of the main methods used in some of the large randomized controlled trials regarding management of the 3rd stage of labor. Use of other clinical parameters such as BP and pulse pressure is not reliable. Hemoglobin determination pre- and post delivery is a more objective method and also clinically important and relevant in that it helps in the decision for the need for blood transfusion or iron supplementation. (It has already been suggested that PPH be defined as a peripartum fall in hematocrit of at least 10% or hemorrhage requiring blood transfusion [ACOG 1989].) In this study, mean blood loss for both groups was only 250 to 300 mL and the incidence of PPH was low, yet 15% of patients still had a 10 to 20% drop in hemoglobin concentration and 18% dropped by > 20% in both groups. Authors suggest future studies on the efficacy of oxytocics on PPH be based on peripartum hemoglobin

	delivered by controlled cord traction. Irrespective of the allocation, an additional dose of syntometrine was given if the uterus was not well contracted or if there was excessive vaginal bleeding as assessed by the midwife or doctor attending the delivery -Sample size was based on 1000 subjects per study group in order to detect a 2% difference in the incidence of PPH with an 80% power at α = 0.05 (incidence of PPH is 4% which is similar among the 3 hospitals; incidence of PPH associated with oral misoprostol was reported to be 6%) -Statistic tests used : chi-square test, Student's *t* test *Goals:* • To compare the efficacy and safety of oral misoprostol with IM syntometrine in the management of the 3rd stage of labor		[95% CI 1.34 – 1.96] $P < 0.05$) - The incidence of side effects (nausea, vomiting, headache, chest pain) was low and similar in both groups; shivering was significantly higher in the misoprostol group (30.2% in the misoprostol group vs 9.9%, RR 3.06 [95% CI 2.49 – 3.76] $P < 0.05$) *Conclusion:* • Misoprostol may be used as an alternative to IM syntometrine in the management of the third stage of labor, especially in situations in which syntometrine is contraindicated or where storage and parenteral administration of oxytocics is a potential problem	change rather than on clinical estimate of blood loss

KEY:

> = greater than
< = less than
≥ = greater than or equal to
PPH = postpartum hemorrhage
BP = blood pressure
DIC = disseminated intravascular coagulation
IM = intramuscular
IU = international units
IV =intravenous
L = liter

mcg = microgram
mL = milliliter
dL = deciliter
CS = cesarean section
min = minutes
Intl = international