International Journal of Gynecology and Obstetrics (2006) **92**, 10—18

International Journal of
GYNECOLOGY
& OBSTETRICS

www.elsevier.com/locate/ijgo

REVIEW ARTICLE

# Misoprostol in preventing postpartum hemorrhage: A meta-analysis

**C. Langenbach** *

*Epidemiology and Biostatistics, School of Public Health, University of California at Berkeley, Berkeley, CA, USA*

Received 25 May 2005; received in revised form 3 October 2005; accepted 4 October 2005

**KEYWORDS**
Misoprostol;
Postpartum hemorrhage;
Prevention;
Third stage of labor;
Resource-poor;
Meta-analysis

**Abstract**

*Objective:* To assess misoprostol's ability to prevent postpartum hemorrhage (PPH) where no alternatives exist. Comparison to oxytocics demonstrates how similarly misoprostol achieves a level of effectiveness—obtainable only in hospitals—in remote locations around the world. *Method:* Using the Mantel—Haenszel fixed-effects model and the DerSirmonian and Laird random-effects model, summary statistics indicated that misoprostol's excess risk of PPH was only 4% when compared to oxytocics. *Result:* This risk difference was well within the range of expected results for all uterotonic agents and does not warrant branding misoprostol as an inferior drug. *Conclusion:* Conventional uterotonic drugs should not be used to set the lowest-accepted level of effectiveness in settings where they are entirely unsuitable. Continuing to weigh the benefits of one effective drug against another only delays the distribution of misoprostol in countries where it is the only feasible choice and must be measured against no treatment at all.


## 1. Introduction

The World Health Organization (WHO) estimated that 529,000 women died from obstetric causes in 2000 [1]. Postpartum hemorrhage (PPH), which afflicts approximately 14 million women annually, caused a quarter of these deaths [2]. Most of these deaths occur in the resource-poor countries of Africa and Asia, particularly in rural areas. Not surprisingly, records of maternal mortality are poor or non-existent where it most often occurs, which implies that even these sobering estimates are greatly underestimated. Indeed, data in remote regions are so scarce and the methods of collection so varied that the WHO warns against the formulation of confidence intervals around the available estimates.

* Fax: +1 757 257 8668.
*E-mail address:* colangenbach@yahoo.com.

0020-7292/$ - see front matter 
doi:10.1016/j.ijgo.2005.10.001

PPH is defined as blood loss of 500 mL or more within 24 h of delivery, but, this quantity is extremely difficult to identify outside of a controlled trial setting. Even trained physicians are reported to typically underestimate blood loss by about half [3]. While there are a few known risk factors, PPH occurrence is random, making it impossible to predict in both low and high risk populations. Furthermore, blood loss can be rapid. In developing countries, where nearly half the women deliver without the aid of a skilled birth attendant [4], there is simply not enough time to seek treatment for PPH, and in most cases none is to be had. The only way to help women without access to trained attendants is through preventative measures.

The most successful method for reducing PPH, Active Management of the Third Stage of Labor (AMTSL), requires prophylactic uterotonic drugs which are unsuitable for use in the remote locations where prevention is most needed. Nonetheless, this nearly universal method has set the precedent for a standard of care unavailable in developing countries. The uterotonic drugs used in AMTSL trials include oxytocics: oxytocin (Syntocinon®, Alliance Pharmaceuticals, Chippenham, UK or Pitocin®, King Pharmaceuticals, Bristol, TN), ergometrine malate (Methergine®, Novartis Pharmaceuticals, East Hanover, NJ) and combinations of the two (Syntometrine®, Alliance Pharmaceuticals, Chippenham, UK) all of which must be administered by injection, which not only requires a sterile needle, syringe and accurate dosing, but someone to administer it. In addition, oxytocics are light-sensitive and require refrigeration to remain pharmacologically active, which limits their use to areas with refrigeration and reliable sources of energy and increases their cost.

Misoprostol (Cytotec®, Pfizer, New York, NY), a prostaglandin E1 analog, registered for the prevention and treatment of gastric ulcers, is well-known for its off-label use as a uterotonic agent. It is inexpensive (one 200 g tablet is approximately US$1 [5]), comes in tablets which can be administered orally, rectally or sublingually, and does not require refrigeration, dark storage or administration by an attendant. However, many studies have found it to be slightly less effective than oxytocics in controlled clinical settings. This circumstance has had the result of branding misoprostol as an inferior drug [6–8], despite repeated praise for the feasibility of its use in resource-poor settings [9–14].

The objective of this review is to analyze all existing trial data in order to reframe the current debate surrounding the use of misoprostol in developing countries, where it is most needed. Misoprostol's value as a prophylactic uterotonic drug lies in its ability to prevent PPH and reduce maternal mortality where no alternatives exist. Comparison to oxytocics should serve only to demonstrate how similarly misoprostol achieves a level of effectiveness—obtainable only in hospitals—in remote locations around the world. To date, this is the largest meta-analysis ever conducted on the efficacy of misoprostol for the prevention of PPH.

## 2. Search criteria

A literature search was conducted for all randomized control trials (RCT) which tested misoprostol's efficacy in preventing PPH. The electronic database PubMed (National Library of Medicine, Bethesda, MD) was searched for published articles, along with the Cochrane CENTRAL database and the Population Council's bibliographic website (www.misoprostol.org). The medical subject heading terms used were: *misoprostol* and *postpartum hemorrhage*, coupled with: *prevention* and *active management*. References from published articles were pursued and primary authors contacted in order to uncover any unpublished RCTs. The search was conducted irrespective of language of publication or geographic region. All studies matching the inclusion criteria and published before May 2005 were included in the analysis.

## 3. Inclusion and exclusion criteria

All RCTs which assessed misoprostol efficacy in preventing PPH during third trimester vaginal births were reviewed for inclusion in this analysis. All studies, irrespective of dose, route of administration (with the exception of vaginal administration due to its infeasibility after a vaginal birth) or type of control substance, were included. Three outcomes were selected before analysis began: blood loss $\geq$500 mL, blood loss $\geq$1000 mL and the need for additional uterotonic agents. Because the side effects of all uterotonic drugs have been well documented [7,11,14,15] and are mild in comparison to the life threatening alternative of PPH, side effects were not considered a relevant outcome for analysis.

A total of 31 relevant studies were identified, but only 22 were selected for inclusion in the meta-analysis. Six studies were excluded due to misoprostol being administered vaginally [16] or after

**Table 1** Studies included in meta-analysis

| Primary author | Year | Location | Validity test score | Misoprostol dose and route | Control agent | No. of participants included | Primary outcomes reported | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Blood loss >500 mL | Blood loss >1000 mL | Need for additional uterotonics |
| Amant | 1999 | Belgium | 7 | Oral 600 μg | Methylergometrine 200 μg | 200 | × | × | × |
| Bamigboye | 1998 | South Africa | 5 | Rectal 400 μg | Placebo | 546 | | × | × |
| Bamigboye | 1998 | South Africa | 5 | Rectal 400 μg | Oxytocin and Ergometrine 2.5 IU | 491 | × | | × |
| Benchimol | 2001 | France | 6 | Oral 400 μg | Placebo<br>Oxytocin 2.5 IU | 602 | × | × | |
| Bugalho | 2001 | Mozambique | 9 | Rectal 400 μg | Oxytocin 10 units | 663 | | | × |
| Caliskan | 2003[a] | Turkey | 8 | Oral 600 μg | Oxytocin 10 units | 772 | × | × | × |
| Caliskan | 2002[a] | Turkey | 8 | Rectal 400 μg | Oxytocin 10 units | 803 | × | × | × |
| Cook | 1999 | Multi-center | 6 | Oral 400 μg | Oxytocin and Ergometrine or Oxytocin 10 IU | 863 | × | × | × |
| El-Refaey | 2000 | England | 6 | Oral 500 μg | Oxytocin 5 units and Ergometrine .5 mg or Oxytocin 10 units or Ergometrine 500 mg | 1000 | × | × | × |
| Gerstenfeld | 2001 | USA | 7 | Rectal 400 μg | Oxytocin 20 units | 325 | × | × | × |
| Gulmezoglu | 2001 | Multi-center | 7 | Oral 600 μg | Oxytocin 10 units | 18530 | × | × | × |
| Hofmeyr | 2001 | South Africa | 5 | Oral 600 μg | Placebo | 600 | | × | × |
| Hofmeyr | 1998 | South Africa | 8 | Oral 400 μg | Placebo | 500 | | × | × |
| Karkanis | 2002[a] | Canada | 6 | Rectal 400 μg | Oxytocin 10 units | 223 | | | × |
| Kundodyiwa | 2001 | Zimbabwe | 8 | Oral 400 μg | Oxytocin 10 units | 499 | × | × | × |
| Lam | 2004[a] | Hong Kong | 8 | Sublingual 600 μg | Oxytocin and Ergometrine 1 mL | 60 | | | × |
| Ng | 2001 | Hong Kong | 7 | Oral 600 μg | Oxytocin and Ergometrine 1 mL | 2058 | × | × | × |
| Oboro | 2003 | Nigeria | 8 | Oral 400 μg | Oxytocin 10 units | 496 | × | × | × |
| Ray | 2001[a] | India | 7 | Oral 400 μg | Methylergometrine 400 μg | 200 | | | × |
| Surbeck | 1999 | Switzerland | 7 | Oral 600 μg | Placebo | 65 | × | | × |
| Vilmala | 2004[a] | India | 7 | Sublingual 400 μg | Methylergometrine 400 μg | 120 | × | | × |
| Walley | 2000 | Ghana | 7 | Oral 400 μg | Oxytocin 10 units | 401 | × | | × |
| | | | | | | Total # of participants: 30017 | | | |

[a] New studies since last meta-analysis.

cesarean deliveries [17,18], or participants not being randomized [19—21]. Data from two other studies [22,23] were already included in other trials and could not be used independently. A final trial was eliminated because it reported a pilot study with no specified outcomes [24].

The studies which were included consisted of five placebo-controlled trials [25—29]and 26 drug equivalency trials [26,30—45] (Table 1). Three studies had multiple treatment arms [26,33,34], but in two instances [33,34], where three different oxytocics were tested, two arms were excluded from the meta-analysis since they could not be pooled and analyzed against the misoprostol arm simultaneously. For these two trials, the oxytocin arm was selected for the analysis since it is the most common prophylactic uterotonic drug. Seven of the included studies [33,34,39,41—44] were published subsequent to the only other meta-analysis on the efficacy of misoprostol, published in 2003 [11].

## 4. Statistical methods

Data were extracted from each study by the author, who was not blinded. A validity analysis was conducted to assess the methodological aspects of each trial. Studies were scored from 0 to 10, using a Jadad Scale [46], on the basis of:

1) A research objective appropriate for this analysis
2) Explicit inclusion and exclusion criteria
3) Exclusion of patients with labor augmentation or induction
4) Explanation of randomization method
5) Reported baseline similarity between groups
6) Masking of the attending physician
7) Measurement of blood loss
8) Reporting of all raw data
9) No losses to follow-up before each outcome level was assessed
10) Criteria for administration of additional uterotonic drugs.

Analysis of the data was performed using STATA 8.0 statistical software package (STATA Corporation, College Station, TX). The raw data published in each article were compiled in two-by-two tables. For only one study was it necessary to calculate cell counts from the reported percentages [26]. However, not every study reported data for each specified outcome. When no data were provided, the study was dropped from the model.

All doses and routes of administration were pooled for three reasons. First, patients within individual studies did not always receive the same dose or route of administration [35,36,38], making it impossible to distinguish between methods. Although the pooling of patients given oxytocics of varying administrations has been heavily criticized, especially in the WHO multi-center trial where intravenous and intramuscular administration was mixed [47—51], the resulting increased heterogeneity only strengthened this meta-analysis. As oral, rectal and sublingual routes are known to have slower up-take than intravenous or intramuscular injections, testing the three slowest methods against the two fastest biased the results against finding a similar relative risk. Therefore, the difference between misoprostol and oxytocics found in this analysis was actually greater than if misoprostol had only been administered by its fastest method (sublingual [15]) and oxytocics by their slowest (intramuscularly). Second, numerous studies on the efficacy of different oxytocics found no significantly statistical difference in blood loss between them [3,6]. And third, comparison of misoprostol to each of these individual drugs has already been well documented [7,11]; given these caveats, the purpose of this analysis was to compare misoprostol to the de facto standard of care (i.e. the collective efficacy of any drug approved for PPH prevention), rather than any specific drug.

For each outcome, a pooled risk ratio (RR) was calculated comparing misoprostol to oxytocics or placebo. The Mantel—Haenszel fixed-effects model was used instead of the inverse-variance method due to sparse outcome data. The test for heterogeneity was based on weights provided by the inverse-variance method. When heterogeneity was detected, the DerSirmonian and Laird random-effects model was used. Sensitivity analyses were conducted to investigate the influence of individual studies on the summary statistic by omitting each study in turn. Egger's weighted regression and Begg's rank correlation, where odds ratios were plotted against study size, were used for the detection of publication bias for each outcome.

## 5. Results

A total of 30,017 participants were included in the 22 studies in the analysis, approximately half of whom received misoprostol, with the remainder receiving either placebo or oxytocics (Table 2). However, in several instances when the studies reported a loss to follow-up for a specific outcome

**Table 2** Summary of outcomes

| Outcome measure | No. of participants | Risk ratio (RR) | Confidence intervals (CI) |
|---|---|---|---|
| 500 mL blood loss | | | |
| Misoprostol vs. oxytocics | $n=26\,870$ | 1.398 | (1.209, 1.617) |
| 1000 mL blood loss | | | |
| Misoprostol vs. placebo[a] | $n=2112$ | 0.85 | (0.63, 1.14) |
| Misoprostol vs. oxytocics | $n=25\,448$ | 1.36 | (1.19, 1.56) |
| Additional uterotonic drugs needed | | | |
| Misoprostol vs. placebo | $n=1706$ | 0.69 | (0.53, 0.90) |
| Misoprostol vs. oxytocics | $n=27\,566$ | 1.23 | (0.93, 1.63) |

[a] One included study only reported outcome measurements for 500 mL.

[25,27,37,38,45], the RR were calculated based on the available data, not the original sample size, to avoid the inherent presumption that those lost to follow-up were not cases. Due to the infrequent incidence of PPH, little difference was found between the odds ratios (OR) and RR for any comparison group.

Whereas five studies compared misoprostol and placebo use, only two reported blood loss >500 mL; thus, no analysis was conducted for this outcome level. Pooling the four studies reporting blood loss >1000 mL and one which only reported blood loss of >500 mL (Fig. 1) ($n=2112$), misoprostol's risk of PPH incidence over the risk of incidence with placebo was 0.85 (RR). Although misoprostol appeared to decrease the risk of PPH, this finding was not statistically significant (95% CI: 0.63, 1.14). One included study specifically stated that its objective was to measure side effects and was not intended to be an efficacy trial due to its lack of statistical power [27], which could help explain this lack of significance. Of interest, including that study with the three other trials reporting a need for additional uterotonic agents when comparing misoprostol to placebo ($n=1706$) produced a RR of 0.69 (95% CI: 0.53, 0.90). Thus, at this level misoprostol demonstrates clear and statistically significant reduction in the need for therapeutic drugs (Fig. 2).

The 15 studies ($n=26,870$) comparing misoprostol and oxytocics for blood loss >500 mL produced a RR of 1.4, which represents an excess risk (or risk difference) of 5% greater incidence of blood loss (Table 3). Despite slight heterogeneity across the studies, a comparison of the fixed effects estimate and the random effects estimate showed little difference between the two models. Although it initially appeared that the largest trial [38] dominated the pooled estimates, removing this study did not significantly alter the results (RR: 1.39; 95% CI: 1.219, 1.588). Further sensitivity analyses demonstrated that the heterogeneity present in these models was the effect of the 15 varied outcomes, not the effect of any single study.

The RR of 1.36 for the 11 studies reporting blood loss >1000 mL for misoprostol versus oxytocics ($n=25,448$) only demonstrated a 1% excess risk of severe PPH (Fig. 3). Removing the largest study

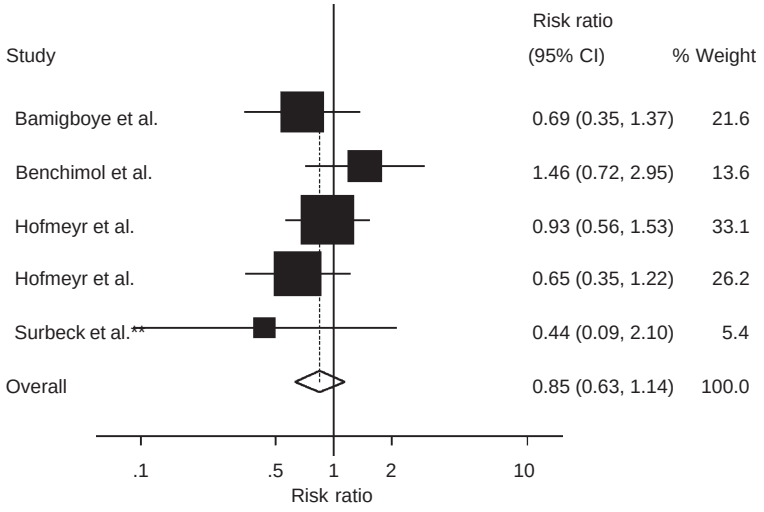


**Figure 1** All studies evaluating misoprostol vs. placebo with outcome blood loss >1000 mL. Mantel—Haenszel fixed-effects model. Heterogeneity chi-squared = 4.09 ($df=4$), $p=0.394$. I-squared (variation in RR attributable to heterogeneity) = 2.1%. Test of RR = 1: $z=1.08$, $p=0.280$. **Estimate reported for 500 mL or greater.

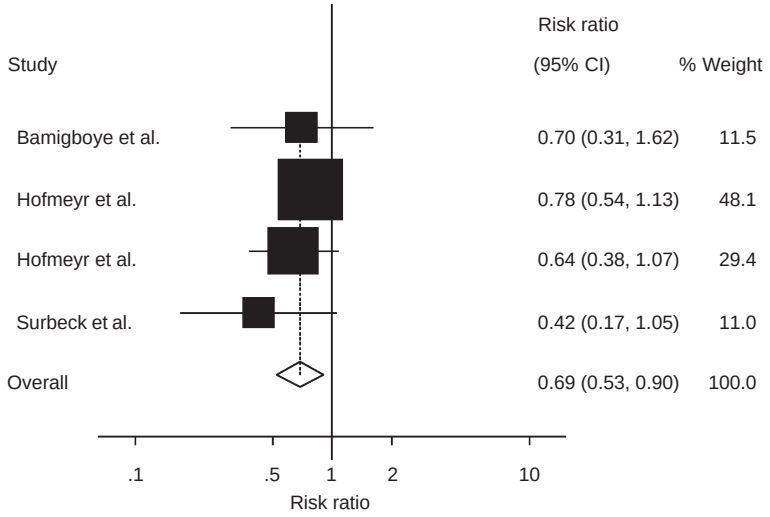


**Figure 2** All studies evaluating misoprostol vs. placebo with outcome of additional uterotonic agents. Mantel–Haenszel fixed-effects model. Heterogeneity chi-squared = 1.62 (*df* = 3), $p = 0.654$. I-squared (variation in RR attributable to heterogeneity) = 0.0%. Test of RR = 1: $z = 2.71$, $p = 0.007$.

from this model produced a statistically insignificant summary estimate (RR: 1.25; 95% CI: 0.94, 0.167), however this outcome was found to be consistent with the other studies' findings and was not excluded for this reason.

The random effects model of the 17 studies comparing the need for additional uterotonic drugs in patients who received prophylactic misoprostol to patients receiving oxytocics ($n = 27{,}566$) produced a summary RR of 1.23 (Fig. 4). The heterogeneity present in this model can, in large part, be explained by the subjective point at which additional uterotonic drugs were administered. Not only did many studies estimate (as opposed to measure) blood loss, but not one specified how many milliliters lost warranted further intervention. Because rectal administration of misoprostol requires a longer time to reach peak concentration levels than oral misoprostol [15], it is possible that many studies intervened with additional uterotonic agents before there was adequate time for the misoprostol to take effect. A sub-analysis of oral and sublingual misoprostol revealed no statistical difference between misoprostol and oxytocics (RR: 1.13, 95% CI: 0.81, 1.56). This observation strongly suggests that the rectal misoprostol had, in fact, not yet peaked when additional uterotonic agents were administered. Therefore, inclusion of rectally administered misoprostol only masked the equivalency of oral and sublingual misoprostol to oxy-

**Table 3** All studies evaluating misoprostol vs. oxytocics with outcome blood loss >500 mL

| Study | Mantel–Haenszel fixed effects | | | | DerSirmonian and Laird random effects | | | |
|---|---|---|---|---|---|---|---|---|
| | RR | [95% CI] | | % Weight | RR | [95% CI] | | % Weight |
| Amant | 0.571 | 0.173 | 1.891 | 0.45 | 0.571 | 0.173 | 1.891 | 1.40 |
| Bamigboye | 2.017 | 0.184 | 22.094 | 0.06 | 2.017 | 0.184 | 22.094 | 0.36 |
| Benchimol | 2.108 | 1.390 | 3.195 | 1.68 | 2.108 | 1.390 | 3.195 | 8.28 |
| Caliskan | 1.237 | 0.768 | 1.992 | 1.80 | 1.237 | 0.768 | 1.992 | 6.84 |
| Caliskan | 1.215 | 0.780 | 1.891 | 2.08 | 1.215 | 0.780 | 1.891 | 7.61 |
| Cook | 2.718 | 1.732 | 4.266 | 1.51 | 2.718 | 1.732 | 4.266 | 7.41 |
| El-Refaey | 1.103 | 0.785 | 1.548 | 3.59 | 1.103 | 0.785 | 1.548 | 10.72 |
| Gerstenfeld | 1.200 | 0.922 | 1.560 | 3.81 | 1.200 | 0.922 | 1.560 | 14.00 |
| Gulmezoglu | 1.439 | 1.347 | 1.537 | 79.71 | 1.439 | 1.347 | 1.537 | 24.49 |
| Kundodyiwa | 1.146 | 0.745 | 1.765 | 2.12 | 1.146 | 0.745 | 1.765 | 7.89 |
| Lam | 2.000 | 0.396 | 10.108 | 0.13 | 2.000 | 0.396 | 10.108 | 0.78 |
| Ng | 1.372 | 0.939 | 2.004 | 2.80 | 1.372 | 0.939 | 2.004 | 9.36 |
| Oboro | 3.024 | 0.317 | 28.876 | 0.06 | 3.024 | 0.317 | 28.876 | 0.41 |
| Vilmala | 5.000 | 0.245 | 102.002 | 0.03 | 5.000 | 0.245 | 102.002 | 0.23 |
| Walley | 0.194 | 0.009 | 4.017 | 0.16 | 0.194 | 0.009 | 4.017 | 0.23 |
| M–H pooled RR | 1.429 | 1.347 | 1.516 | 100.00 | 1.398 | 1.209 | 1.617 | 100.00 |

95% CI = 95% Confidence intervals.
M–H pooled RR = Mantel–Haenszel pooled risk ratios.

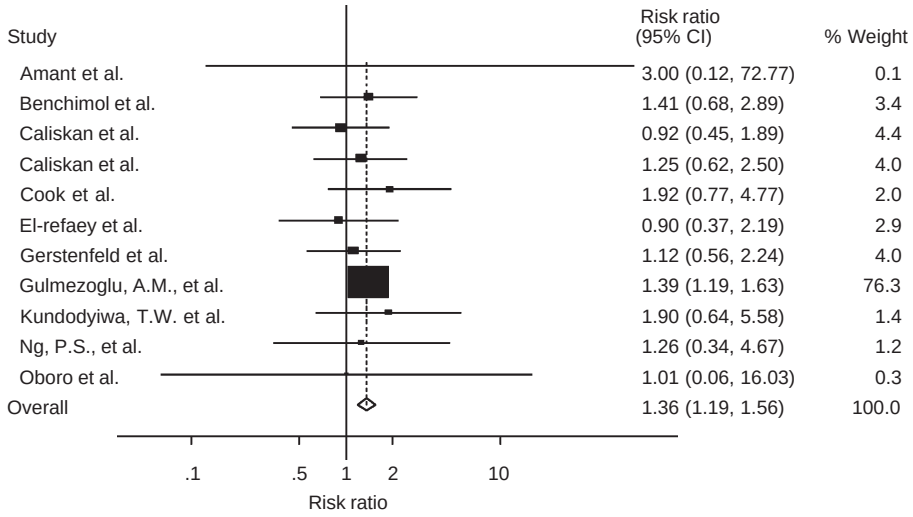


**Figure 3** All studies evaluating misoprostol vs. oxytocics with outcome blood loss >1000 mL. Mantel—Haenszel fixed-effects model. Heterogeneity chi-squared = 3.64 (*df* = 10), $p = 0.962$. I-squared (variation in RR attributable to heterogeneity) = 0.0%. Test of RR = 1: $z = 4.41$, $p = 0.000$.

tocics. Despite many misoprostol patients receiving doses which had not fully taken effect, only 4% more received therapeutic drugs than patients in the control group.

## 6. Discussion

Due to the small sample sizes and PPH's high variability in general (even with oxytocics PPH occurs in 5—18% of live births [52]), many trial findings were not statistically significant. The wide confidence intervals reflected the high probability of chance in each of these trials. Therefore, the RR of each trial were not definitive estimates, as it was impossible to distinguish between individual RR with overlapping confidence intervals. However, the fact that the RR were consistent with individual studies' findings, demonstrated that the overall risk of PPH when misoprostol was used was only 4%

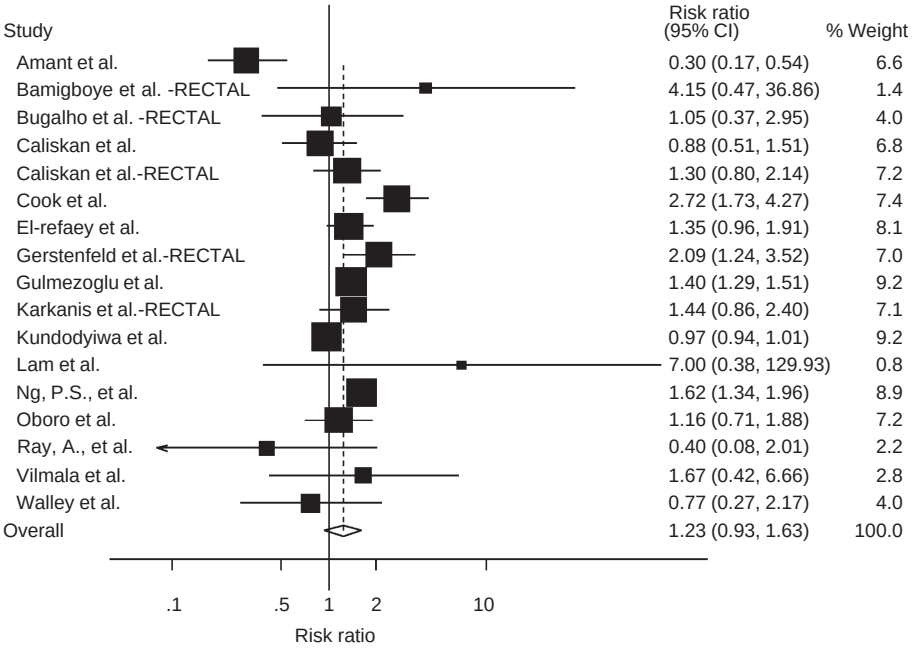


**Figure 4** All studies evaluating misoprostol vs. oxytocics with outcome of additional uterotonic agents. DerSirmonian and Laird random-effects model. Heterogeneity chi-squared = 343.00 (*df* = 16), $p = 0.000$. I-squared (variation in RR attributable to heterogeneity) = 95.3%. Estimate of between-study variance Tau-squared = 0.2171. Test of RR = 1: $z = 1.47$, $p = 0.141$.

greater than when oxytocics were used. This risk difference was well within the range of expected results for any uterotonic agent [52] and was not unique to misoprostol. Not surprisingly, the meta-analysis published in 2003 [11] had similar findings. In that review, Joy et al. reported OR for misoprostol versus oxytocin of 1.51 at blood loss >500 mL and 2.14 for additional oxytocics needed. Stated another way, these OR only represented an excess risk of 5.8% and 4.5%, respectively. Although the report stated that misoprostol was "inferior" to other uterotonic drugs, its value in developing countries was not dismissed due to its efficacy over placebo.

The primary limitation of this meta-analysis was the inability to conduct sub-analyses due to the small number of studies using each dose, administration and uterotonic drug. Potential systematic biases, mentioned previously, were the inconsistency in blood loss measurement and lack of double-masking. Because all outcomes were dependent on the amount of blood lost, it was critical to have uniform measurement across, as well as within, studies. Furthermore, because determining the severity of blood loss requires subjective judgment, having all trial investigators and attending physicians masked to drug allocation was exceedingly important. For these reasons, both double-masking and blood measurement were criteria for the validity test. The tests for publication bias showed no strong evidence of bias for any outcome level. Nonetheless, there was a surprising lack of placebo trials, despite nearly every study concluding with a request for more trials of this nature.

Conventional uterotonic drugs, limited in their use in remote areas, should not be used to set the lowest-accepted standard for situations where they are entirely unsuitable. Continuing to weigh the benefits of one effective drug against another, when only misoprostol is currently feasible in developing countries, only delays its necessary distribution.

## References


[1] Maternal Mortality in 2000: estimates developed by WHO, UNICEF and UNFPA. Geneva: The World Health Organization; 2004.

[2] Mother—baby package: implementing safe motherhood in countries, vol. 94. Geneva: World Health Organization, 1998; p. 11.

[3] Tsu VD, Langer A, Aldrich T. Postpartum hemorrhage in developing countries: is the public health community using the right tools? Int J Gynaecol Obstet 2004;85(Suppl 1): S42–51.

[4] Coverage of Maternity Care: a listing of available information. Fourth edn. Geneva: World Health Organization; 1997.

[5] Roman AS, Andrei R. Seven ways to control postpartum hemorrhage. Contemp OB/GYN 2003;3:34–53.

[6] Chong YS, Su LL, Arulkumaran S. Current strategies for the prevention of postpartum haemorrhage in the third stage of labour. Curr Opin Obstet Gynecol 2004;16(2):143–50.

[7] Villar J, Gulmezoglu AM, Hofmeyr GJ, Forna F. Systematic review of randomized controlled trials of misoprostol to prevent postpartum hemorrhage. Obstet Gynecol 2002; 100(6):1301–12.

[8] Mousa HA, Walkinshaw S. Major postpartum haemorrhage. Curr Opin Obstet Gynecol 2001;13(6):595–603.

[9] Darney PD. Misoprostol: a boon to safe motherhood or not? Lancet 2001;358(9283):682–3.

[10] El-Refaey H, Rodeck C. Post-partum haemorrhage: definitions, medical and surgical management. A time for change. Br Med Bull 2003;67:205–17.

[11] Joy SD, Sanchez-Ramos L, Kaunitz AM. Misoprostol use during the third stage of labor. Int J Gynaecol Obstet 2003;82(2):143–52.

[12] Miller S, Lester F, Hensleigh P. Prevention and treatment of postpartum hemorrhage: new advances for low-resource settings. J Midwifery Women's Health 2004;49(4):283–92.

[13] Potts M, Campbell M. Three meetings and fewer funerals—misoprostol in postpartum haemorrhage. Lancet 2004; 364(9440):1110–1.

[14] McCormick ML, Sanghvi HC, Kinzie B, McIntosh N. Preventing postpartum hemorrhage in low-resource settings. Int J Gynaecol Obstet 2002;77(3):267–75.

[15] Hofmeyr GJ, Walraven G, Gulmezoglu AM, Maholwana B, Alfirevic Z, Villar J. Misoprostol to treat postpartum haemorrhage: a systematic review. BJOG 2005;112(5): 547–53.

[16] Diaz QR, Arechiga EM, Resendiz BV, Lopez CO, Ayup HS, Cuervo MJ. Vaginal misoprostol in the prevention of postpartum hemorrhage. Ginecol Obstet Mex 2002;70:572–5.

[17] Acharya G, Al-Sammarai MT, Patel N, Al-Habib A, Kiserud T. A randomized, controlled trial comparing effect of oral misoprostol and intravenous syntocinon on intra-operative blood loss during cesarean section. Acta Obstet Gynecol Scand 2001;80(3):245–50.

[18] Lokugamage AU, Paine M, Bassaw-Balroop K, Sullivan KR, Refaey HE, Rodeck CH. Active management of the third stage at caesarean section: a randomised controlled trial of misoprostol versus syntocinon. Aust N Z J Obstet Gynaecol 2001;41(4):411–4.

[19] Chong YS, Chua S, El-Refaey H, Choo WL, Chanrachakul B, Tai BC, et al. Postpartum intrauterine pressure studies of the uterotonic effect of oral misoprostol and intramuscular syntometrine. BJOG 2001;108(1):41–7.

[20] 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.

[21] El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. Br J Obstet Gynaecol 1997;104(3):336–9.

[22] Lumbiganon P, Villar J, Piaggio G, Gulmezoglu AM, Adetoro L, Carroli G. Side effects of oral misoprostol during the first 24 hours after administration in the third stage of labour. BJOG 2002;109(11):1222–6.

[23] Wright JM, Newton W. Is rectal misoprostol as effective as oxytocin in preventing postpartum hemorrhage? J Fam Pract 2003;52(4):281–2.

[24] Lumbiganon P, Hofmeyr J, Gulmezoglu AM, Pinol A, Villar J. Misoprostol dose-related shivering and pyrexia in the third stage of labour. WHO Collaborative Trial of Misoprostol in the Management of the Third Stage of Labour. Br J Obstet Gynaecol 1999;106(4):304–8.

[25] Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. Am J Obstet Gynecol 1998; 179(4):1043–6.
[26] Benchimol M, Gondry J, Mention JE, Gagneur O, Boulanger JC. Role of misoprostol in the delivery outcome. J Gynecol Obstet Biol Reprod (Paris) 2001;30(6):576–83.
[27] Hofmeyr GJ, Nikodem VC, de Jager M, Drakely A. Side-effects of oral misoprostol in the third stage of labour—a randomised placebo-controlled trial. S Afr Med J 2001; 91(5):432–5.
[28] Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. Br J Obstet Gynaecol 1998; 105(9):971–5.
[29] Surbek DV, Fehr PM, Hosli I, Holzgreve W. Oral misoprostol for third stage of labor: a randomized placebo-controlled trial. Obstet Gynecol 1999;94(2):255–8.
[30] Amant F, Spitz B, Timmerman D, Corremans A, Van Assche FA. Misoprostol compared with methylergometrine for the prevention of postpartum haemorrhage: a double-blind randomised trial. Br J Obstet Gynaecol 1999;106(10): 1066–70.
[31] Bamigboye AA, Merrell DA, Hofmeyr GJ, Mitchell R. Randomized comparison of rectal misoprostol with Syntometrine for management of third stage of labor. Acta Obstet Gynecol Scand 1998;77(2):178–81.
[32] Bugalho A, Daniel A, Faundes A, Cunha M. Misoprostol for prevention of postpartum hemorrhage. Int J Gynaecol Obstet 2001;73(1):1–6.
[33] Caliskan E, Dilbaz B, Meydanli MM, Ozturk N, Narin MA, Haberal A. Oral misoprostol for the third stage of labor: a randomized controlled trial. Obstet Gynecol 2003;101(5 Pt 1):921–8.
[34] Caliskan E, Meydanli MM, Dilbaz B, Aykan B, Sonmezer M, Haberal A. Is rectal misoprostol really effective in the treatment of third stage of labor? A randomized controlled trial. Am J Obstet Gynecol 2002;187(4):1038–45.
[35] 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 N Z J Obstet Gynaecol 1999;39(4):414–9.
[36] El-Refaey H, Nooh R, O'Brien P, Abdalla M, Geary M, Walder J, et al. The misoprostol third stage of labour study: a randomised controlled comparison between orally administered misoprostol and standard management. BJOG 2000;107(9):1104–10.
[37] Gerstenfeld TS, Wing DA. Rectal misoprostol versus intravenous oxytocin for the prevention of postpartum hemorrhage after vaginal delivery. Am J Obstet Gynecol 2001;185(4):878–82.
[38] Gulmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001;358(9283):689–95.
[39] Karkanis SG, Caloia D, Salenieks ME, Kingdom J, Walker M, Meffe F, et al. Randomized controlled trial of rectal misoprostol versus oxytocin in third stage management. J Obstet Gynaecol Can 2002;24(2):149–54.
[40] Kundodyiwa TW, Majoko F, Rusakaniko S. Misoprostol versus oxytocin in the third stage of labor. Int J Gynaecol Obstet 2001;75(3):235–41.
[41] Lam H, Tang OS, Lee CP, Ho PC. A pilot-randomized comparison of sublingual misoprostol with syntometrine on the blood loss in third stage of labor. Acta Obstet Gynecol Scand 2004;83(7):647–50.
[42] Oboro VO, Tabowei TO. A randomised controlled trial of misoprostol versus oxytocin in the active management of the third stage of labour. J Obstet Gynaecol 2003;23(1): 13–6.
[43] Ray A, Mukherjee P, Basu G, Chatterjee A. Misoprostol and third stage of labour. J Obstet Gynecol Ind 2001 (November/December);51(6):53–4.
[44] Vimala N, Mittal S, Kumar S, Dadhwal V, Mehta S. Sublingual misoprostol versus methylergometrine for active management of the third stage of labor. Int J Gynaecol Obstet 2004;87(1):1–5.
[45] Walley RL, Wilson JB, Crane JM, Matthews K, Sawyer E, Hutchens D. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. BJOG 2000;107(9):1111–5.
[46] Jadad A. Randomized control trials. London: BMJ Books; 1998.
[47] El-ReFaey H. Use of misoprostol in third stage of labour. Lancet 2002;359(9307):707–8 [discussion 709—710].
[48] El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Misoprostol for third stage of labour. Lancet 1996; 347(9010):1257.
[49] Khan R, Sharma S. Use of misoprostol in third stage of labour. Lancet 2002;359(9307):708–9 [author reply 709—710].
[50] O'Brien P, Lokugamage AU, Guillebaud J, Rodeck CH. Use of misoprostol in third stage of labour. Lancet 2002; 359(9307):708 [author reply 709—710].
[51] Shannon C, Winikoff B. Use of misoprostol in third stage of labour. Lancet 2002;359(9307):709 [author reply 709—710].
[52] McDonald S, WJP, DE. Prophylactic syntometrine vs. oxytocin in the third stage of labour. The Cochrane Library; 1998. p. 3.