# Should oral misoprostol be used to prevent postpartum haemorrhage in home birth settings in low resource countries? A systematic review of the evidence.

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**Should oral misoprostol be used to prevent postpartum haemorrhage in home birth settings in low resource countries? A systematic review of the evidence.**


## Abstract

*Background:* Using misoprostol to prevent postpartum haemorrhage (PPH) in home birth settings remains controversial.

*Objective*: To review the safety and effectiveness of oral misoprostol in preventing PPH in home birth settings.

*Search Strategy*: the Cochrane Library, PubMed, and POPLINE were searched for articles published until 31 March 2012.

*Selection criteria*: Studies, conducted in low resource countries, comparing oral misoprostol to a placebo or no treatment in a home birth setting. Studies of misoprostol administered by other routes were excluded.

*Data collection and analysis:* Data were extracted by two reviewers and independently checked for accuracy by a third. Quality of evidence was assessed using GRADE criteria. Data were sythesised and meta-analysis performed where appropriate.

*Main results:* Ten papers describing two randomised and four non-randomised trials. Administration of misoprostol was associated with a significant reduction in the incidence of PPH (RR = 0.58, 95% CI: 0.38 to 0.87), additional uterotonics (RR = 0.34, 95% CI: 0.16 to 0.73) and referral for PPH (RR = 0.49, 95% CI: 0.37 to 0.66). None of the studies was large enough to detect a difference in maternal mortality and none reported neonatal mortality. Shivering and pyrexia were the most common side effects.

*Conclusions:* The finding that distribution of oral misoprostol through frontline health workers is effective in reducing the incidence of PPH could be a significant step forward in reducing maternal deaths in low resource countries. However, given the limited number of high quality studies in this review, further randomised control trials are required to confirm the association, particularly in different implementation settings. Adverse effects have not been systematically captured, and there has been limited consideration of the potential for inappropriate or inadvertent use of misoprostol. Further evidence is needed to inform the development of implementation and safety guidelines on the routine availability of misoprostol.



*Keywords***:** misoprostol, postpartum haemorrhage, home birth settings, low resource countries.

## Introduction

Considerable debate surrounds the use of misoprostol to prevent postpartum haemorrhage (PPH) in home birth settings. PPH is traditionally defined as "blood loss greater than or equal to 500 ml within 24 hours after birth"[1]. Haemorrhage remains the leading cause of maternal mortality in sub-Saharan Africa and South-east Asia[2]. Oxytocin is acknowledged as the drug of choice for the active management of the third stage of labour and is therefore recommended for the prevention of PPH within a facility setting[3,4]. However, there has been significant interest in the role that misoprostol might play in countries where a high proportion of births occur at home. For example, it is estimated that in rural areas of Bangladesh and Ethiopia more than 90% of women give birth at home[5]. In such circumstances the proportion of births attended by skilled health personnel is low; 18% of births in Bangladesh and 6% in Ethiopia[5]. Although the picture is improving, it is estimated that 130-180 million women (43-48%) in sub-Saharan Africa and South Asia will give birth without a skilled attendant in the next 5 years[6]. Misoprostol has attracted interest because it is inexpensive[7], does not require cold chain storage[8], and it has been suggested that it can be administered by a non-skilled attendant without additional equipment[9]. Supporters of community distribution argue that giving misoprostol to women in areas without skilled birth attendants will have a significant impact on the prevention of PPH[10-12]; with one simulation model, based on clinical data, suggesting as much as a 38% reduction in maternal deaths due to PPH[13]. Others, including the World Health Organization, have suggested that further evidence is required before distribution to non-skilled attendants and to women can be recommended[14]. Concerns include inappropriate use (where misoprostol is used for a reason other than PPH prevention) or incorrect use of the tablets (such as administration prior to the birth of the baby), adverse effects (that may include fever and/or chills, nausea and vomiting, diarrhea, and pain[15]), and the possibility that community distribution of misoprostol may distract from the message about the importance of facility birth[16,17]. Despite these concerns, there is evidence of widespread use of misoprostol, facilitated in part by government approval[18,19], the addition of misoprostol to national essential medicine lists[20,21] and more recently to the *WHO Model List of Essential Medicines*[22].

We sought to examine the evidence base on misoprostol as a potential add-on for a clean birth kit (CBK). CBKs vary considerably in name and content, but at a minimum these single-use, prevention kits should contain components to facilitate a clean surface for delivery (e.g. a plastic sheet), clean hands of the birth attendant (e.g. soap), and clean cutting of the umbilical cord

(e.g. razor blade)[23]. In an earlier review of the contents of CBKs we found that most kits included a plastic sheet, soap, a clean blade, and a clean cord tie or clamp[24]. Some kits had other components such as gloves and gauze swabs, but there was no evidence of the inclusion of misoprostol within the kits. However, subsequent to this review a company has begun producing and distributing CBKs containing misoprostol tablets[25] as part of a substantial programme to prevent PPH after home birth[26]. Given the interest in this area, we aimed to review the safety and effectiveness of oral misoprostol in reducing the incidence of PPH in home birth settings[a] in low resource countries (LRCs). Previous reviews have examined misoprostol use, but have not specifically focused on home birth settings[27].

## Methods

Electronic databases were searched from the starting date of the database to 31 March 2012. Two independent searches were conducted; the first search was limited to randomised controlled trials, while the second search included all studies reporting effectiveness. The search strategy was expanded to account for limited findings in the first search, particularly with regard to secondary outcomes such as the use of additional uterotonics and referral. We did not limit the second search by study design to ensure as wide a search as possible. The search strategy took into account the participants (LRCs) and the intervention (oral misoprostol). An LRC was defined as any country in the World Bank income groups of "low income", "lower middle income" and "upper middle income"[28]. We included only studies of oral misoprostol compared with a placebo or no treatment in a home birth setting. Administration of misoprostol via the oral route ensures a fast uptake, but a shorter duration of action than either the sublingual or buccal routes[29]. This would be appropriate if the medication is to be included within CBKs that may be used by women in the absence of a skilled birth attendant. We chose not to include sublingual administration as part of the intervention considered in this review, since this route has been associated with a higher rate of maternal fever than the oral route[30] and could require more training in administration. Outcomes were not specified terms in the search strategy to ensure as wide a search as possible. The Cochrane Library, PubMed, and POPLINE were searched. The search strategy was guided by a library science expert. Medical subject headings (MESH) included "Parturition", and "Delivery, Obstetric". Keywords were: "labour" or "labor, ""clean delivery", "safe delivery", "birth*", "childbirth*", "intrapartum",

[a] In addition to the home, this includes home-like settings within the community (for example birth huts). It does not include facilities, either hospitals or health centers.

"peripartum", "perinatal", "postpartum", "postnatal", "obstetric*", "misoprostol" and "haemorrhage" or "hemorrhage". Additional studies were identified through reference lists of retrieved articles, recommendations sent to the researchers by experts in maternal and child health, and contact with authors of published articles. The search was limited to human subjects only. Just prior to submission of this paper a further systematic review was published[31]. This did not attempt to isolate the effectiveness of oral misoprostol for prevention PPH in home birth settings. Nor did it include the wider range of studies and outcomes included in this review.

Titles and abstracts of identified studies were screened by three researchers (BA, CS, & VH). Studies were included if they were conducted in LRCs, in a home birth setting, and compared oral misoprostol use to placebo or no treatment. Studies evaluating the use of misoprostol administered by other routes, in facility settings, or for reasons other than the prevention of postpartum haemorrhage, were excluded (Figure 1); in some cases this could only be ascertained after full text review. Full text papers were reviewed and data extracted (by CS & VH). The extracted data was independently checked for accuracy and detail (by BA). Where a study was reported in more than one paper, all papers were reviewed to ensure that all the relevant data were extracted. Methodological quality of the studies was assessed and a simple quality score[32] was applied to reflect the researchers' confidence that the study analysis was assessing a causal association.

The relative risk, with 95% confidence intervals, was calculated (by BA) where this was not provided by the authors. Meta-analysis was performed using Review Manager (RevMan) version 5 statistical software (by BA). Findings with reported zero events in their study arms were excluded from the analysis. The findings across interventions were synthesised using a random effects model, which takes into account the heterogeneity of the studies, to estimate the relative risk of postpartum haemorrhage, use of additional uterotonics, shivering and pyrexia for the misoprostol group compared with the placebo group. To test the diversity and heterogeneity of the pooled estimates, the $\chi^2$ test of heterogeneity at 5% significance level was used and the degree of heterogeneity was quantified on the basis of $^{12}$ test. Further meta-analysis focused on high quality studies by restricting the analysis to randomised controlled trials (RCTs) only. The GRADE system was used to classify the overall quality of evidence for each outcome[33]. This was done in two stages - for all studies and for RCTs only (by BA).

## Results

Fourteen relevant papers[34-47] were identified (Figure 1). Ten of these, comprising a total of six studies[34,39,40,43-45] (one study being reported in five papers[34-38]), had data on the effectiveness of misoprostol. There was one pilot study[41], one program report[42], and an evaluation of a training package for misoprostol administration without effectiveness data[46]. One study examining the effectiveness of community mobilisation in the uptake of misoprostol did not have a control or comparison group[47]. All four of these studies were subsequently excluded from the review.

*Characteristics of included studies*

Two of the six studies were double-blind randomised controlled trials (RCTs)[34,43], while the others were contemporaneous controlled non-randomised trials[39,40,44,45] (Online tables 1 and 2). Five studies in this review used a 600mcg dose of misoprostol, however the most recent used a lower dose of 400mcg[45]. All were conducted in a home-like setting, with five of the six studies focusing on home birth only[39,40,43-45] and the sixth study also including 'village sub-centres'[34]. In four of these studies the misoprostol was administered to women at birth by a frontline health worker (a trained Traditional Birth Attendant (TBA)[40,43], Auxiliary Nurse Midwife (ANM)[34] or a Community Health Worker (CHW)[45]), while in two studies it was distributed to the pregnant woman following counseling during antenatal care and was administered at birth either by the woman or her attendant[39,44]. All studies included some form of training for the health worker or education for the woman. In five of the six studies this was equally applied to both intervention and control arms[34,39,40,43,44]; however in the most recent study only the intervention group received education[45]. One RCT had a substantial program of training for TBAs in both arms of the study, which included the components of active management of the third stage of labour[43]. In the other three studies where misoprostol was given to the health worker training focused on the study protocol, identifying high risk women and danger signs[34,40,45]. One of these studies also included education for women and their families on PPH and the use of misoprostol[45]. In the two studies where only the women received the misoprostol, the education focused on birth preparedness, danger signs, and the correct timing and use of misoprostol[39,44].

Details of the person who actually administered the misoprostol were difficult to ascertain in most studies. Only one study reported that 'all women received study medication per protocol', in this case via the trained TBA[43]. In one of the studies where misoprostol was distributed directly to the woman, a considerable proportion of women gave birth alone or with a family member only (21%) suggesting that the misoprostol was essentially self-administered[39]. In the

other study the majority of women had a skilled birth attendant (54.5%) or TBA (43.9%) at the birth[44].

All studies recruited women who were planning to give birth at home; however the actual place of delivery was not always the home. Three studies included only women who delivered at home. In one study women were randomised during the third stage of labour, thus ensuring only home births[43]. In the second study, women who did not have a delivery at home were withdrawn[39]; while the most recent study randomly selected women who delivered at home from the delivery register[45]. In the remaining three studies the proportion of home births was highest in the two contemporaneous controlled non-randomised trials (91%[44] and 79%[39]) and lowest in the RCT by Derman et al. (less than 50% in both arms)[34].

Details of the individual study results are available in online tables 3 and 4. The pooled results are shown in Figures 2 and 3, while the assessment of the quality of evidence according to GRADE is shown in online table 5.

*Effectiveness*

All six studies examined some measure of effectiveness, but there was some heterogeneity (online table 3). Both RCTs demonstrated a significant reduction in the incidence of postpartum haemorrhage (defined as blood loss $\geq$500ml) in the misoprostol group[34,43]. One controlled non-randomised trial reported a reduction in PPH (blood loss $\geq$500ml)[45] and another reported a reduction in the incidence of 'excessive blood loss' rather than PPH[44]. The pooled relative risk (RR) of the data from these four studies is 0.58 (95% CI: 0.38 to 0.87) (Figure 2), with a very low overall grade of evidence (online table 5). Restricting the analysis to only RCTs gave a pooled RR = 0.65 (95% CI: 0.46 to 0.91), with a high overall grade of evidence (online table 5).

Three of the six studies reported a reduced need for additional uterotonics in the misoprostol group; pooled RR = 0.34 (95% CI: 0.16 to 0.73), with a very low overall grade of evidence (online table 5). Three studies reported a reduction in the need for referral for PPH; pooled RR = 0.49 (95% CI: 0.37 to 0.66). Misoprostol also appears to confer benefit by reducing the need for manual removal of placenta[43], blood transfusion[34,40,45] and a drop in haemoglobin postpartum[43] (online table 3). None of the studies was large enough to detect a difference in maternal mortality.

*Safety*

Shivering and fever were the most common side effects (online table 4). Four of the five studies that examined shivering reported an increase in shivering in the misoprostol group; pooled RR = 2.18 (95% CI: 1 to 4.72) (Figure 3), with a very low overall grade of evidence (online table 5). The effect was more pronounced and statistically significant when only RCTs were included in the meta-analysis; pooled RR = 2.91 (95% CI: 2.49 to 3.4), with a moderate overall grade of evidence (online table 5). The association between misoprostol and pyrexia was less clear, with two studies suggesting an increase in pyrexia, one finding no difference between groups, and one suggesting a decrease (online table 4); pooled RR= 1.4 (95% CI: 0.16 to 12.09) (Figure 3), with a very low overall grade of evidence (online table 5). Restricting the analysis to only the RCTs resulted in a pooled RR= 1.64 (95% CI: 0.28 to 9.5), with a low overall grade of evidence (online table 5).

Other adverse effects were poorly reported, or not reported at all. Only one study considered neonatal effects and this was reported following a post-hoc analysis[35]. Patted et al. examined neonatal vomiting, fever and diarrhea and found no difference between babies whose mothers took misoprostol and those that took the placebo[35]. None of the studies reported neonatal mortality.

Only the two studies where misoprostol was distributed to the pregnant woman examined whether it was administered correctly[39,44]. Sanghvi et al found that all 1421 women who took misoprostol did so after the birth of the baby and in all 20 cases of twins the woman took the misoprostol after the birth of the second baby[39]. In the other study, qualitative data suggested that women took the misoprostol ‘at the correct time’[44].

**Discussion**

Our review focuses specifically on the prevention of PPH in home birth settings, a major public health challenge in LRCs. Previous reviews that have considered the effectiveness of misoprostol[27,31] have not discriminated by setting (including both facility and community settings) and included routes of administration that could be argued to be difficult for women or untrained attendants to correctly administer. We found quality evidence that administration of oral misoprostol through frontline health workers in home birth settings in LRCs is associated with a significant reduction in the incidence of PPH. These frontline workers included auxiliary midwives (classified by WHO as midwifery personnel), and trained TBAS and CHWs (classified

by WHO as community/traditional health workers[48]). The association seems to be maintained when misoprostol is distributed directly to women, rather than through a health worker, and administered either by the woman or her attendant; however the quality of this evidence is very low. In all studies in this review misoprostol was distributed as part of a package of care that included training of birth attendants and/or education of women. This is an important consideration if misoprostol is to be considered for inclusion in clean birth kits (CBKs). Previous research suggests that CBKs are also typically distributed as part of a broader package of care that includes training and/or education[49], and therefore extending this to include information about misoprostol administration may be feasible.

The quality evidence regarding the incidence of PPH might appear to warrant a "strong" recommendation for the use of misoprostol, particularly when the evidence from RCTs alone is considered[33]. However, the GRADE system also includes consideration of undesirable effects. Our review clarifies the positive association between oral misoprostol use and shivering, however the association with pyrexia remains unclear. It is likely that this uncertainty is due to measurement issues, as in all studies side effects were based on women's reports. Mobeen *et al.* note that they did not attempt to systematically measure body temperature as an indicator of pyrexia, and that low rates of adverse effects could be a result of recall bias[43]. Previous research examining oral and sublingual misoprostol administration in facility settings found a significant increase in pyrexia, and this was greater where the dose was 600mcg compared to 400mcg[29]. Although expert groups have recommended 600mcg as the oral dose of misoprostol for PPH prevention where other treatments are unavailable, they acknowledge the limited evidence base for this recommendation[15,31]. Our findings do not clarify the picture. Most of the studies in this review used the higher dose of misoprostol and the one study that examined the use of a lower dose in the home setting did not collect data on side effects in the control arm (personal communication)[45]. In addition, the inclusion of 'intensive maternity services' in the intervention arm of this study could have explained the reduced incidence of PPH[45]. Further research is needed to examine the effectiveness of using a lower dose in a home setting. Other adverse effects have not been systematically captured in studies; the only study to explicitly examine neonatal outcomes found no differences in the incidence of neonatal fever, vomiting and diarrhea on the first postpartum day[35].

We found limited information in the studies in our review to address concerns about the potential for inappropriate or inadvertent use. Hofmeyer and Gulmezoglu noted the potential for

misoprostol to be used to augment labour, or to be taken in error, particularly in the case of twins[50]. In our review, only three studies examined the timing of administration and they found no cases of error[39,44,45]. Indeed Sanghvi et al. report that 96% of women took the misoprostol immediately after delivery of the baby and before the placenta was delivered[39]. In the study by Nasreen et al. 92% of women received the misoprostol from CHWs within 30 minutes of birth[45]. However, all three studies included substantial programmes of education and the two studies that distributed misoprostol to women only did so to those women who were able to 'demonstrate understanding' of correct and safe use[39,44]. The three studies that examined misoprostol administration by trained attendants did not report details on safe administration. However, personal communication with the author of the most recent RCT confirmed that all trained TBAs followed the study protocol and that there were no errors[43]. A program report from Bangladesh suggests that timing may be an issue, with "a considerable delay in taking the tablets after delivery observed in several cases" and a number of women who forgot to take them[41]. The findings from the recent community mobilisation in Nigeria also raise concerns[47]. Despite a significant programme of educational interventions, the study found that 18% of women did not get or did not take misoprostol. Of those women who did take the misoprostol, 12% took the dose at the wrong time and 2% took the wrong dose[47]. A symposium held in January of this year by USAID indicated that a number of countries are rolling out programs of community-based misoprostol administration and it is hoped that these will add to knowledge on safe administration. Early data from a pilot project in Nepal suggests that 93% of women report taking misoprostol after the birth of the baby but before the delivery of the placenta, with the remaining 7% taking after both baby and placenta have been delivered[51]. In Senegal, no administration errors were detected following the introduction of misoprostol at community level[46]. This was achieved through a 6 day training program for auxiliary midwives and supervisors on misoprostol administration, and strict controls on storage and distribution of the tablets. Further research is needed to examine compliance by both trained birth attendants and women.

None of the six studies indicated that the misoprostol tablets were used for anything other than the prevention of PPH. However, further research is needed to assess the impact of misoprostol distribution outside of the tight controls of clinical trials. The impact that distributing misoprostol might have on perceptions regarding the need for skilled care also needs to be examined. Less than half of the women who received education about PPH as part of a recent programme of community-based distribution of misoprostol acknowledged the need for referral in the event of

PPH[47]. It was suggested that more needed to be done to get the educational message through, however the potential for community based interventions to act as a disincentive to facility care also needs to be examined.

Our review is limited by our focus on English language papers and relevant studies published in other languages could have been missed. However, we found no non-English language abstracts and no additional non-English language studies were recommended by experts in the field. We excluded studies where misoprostol tablets were administered sublingually, since this route has been associated with a higher rate of maternal fever than the oral route[28] and could require more training in administration, thus making it less amenable for home use. Although this could be considered a limitation, in fact most studies using sublingual misoprostol were conducted within a facility setting and so would have been excluded from our review for this reason. All studies in the review had some elements of measurement bias with respect to the side effects because they relied upon women's recall of shivering and pyrexia. This may have led to an underestimation of the side effects. Although the non-randomised studies also had issues with regard to measurement of PPH, the two randomised controlled trials used the most stringent measurement methods possible given the community setting. There were similar issues in the non-randomised studies with regard to the administration of misoprostol and this might be a cause of bias. However, there was no potential for drug administration bias in the RCTs as both had very clear protocols. Both RCTs noted temporal trends with a reduction in PPH occurring in both the intervention and the control group as the trials progressed[34,43]. The authors surmised that other factors such as a raised awareness of PPH or a training effect could have contributed to the reduction in the placebo group. A significantly greater reduction in the incidence of PPH was seen in the intervention arms in both trials, suggesting an association with misoprostol use. However, further high quality randomised control trials are required to confirm the association, particularly in different implementation settings. Caution must also be exercised in generalising beyond low risk women, since both RCTs excluded women with a history of high risk conditions.

**Conclusion**

There is quality evidence that distribution of oral misoprostol through frontline health workers in home birth settings in LRCs is associated with a significant reduction in the incidence of PPH, as well as in the need for additional uterotonics and for referral. This association seems to be maintained when misoprostol is distributed directly to women, rather than through a health

worker, and administered either by the woman or her attendant; however the quality of this evidence is very low. Adverse effects have not been systematically captured, and there has been limited consideration of the potential for inappropriate or inadvertent use of misoprostol. The finding that distribution of oral misoprostol through frontline health workers is effective in reducing the incidence of PPH may be a significant step forward in reducing maternal deaths in low resource countries. Further evidence is needed to inform the development of implementation and safety guidelines on the routine availability of misoprostol in different home birth settings.

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**Disclosure of interests**
VH had financial support from Maternal Health TaskForce for the submitted work; there are no other relationships or activities that could appear to have influenced the submitted work.

**Contribution to authorship**
WG conceived the review and, with VH, secured funding for the work. BA, CS & VH conducted the literature search, reviewed the identified studies for inclusion, extracted data for the review, and synthesised the research findings. BA and VH devised the modified quality assessment score and assigned levels to the studies in the review. BA conducted the meta-analysis. All authors contributed to the discussion and interpretation of the findings. VH wrote the first draft of the paper and managed the editorial process. All authors contributed to the writing of the paper and approved the final version.

**Details of ethical approval**
The systematic review was conducted using data from published manuscripts. Ethical approval was not required.

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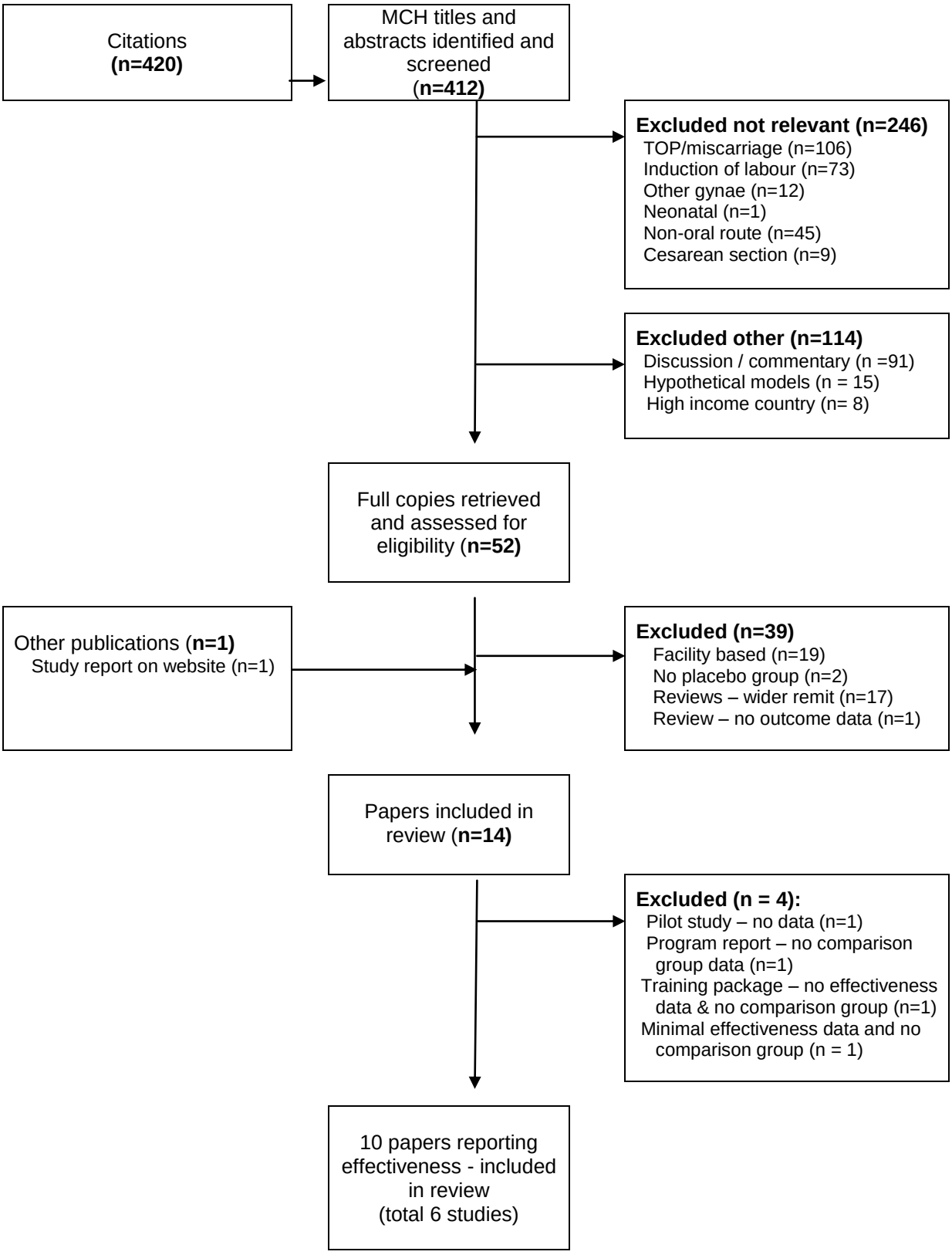
**Figure 1. Search and selection process**

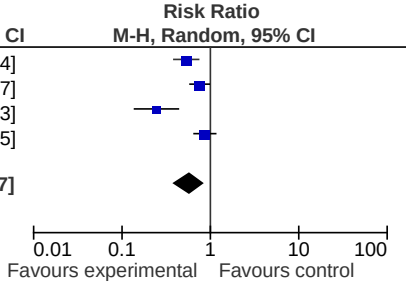


## Figure 2. Pooled relative risk for key variables on effectiveness

### 1. Incidence of PPH

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Derman et al, 2006 | 52 | 812 | 97 | 808 | 26.0% | 0.53 [0.39, 0.74] |
| Mobeen et al, 2010 | 85 | 514 | 122 | 558 | 27.8% | 0.76 [0.59, 0.97] |
| Nasreen et al. 2011 | 14 | 884 | 65 | 1008 | 19.3% | 0.25 [0.14, 0.43] |
| Sanghvi et al, 2004 | 117 | 999 | 66 | 489 | 27.0% | 0.87 [0.65, 1.15] |
| **Total (95% CI)** | | **3209** | | **2863** | **100.0%** | **0.58 [0.38, 0.87]** |
| Total events | 268 | | 350 | | | |

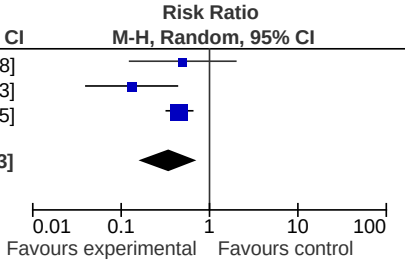
Heterogeneity: Tau² = 0.14; Chi² = 18.30, df = 3 (P = 0.0004); I² = 84%
Test for overall effect: Z = 2.65 (P = 0.008)




### 2. Use of additional uterotonics

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Derman et al, 2006 | 3 | 812 | 6 | 808 | 20.4% | 0.50 [0.12, 1.98] |
| Nasreen et al. 2011 | 3 | 884 | 26 | 1008 | 24.6% | 0.13 [0.04, 0.43] |
| Prata et al, 2009 | 42 | 485 | 91 | 481 | 55.0% | 0.46 [0.32, 0.65] |
| **Total (95% CI)** | | **2181** | | **2297** | **100.0%** | **0.34 [0.16, 0.73]** |
| Total events | 48 | | 123 | | | |

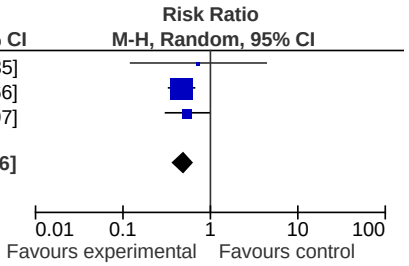
Heterogeneity: Tau² = 0.25; Chi² = 4.09, df = 2 (P = 0.13); I² = 51%
Test for overall effect: Z = 2.75 (P = 0.006)




### 3. Need for referral for PPH

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Mobeen et al, 2010 | 2 | 533 | 3 | 583 | 2.6% | 0.73 [0.12, 4.35] |
| Prata et al, 2009 | 43 | 485 | 91 | 481 | 72.0% | 0.47 [0.33, 0.66] |
| Sanghvi et al, 2004 | 28 | 1322 | 19 | 489 | 25.4% | 0.55 [0.31, 0.97] |
| **Total (95% CI)** | | **2340** | | **1553** | **100.0%** | **0.49 [0.37, 0.66]** |
| Total events | 73 | | 113 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 4.81 (P < 0.00001)

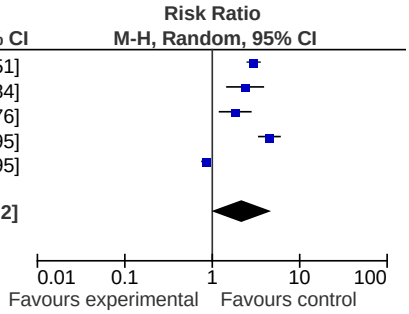


## Figure 3. Pooled relative risk for key variables on safety

### 1. Shivering

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Derman et al, 2006 | 419 | 812 | 140 | 808 | 20.5% | 2.98 [2.53, 3.51] |
| Mobeen et al, 2010 | 50 | 533 | 23 | 583 | 19.2% | 2.38 [1.47, 3.84] |
| Prata et al, 2009 | 59 | 485 | 32 | 481 | 19.6% | 1.83 [1.21, 2.76] |
| Sanghvi et al, 2004 | 442 | 999 | 48 | 489 | 20.2% | 4.51 [3.42, 5.95] |
| Sanghvi et al, 2010 | 575 | 2039 | 381 | 1148 | 20.6% | 0.85 [0.76, 0.95] |
| **Total (95% CI)** | | **4868** | | **3509** | **100.0%** | **2.18 [1.00, 4.72]** |
| Total events | 1545 | | 624 | | | |

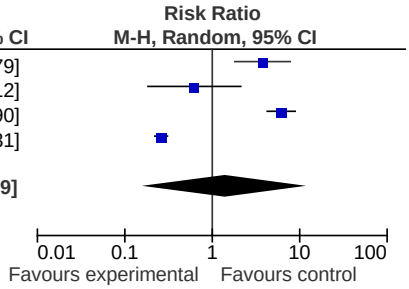
Heterogeneity: Tau² = 0.75; Chi² = 249.20, df = 4 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.97 (P = 0.05)




### 2. Pyrexia

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Derman et al, 2006 | 34 | 812 | 9 | 808 | 25.0% | 3.76 [1.81, 7.79] |
| Mobeen et al, 2010 | 4 | 533 | 7 | 583 | 23.8% | 0.63 [0.18, 2.12] |
| Sanghvi et al, 2004 | 352 | 999 | 28 | 489 | 25.5% | 6.15 [4.25, 8.90] |
| Sanghvi et al, 2010 | 173 | 2039 | 374 | 1148 | 25.7% | 0.26 [0.22, 0.31] |
| **Total (95% CI)** | | **4383** | | **3028** | **100.0%** | **1.40 [0.16, 12.09]** |
| Total events | 563 | | 418 | | | |

Heterogeneity: Tau² = 4.70; Chi² = 299.51, df = 3 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.31 (P = 0.76)



**Additional online table 1. Studies examining the effects of oral misoprostol**

| Source | Location of study | Participants | Intervention | Control | Primary outcome measures |
|---|---|---|---|---|---|
| ***Contemporaneous Controlled Randomised Trials*** | | | | | |
| Mobeen et al., 2010 | Remote villages of Chitral, Khyber Pakhtunkwa Province, Pakistan<br>Planned home births | 1119 women without pregnancy complications (I=534, C=585) | 600 mcg oral misoprostol administered by trained TBAs. Training on AMTSL | Placebo<br>Training for TBAs on AMTSL | Blood loss $\geq$ 500ml<br>Drop in haemoglobin > 2g/dl |
| Derman et al., 2006 | Rural Belgaum District, Karnataka State, India<br>Home-birth settings (home & village sub centres) | 1620 low-risk women (I =812, C=808) | 600 mcg oral misoprostol administered by ANMs<br>Training for ANMs on study protocol, identifying high risk women and danger signs | Placebo<br>Training for ANMs on study protocol, identifying high risk women and danger signs | Blood loss $\geq$ 500ml |
| ***Contemporaneous Controlled Non-Randomised Trials*** | | | | | |
| Nasreen et al., 2011 | Rural Nilphamari and Naogaon districts in Bangladesh.<br>Home births | 2017 women (I = 1009 – 884 received misoprostol, C=1008) | Education by CHW, intensive maternity care + 400mcg oral misoprostol administered by CHWs. | Essential health care | Blood loss $\geq$ 500ml |
| Sanghvi et al., 2010 | 6 rural districts chosen from Faryab, Jawzjan & Kabul provinces, Afghanistan.<br>Home births | 3187 women (I=2039 - 1421 took misoprostol, C=1148) | Education by CHW + 600 mcg oral misoprostol + pictorial messages given to women | Education by CHW | Misoprostal use; Reported symptoms; Adverse effects; Acceptability; Feasibility – willingness & motivation |
| Prata et al., 2009 | Rural Tigray, Ethiopia<br>Home births | 1000 women - assisted deliveries were then excluded 966 women (I=485, C=481) | 600 mcg oral misoprostol administered by trained TBAs<br>Training on study protocol | Current practice<br>Training on study protocol | Reported symptoms; Referrals; Additional interventions |
| Sanghvi et al., 2004 | Rural Bandung and Subang districts, Indonesia.<br>Home births | 1855 women (I=1360 – 999 took misoprostol, C=495) | Education by CHW + 600 mcg oral misoprostol + pictorial messages given to women | Education by CHW | Acceptability & uptake; Excessive blood loss; Emergency referral; Adverse effects |

**Additional online table 2. Critical appraisal of studies**

| Source | Study design[b] | Sample | Control group | Measurements and outcomes | Completeness | Distorting influences |
|---|---|---|---|---|---|---|
| ***Contemporaneous Controlled Randomised Trials*** | | | | | | |
| Mobeen et al., 2010 | ++ | Included only women 'in general good health' and planning to give birth at home. | Random allocation – computer generated random code in blocks - independently implemented | Double blind – placebo. PPH collected using a drape and weighed (early challenges were considered pilot phase). Indirect measurement (self-report) of pyrexia & shivering | Loss to follow-up = 1 intervention, 2 control. Missing blood loss data = 19 intervention, 25 control. Intention-to-treat analyses. | All data collected in first 7 months excluded due to measurement issues. Temporal trends - other factors (e.g. training) may have contributed to PPH reduction. |
| Derman et al., 2006 | ++ | Excluded women with pregnancy complications or history of high risk conditions | Random allocation - computer-generated list - independently implemented | Double blind – placebo. PPH measured using a calibrated collection drape. Indirect measurement (self-report) of pyrexia & shivering | No loss to follow-up reported. Intention-to-treat analyses. | Temporal trend - declining PPH also noted in placebo group. |
| ***Contemporaneous Controlled Non-Randomised Trials*** | | | | | | |
| Nasreen et al., 2011 | - | Randomly selected from birth register in one district. | Control - non-users in second district. No randomisation and no blinding. | Self reported measurement of PPH, pyrexia & shivering. | Analysis based on 87% of intervention group who received misoprostol. | Lack of adequate control over confounding factors (education, & financial state). Intervention included intensive service |
| Sanghvi et al., 2010 | + | All pregnant women in one district. | Control - non-users in second district. No randomisation & no blinding. | Self reported measurement of PPH (2 soaked cloths), pyrexia & shivering. | 18 women in intervention not offered misoprostol. No loss to follow-up reported for main outcomes, but 3 women not available for follow-up interview. | Lack of adequate control over confounding factors. |
| Prata et al., 2009 | + | Pregnant women in selected villages - limited information on selection criteria. | Control - non-users in selected villages. No randomisation & no blinding. | Visual inspection method to assess PPH. Self reported measurement of pyrexia & shivering. | 34 women withdrawn (15 intervention, 19 control) because did not have vaginal birth at home. 5 maternal deaths (1 intervention, 4 control). | Lack of adequate control over confounding factors (reproductive history of PPH & education). |
| Sanghvi et al., 2004 | + | All pregnant women in one district. | Control - non-users in 'comparable' second district. No randomisation & no blinding. | Self reported measurement of PPH, pyrexia & shivering. | 41 women lost to follow up – moved or pregnancy loss (36 intervention, 5 control). Three maternal deaths (2 intervention, 1 control). | Lack of adequate control over confounding factors (education, parity & reproductive history of PPH). |

[b] Adapted from the SIGN levels of evidence. Key: **++** (High level of confidence the analysis is assessing a causal association e.g. good analysis of cluster-randomised trial) **+** (Moderate level of confidence the analysis is assessing a causal association e.g. poor cluster-randomised trial; non-randomised cluster-controlled trial without obvious important confounding; before-after study of comparable groups, with no reason to suspect important time trends; possibly 'causal' analyses of cross-sectional data e.g. propensity scores / instrumental variable) _ (Low level of confidence the analysis is assessing a causal association e.g. Cross-sectional user / non-user comparisons, with adjustment for socio-economic and relevant behavioural differences.) _ _ (Very Low level of confidence the analysis is assessing a causal association e.g. cross-sectional user / non-user comparisons without adequate adjustment, or where large differences require large adjustments.)

**Additional online table 3. Blood loss and associated sequelae**

| Source | Intervention | Control | Effect size RR (95% CI) | Significance |
|---|---|---|---|---|
| *Incidence of PPH ≥500ml* | | | | |
| Mobeen et al. 2010 | 85/514 | 122/558 | 0.76 (0.59, 0.97) | 0.03 |
| Derman et al. 2006 | 52/812 | 97/808 | 0.53 (0.39, 0.74) | < 0.001 |
| Nasreen et al. 2011 | 14/884 | 65/1008 | 0.25 (0.14, 0.43) | < 0.001 |
| *'Excessive blood loss'* | | | | |
| Sanghvi, et al. 2004 | 117/999 | 66/489 | 0.87 (0.65, 1.15) | 0.32 |
| *Use of additional uterotonics* | | | | |
| Derman et al. 2006 | 3/812 | 6/808 | 0.50 (0.12, 1.98) | 0.32 |
| Nasreen et al. 2011 | 3/884 | 26/1008 | 0.13 (0.04, 0.43) | < 0.001 |
| Sanghvi et. al. 2010 | 54/1420 | | | |
| Prata et al. 2009 | 42/485 | 91/481 | 0.46 (0.32, 0.65) | < 0.001 |
| *Use of any uterotonic* | | | | |
| Sanghvi et. al. 2010 | 1960/2039 | 295/1148 | 3.74 (3.39, 4.13) | < 0.001 |
| *Need for referral for PPH* | | | | |
| Mobeen et al. 2010 | 2/533 | 3/583 | 0.73 (0.12, 4.35) | 0.73 |
| Prata et al. 2009 | 43/485 | 91/481 | 0.47 (0.33, 0.66) | < 0.001 |
| Sanghvi, et al. 2004 | 28/1322 | 19/489 | 0.55 (0.31, 0.97) | 0.04 |
| *Interval between delivery of baby & placenta (>30 min)* | | | | |
| Nasreen et al. 2011 | 31/884 | 52/1008 | 0.68 (0.44, 1.05) | 0.08 |
| *Manual removal of placenta* | | | | |
| Nasreen et al. 2011 | 26/884 | 68/1008 | 0.44 (0.28, 0.68) | < 0.001 |
| *Blood transfusion* | | | | |
| Derman et al. 2006 | 1/812 | 7/808 | 0.14 (0.02, 1.15) | 0.07 |
| Nasreen et al. 2011 | 0/884 | 2/1008 | - | |
| Prata et al. 2009 | 4/485 | 30/481 | 0.13 (0.05, 0.37) | < 0.001 |
| *Drop in Hb > 3g/dl* | | | | |
| Mobeen et al. 2010 | 27/528 | 55/572 | 0.53 (0.34, 0.83) | < 0.01 |
| *Maternal death* | | | | |
| Mobeen et al. 2010 | 0/534 | 0/585 | - | |
| Derman et al. 2006 | 0/812 | 1/678 | - | |
| Sanghvi et. al. 2010 | 1/2039 | 0/1148 | - | |
| Prata et al. 2009 | 1/500 | 4/500 | - | |
| Sanghvi, et al. 2004 | 2/1360 | 1/495 | - | |

**Additional online table 4. Adverse effects**

| Source | Intervention | Control | Effect size RR (95% CI) | Significance |
|---|---|---|---|---|
| *Shivering* | | | | |
| Mobeen et al. 2010 | 50/533 | 23/583 | 2.38 (1.47, 3.84) | < 0.001 |
| Derman et al. 2006 | 419/812 | 140/808 | 2.98 (2.53, 3.51) | < 0.001 |
| Sanghvi et. al. 2010 | 575/2039 | 381/1148 | 0.85 (0.76, 0.95) | < 0.01 |
| Prata et al. 2009 | 59/485 | 32/481 | 1.83 (1.21, 2.76) | < 0.01 |
| Sanghvi, et al. 2004 | 442/999 | 48/489 | 4.51 (3.42, 5.95) | < 0.001 |
| *Pyrexia (≥38°C)* | | | | |
| Mobeen et al. 2010 | 4/533 | 7/583 | 0.63 (0.18, 2.12) | 0.45 |
| Derman et al. 2006 | 34/812 | 9/808 | 3.76 (1.81, 7.79) | < 0.001 |
| Sanghvi et. al. 2010 | 173/2039 | 374/1148 | 0.26 (0.22, 0.31) | < 0.001 |
| Sanghvi, et al. 2004 | 352/999 | 28/489 | 6.15 (4.25, 8.90) | < 0.001 |
| *Need for referral for any complication* | | | | |
| Mobeen et al. 2010 | 18/533 | 20/583 | 0.98 (0.53, 1.84) | 0.96 |
| Derman et al. 2006 | 4/812 | 12/808 | 0.33 (0.11, 1.02) | 0.06 |
| Nasreen et al. 2011 | 3/884 | 11/1008 | 0.31 (0.09, 1.11) | 0.07 |
| Sanghvi, et al. 2004 | 114/1322 | 62/489 | 0.68 (0.51, 0.91) | < 0.01 |
| . | | | | |

## Additional online table 5. GRADE classification of the overall quality of evidence for each outcome

### All studies

| Outcomes | Anticipated absolute effects | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with control | Risk difference with blood loss & associated sequelae (95% CI) | | | |
| **PPH-1** | **Study population** | | **RR 0.58** (0.38 to 0.87) | 6072 (4 studies) | ⊕⊖⊖⊖ **very low**[1,2] due to risk of bias, indirectness |
| | **122 per 1000** | **51 fewer per 1000** (from 16 fewer to 76 fewer) | | | |
| | **Moderate** | | | | |
| | **128 per 1000** | **54 fewer per 1000** (from 17 fewer to 79 fewer) | | | |
| **Use of additional uterotonics** | **Study population** | | **RR 0.34** (0.16 to 0.73) | 4478 (3 studies) | ⊕⊖⊖⊖ **very low**[2,3] due to risk of bias, inconsistency, indirectness, imprecision |
| | **54 per 1000** | **35 fewer per 1000** (from 14 fewer to 45 fewer) | | | |
| | **Moderate** | | | | |
| | **26 per 1000** | **17 fewer per 1000** (from 7 fewer to 22 fewer) | | | |
| **shivering-1** | **Study population** | | **RR 2.18** (1 to 4.72) | 8377 (5 studies) | ⊕⊖⊖⊖ **very low**[1,3,4,5,6] due to risk of bias, inconsistency, indirectness, large effect |
| | **178 per 1000** | **210 more per 1000** (from 0 more to 662 more) | | | |
| | **Moderate** | | | | |
| | **98 per 1000** | **116 more per 1000** (from 0 more to 365 more) | | | |
| **pyrexia-1** | **Study population** | | **RR 1.4** (0.16 to 12.09) | 7411 (4 studies) | ⊕⊖⊖⊖ **very low**[1,3,5,6] due to risk of bias, indirectness, large effect |
| | **138 per 1000** | **55 more per 1000** (from 116 fewer to 1000 more) | | | |
| | **Moderate** | | | | |
| | **35 per 1000** | **14 more per 1000** (from 29 fewer to 388 more) | | | |

### RCTs only

| Outcomes | Anticipated absolute effects | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with control | Risk difference with blood loss & associated sequelae (95% CI) | | | |
| **PPH-2** | **Study population** | | **RR 0.65** (0.46 to 0.91) | 2692 (2 studies) | ⊕⊕⊕⊕ **high** |
| | **160 per 1000** | **56 fewer per 1000** (from 14 fewer to 87 fewer) | | | |
| | **Moderate** | | | | |
| | **169 per 1000** | **59 fewer per 1000** (from 15 fewer to 91 fewer) | | | |
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| **shivering-2** | **Study population** | | **RR 2.91** (2.49 to 3.4) | 2736 (2 studies) | ⊕⊕⊕⊖ **moderate**[5,6] due to imprecision |
| | **117 per 1000** | **224 more per 1000** (from 175 more to 281 more) | | | |
| | **Moderate** | | | | |
| | **106 per 1000** | **202 more per 1000** (from 158 more to 254 more) | | | |
| **pyrexia-2** | **Study population** | | **RR 1.64** (0.28 to 9.5) | 2736 (2 studies) | ⊕⊕⊖⊖ **low**[5,6] due to indirectness, imprecision |
| | **12 per 1000** | **7 more per 1000** (from 8 fewer to 98 more) | | | |
| | **Moderate** | | | | |
| | **12 per 1000** | **8 more per 1000** (from 9 fewer to 102 more) | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio;

**GRADE Working Group grades of evidence**: **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.

1. Sanghvi *et al*, 2004 (NON-RCT): No randomisation, no blinding, lack of adequate control over confounding (education, parity, etc.). Asian (primarily rural) population. Self reported measurement of PPH, pyrexia and shivering. Self-administration of misoprostol, and non-user (non-placebo) as control group.
2. Nasreen *et al*, 2011 (NON-RCT): No randomisation, no blinding, lack of adequate control over confounding (education, financial status, etc.). Asian (primarily rural) population. Self reported measurement of PPH, pyrexia and shivering. Non-user (non-placebo) as control group.
3. Sanghvi *et al*, 2010 (NON-RCT): No randomisation, no blinding, lack of adequate control over confounding. Asian rural population. Self reported measurement of PPH, pyrexia and shivering. Self-administration of misoprostol, and non-user (non-placebo) as control group.
4. Prata *et al*, 2009 (NON-RCT): No randomisation, no blinding, lack of adequate control over confounding (age, education, etc.). African rural population. Visual inspection method to assess PPH. Self reported measurement of pyrexia and shivering. Non-user (non-placebo) as control group.
5. Darmen *et al*, 2006 (RCT): Asian rural population. Indirect measurement (self-report) of pyrexia and shivering.
6. Mobeen *et al*, 2010 (RCT): Asian rural population. Indirect measurement (self-report) of pyrexia and shivering.