

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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Accepted 10 July 2012. Published Online 27 November 2012.

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

Objectives 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 with 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. The quality of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. Data were synthesised and meta-analysis was 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 0.38–0.87), additional uterotonics (RR 0.34, 95% CI 0.16–0.73), and referral for PPH (RR 0.49, 95% CI 0.37–0.66). 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.

Author's conclusions The finding that the distribution of oral misoprostol through frontline health workers is effective in reducing the incidence of PPH could be a significant step forwards in reducing maternal deaths in low-resource countries. However, given the limited number of high-quality studies in this review, further randomised controlled 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 Haemorrhage, home-birth settings, low-resource countries, misoprostol, postpartum.

Please cite this paper as: Hundley V, Avan B, Sullivan C, Graham W. Should oral misoprostol be used to prevent postpartum haemorrhage in home-birth settings in low-resource countries? A systematic review of the evidence. BJOG 2012; DOI: 10.1111/1471-0528.12049.

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 Southeast 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 as a result of PPH.¹³ Others, including the World Health Organization, have suggested that further evidence is required before distribution to non skilled attendants and to women themselves 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 the 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 (including home-like settings within the community, e.g. birthing huts) in low-resource countries (LRCs). The review does not include

facility based settings, either hospitals or health centres. 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, whereas 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, as this route has been associated with a higher rate of maternal fever than the oral route,³⁰ and could require more training in administration. We did not use specified terms for outcomes 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', '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 the authors of published articles. The search was limited to human subjects only. Just prior to submission of this article a further systematic review was published.³¹ This did not attempt to isolate the effectiveness of oral misoprostol for the prevention of PPH in home-birth settings. Nor did it include the wider range of studies and outcomes included in this review.

Titles and abstracts of the studies identified were screened by three researchers (B.A., C.S., and V.H.). Studies were included if they were conducted in LRCs, in a home-birth setting, and compared oral misoprostol use with 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 were extracted (by C.S. and V.H.). The extracted data were independently checked for accuracy and detail (by B.A.). Where a study was reported in more than one paper, all papers were reviewed to ensure that all the relevant data were extracted. The methodological quality of the studies was assessed and a simple quality score³² 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 B.A.) where this was not provided by the

authors. Meta-analysis was performed using REVMAN 5 (by B. A.). Findings with zero reported 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-square test of heterogeneity at 5% significance level was used, and the degree of heterogeneity was quantified on the basis of the I2 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

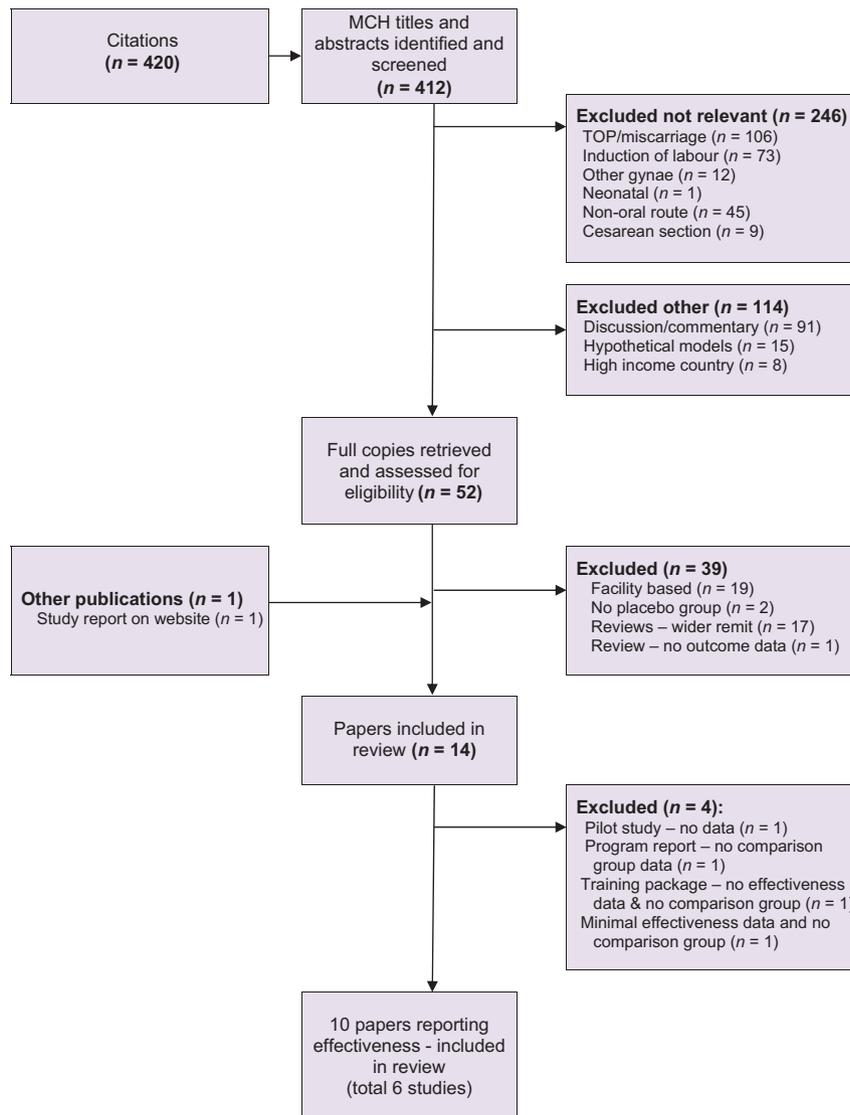


Figure 1. Search and selection process.

overall quality of evidence for each outcome³³: first, for all studies; and second, for RCTs only (by B.A.).

Results

Fourteen relevant papers were identified (Figure 1).^{34–47} Ten of these, comprising a total of six studies^{34,39,40,43–45} (with one study being reported in five papers),^{34–38} had data on the effectiveness of misoprostol. There was one pilot study,⁴¹ one programme 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 the studies included

Two of the six studies were double-blind RCTs,^{34,43} whereas the others were contemporaneous controlled non randomised trials (Tables S1 and S2).^{39,40,44,45} Five studies in this review used a 600- μ g dose of misoprostol; however, the most recent used a lower dose of 400 μ g.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 subcentres'.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], whereas in two studies it was distributed to the pregnant women following counselling during antenatal care, and was administered at birth by either the woman herself 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 the 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 programme 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 women, 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 whereas 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 (79% and 91%),^{39,44} and lowest in the RCT performed by Derman et al. (<50% in both arms).³⁴

Details of the individual study results are available in Tables S3 and S4. The pooled results are shown in Figures 2 and 3, whereas the assessment of the quality of evidence according to GRADE is shown in Table S5.

Effectiveness

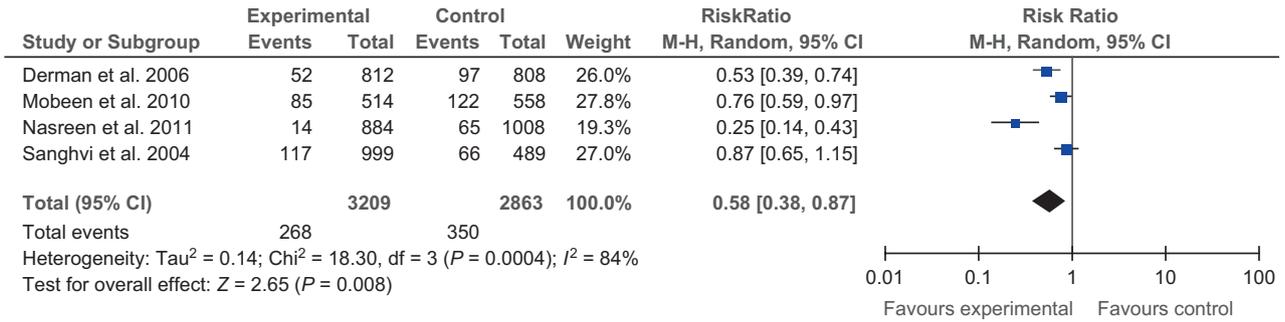
All six studies examined some measure of effectiveness, but there was some heterogeneity (Table S3). Both RCTs demonstrated a significant reduction in the incidence of postpartum haemorrhage (defined as blood loss \geq 500 ml) in the misoprostol group.^{34,43} One controlled non randomised trial reported a reduction in PPH (blood loss \geq 500 ml),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 0.38–0.87; Figure 2), with a very low overall grade of evidence (Table S5). Restricting the analysis to only RCTs gave a pooled RR 0.65 (95% CI 0.46–0.91), with a high overall grade of evidence (Table S5).

Three of the six studies reported a reduced need for additional uterotonics in the misoprostol group: pooled RR 0.34 (95% CI 0.16–0.73), with a very low overall grade of evidence (Table S5). Three studies reported a reduction in the need for referral for PPH; pooled RR 0.49 (95% CI 0.37–0.66). Misoprostol also appears to confer benefit by reducing the need for the manual removal of placenta,⁴³ blood transfusion,^{34,40,45} and a drop in haemoglobin postpartum (Table S3).⁴³ None of the studies was large enough to detect a difference in maternal mortality.

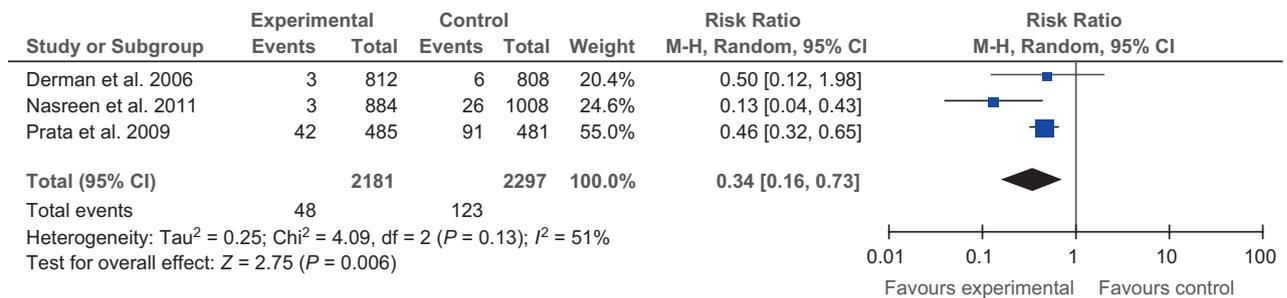
Safety

Shivering and fever were the most common side effects (Table S4). Four of the five studies that examined shivering

1. Incidence of PPH



2. Use of additional uterotonics



3. Need for referral for PPH

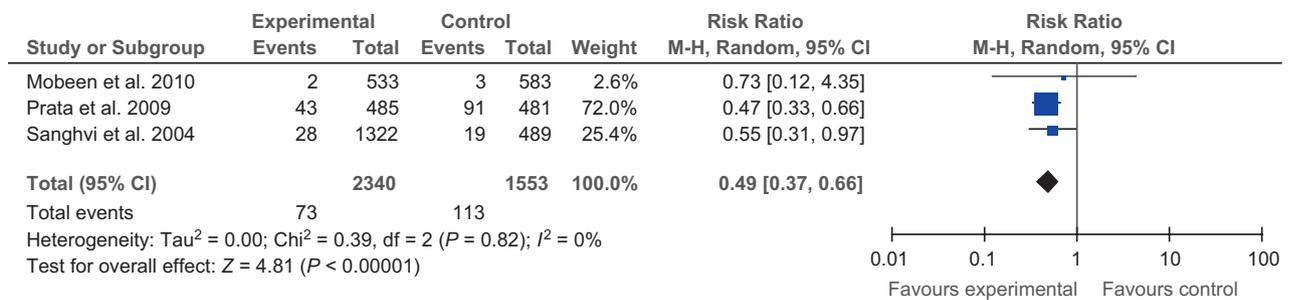


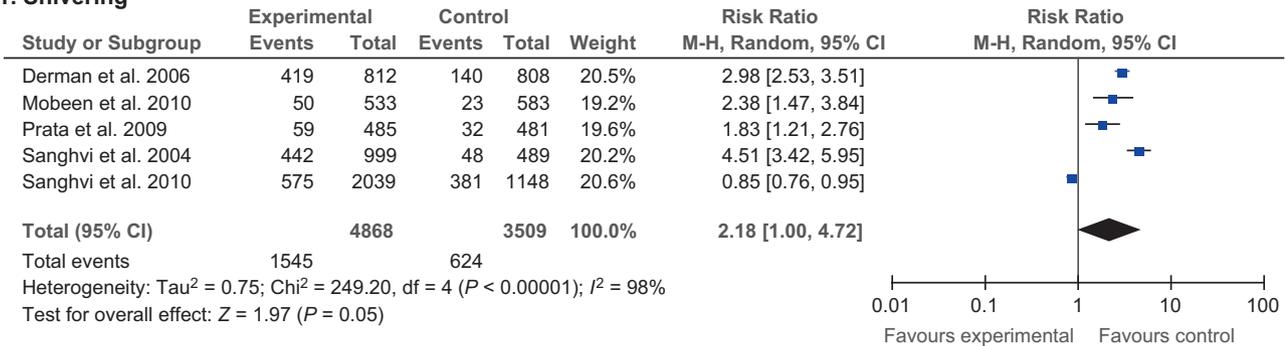
Figure 2. Pooled relative risk for key variables on effectiveness.

reported an increase in shivering in the misoprostol group: pooled RR 2.18 (95% CI 1.00–4.72; Figure 3), with a very low overall grade of evidence (Table S5). The effect was more pronounced and statistically significant when only RCTs were included in the meta-analysis: pooled RR 2.91 (95% CI 2.49–3.4), with a moderate overall grade of evidence (Table S5). The association between misoprostol and pyrexia was less clear, with two studies suggesting an increase in pyrexia, one finding no difference between the groups, and one suggesting a decrease (Table S4): pooled RR 1.4 (95% CI 0.16–12.09; Figure 3), with a very low overall grade of evidence (Table S5). Restricting the analysis to only RCTs resulted in a pooled RR of 1.64 (95% CI 0.28–9.5), with a low overall grade of evidence (Table S5).

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.³⁵ examined neonatal vomiting, fever, and diarrhea, and found no difference between babies whose mothers took misoprostol and those that took the placebo. None of the studies reported neonatal mortality.

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

1. Shivering



2. Pyrexia

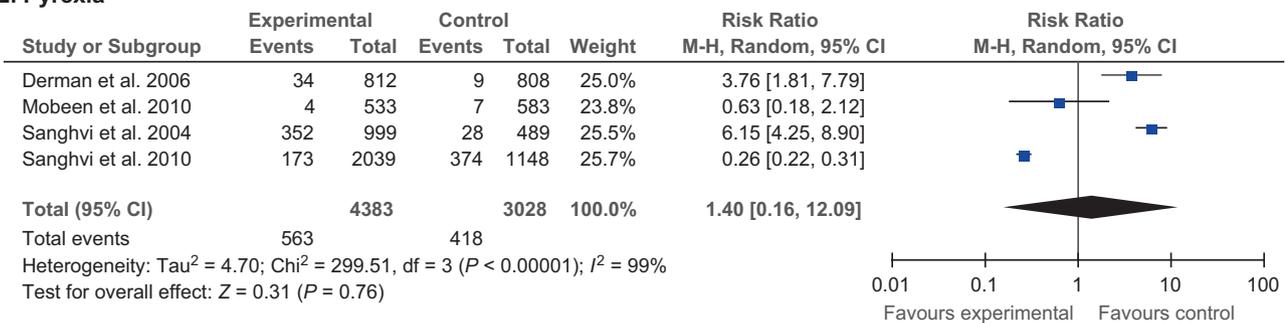


Figure 3. Pooled relative risk for key variables on safety.

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 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.^{27,31} 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 or 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 the training of birth attendants and/or education of women. This is an important consideration if misoprostol is to be considered for inclusion in 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 of 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 arises from measurement issues, as in all studies side effects were based on women's reports. Mobeen et al.⁴³ 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. 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 600 compared with 400 μg .²⁹ Although expert groups have recommended 600 μg 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 (Hashima-E-Nasreen, 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 Gulmezoglu⁵⁰ noted the potential for misoprostol to be used to augment labour, or to be taken in error, particularly in the case of twins. 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.³⁹ report that 96% of women took the misoprostol immediately after delivery of the baby and before the placenta was delivered. In the study by Nasreen et al.,⁴⁵ 92% of women received the misoprostol from CHWs within 30 minutes of birth. However, all three studies included substantial programmes of education, and the two studies that distributed misoprostol to women only did so to the women who were able to 'demonstrate an understanding' of correct and safe usage.^{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 programme 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 United States Agency for International Development (USAID) indicated that a number of countries are rolling out programmes of community-based misoprostol administration, and it is hoped that these will add to the 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 misoprostol after both the baby and the placenta have been delivered.⁵¹ In Senegal, no administration errors were detected following the introduction of misoprostol at the community level.⁴⁶ This

was achieved through a 6-day training programme for auxiliary midwives and supervisors on misoprostol administration, and strict controls on the 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 across; 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, as 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 the 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 groups 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 this association, particularly in different implementation settings. Caution must also be exercised in generalising beyond low-risk women, as both RCTs excluded women with a history of high-risk conditions.

Conclusion

There is quality evidence that the 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 uterotonic agents 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 the inappropriate or inadvertent use of misoprostol. The finding that the distribution of oral misoprostol through frontline health workers is effective in reducing the incidence of PPH may be a significant step forwards in reducing maternal deaths in LRCs. Further evidence is needed to inform the development of implementation and safety guidelines on the routine availability of misoprostol in different home-birth settings.

Disclosure of interests

VH received financial support from the Maternal Health TaskForce for this work. There are no other relationships or activities that could have influenced this work.

Contribution to authorship

W.G. conceived the review and, with VH, secured funding for the work. BA, CS and 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 article and managed the editorial process. All authors contributed to the writing of the article and approved the final version.

Details of ethics approval

The systematic review was conducted using data from published manuscripts. Ethical approval was not required.

Funding

This study was funded by the Maternal Health TaskForce, EngenderHealth. The funding body had no role in the design or conduct of the review, or in the writing of the article.

Acknowledgements

We are grateful to Christine Clar for initiating the data search for this review. We thank all of the maternal and child health groups, researchers, and clinicians who provided us with information for the review.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Studies examining the effects of oral misoprostol.

Table S2. Critical appraisal of studies.

Table S3. Blood loss and associated sequelae.

Table S4. Adverse effects.

Table S5. GRADE classification of the overall quality of evidence for each outcome. ■

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Commentary on 'Should oral misoprostol be used to prevent postpartum haemorrhage in home-birth settings in low-resource countries? A systematic review of the evidence'

Misoprostol is an exciting and fascinating drug, but never seems to be far from controversy. Maybe it is not surprising given that it has the potential not only to cheaply prevent thousands of maternal deaths each year, but also provides a highly effective but clandestine method for induced abortion. Misoprostol has therefore attracted passionate advocates and opponents in equal measure.

In the last decade, the Bill and Melinda Gates Foundation, WHO and Gynuity Health Projects have put enormous time, effort and money into sorting out the optimal role for misoprostol. And, as a result, following 20 years of politics, intrigue and largely uncoordinated research, a global consensus is finally emerging regarding the science (if not the politics) around this drug. Both WHO and International Federation of Gynecology and Obstetrics (FIGO) have recently produced robust guidelines on misoprostol use, and there has been general acceptance of the appropriate dosages.

One area of continued debate, however, has been the use of misoprostol for the prevention of postpartum haemorrhage (PPH) in the community. This is one of the most exciting areas of misoprostol research and, given that the population is the one in which most maternal deaths occur, it has the greatest potential for maternal benefit. Although a large misoprostol study from WHO has shown that it was not quite as effective as oxytocin (Gulmezoglu *Lancet* 2001;358:689–695), it had been unclear whether it was still worth using it if oxytocin is not available. Some early hospital-based studies had suggested that it might be no better than a placebo, but more recent studies have found it to be effective.

This systematic review examines the studies on oral misoprostol use within the community. Using controlled studies (both randomised and non-randomised) they have formally reviewed the evidence using the latest meta-analysis techniques. Like the reviews of both WHO and FIGO, they conclude that misoprostol is effective, although they caution that better evidence is required on adverse events and on its use in 'different implementation settings'. Their findings are convincing and robust, and are largely uncontroversial.

One of the 'different implementation settings' to which they are referring is unattended home birth. The proposed strategy is for women to be provided with misoprostol antenatally so that they can self-administer the tablets immediately after birth. However, although this could 'reach the women that other oxytocics cannot reach', there are concerns that some women might not take the tablets or take them before giving birth without realising the serious risks of doing this. One of the observational trials in this review studied this strategy and found it to be effective and safe (Sanghvi *Int J Gynecol Obstet* 2010;108:276–281). On that basis, many healthcare groups have started to provide misoprostol to women antenatally. But as yet there are no formal randomised controlled trials (RCTs) of this strategy, and the cautious point to the errors made with hormone replacement therapy as a result of a misguided reliance on observational data. A large placebo-controlled RCT (the MamaMiso Study) in which pre- and post-delivery haemoglobin are measured is therefore currently in progress in Uganda, and should soon provide further data as to its safety and effectiveness. The lack of reported adverse events related to antenatal use from continuing misoprostol distribution programmes is also reassuring. Between them, this issue should be resolved finally within the next 2 years.

Disclosure of interests

Prof. Weeks runs the independent, non-profit website called www.misoprostol.org that seeks to disseminate reliable information about misoprostol use in reproductive health. He has a grant from Gynuity Health Projects to run the MamaMiso study, a randomised trial of self-administered misoprostol for PPH prophylaxis in Uganda. He is also Director of the WHO Collaborating Centre for Research and Research Synthesis in Reproductive Health in Liverpool, and has been part of PPH/misoprostol guideline development groups for both WHO and FIGO. ■

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Reviewer's commentary on 'Should oral misoprostol be used to prevent postpartum haemorrhage in home-birth settings in low-resource countries? A systematic review of the evidence'

We disagree with Hundley et al's conclusion that there is 'quality evidence' to support misoprostol use. In an otherwise thorough review of misoprostol for prevention of postpartum haemorrhage (PPH) among women in low resource countries, the authors pay insufficient attention to design weaknesses and lack of generalisability of findings, overemphasizing tests of statistical significance and study type. Furthermore, the SIGN-GRADE criteria expose critical limitations in all of the studies included, both randomised and non-randomised. These are such that there are no good grounds, on this evidence, to support misoprostol use.

The authors assigned a quality score to the studies, adapted from SIGN-GRADE criteria for levels of confidence (see the footnote to Table 2 and SIGN methodology, www.sign.ac.uk/methodology/index.html). SIGN criteria for assessing the strength of evidence include: quantity, quality, and consistency of evidence; external validity (generalisability) of studies and directness of application to the target population for the guideline. The authors rated papers according to whether there was confidence that the analysis was assessing causal association as follows: '++' (high level of confidence), '+' (moderate level of confidence), '-' (low level of confidence), and '--' (very low level of confidence).

Two randomised controlled trials (RCTs) were graded '++' (Table 2), i.e. high level of confidence of causal association, but insufficient attention was paid to study design and confounding factors. Both RCTs exhibit temporal trends (noted in Table 2) in the intervention and control arms, suggesting effects from factors other than misoprostol. Moreover, the findings are not generalisable because both RCTs excluded women with or at high risk of complications. Indeed, the authors of the RCTs themselves highlight the non-generalisability of their findings. Had Hundley et al. followed the SIGN criteria, the grading would be '-', i.e. low level of confidence.

Similarly, the authors graded three of the four non-randomised studies as '+' (moderate probability the relationship is causal), but failed to consider confounding factors in study design. In the non-randomised studies included in the review, differences existed between the intervention and control arms in birth attendant training and active management of third stage of labour (AMTSL) practices. Blood loss was not measured at all in one study, was reported subjectively by recall in one, and was just estimated in two studies. Once again if the SIGN criteria had been correctly applied the appropriate grading would be '--', i.e. very low level of confidence.

National Institute for Health and Clinical Excellence (NICE) guidance on the use of SIGN-GRADE criteria for practice recommendations is that 'Usually, studies rated as '-' should not be used as a basis for making a recommendation' (NICE, Feb 2004, updated 2005, *Guideline Development Methods*, UK, www.nice.org.uk/niceMedia/pdf/GDM_Chapter7_0305.pdf, p. 7–7).

This review highlights the difficulties in conducting high-quality studies on PPH in low-resource countries, and, as a consequence, the paucity of evidence supporting oral misoprostol use in home-birth settings, findings confirmed in another recent review co-authored by two of us (Chu CS, et al. *Journal of the Royal Society of Medicine* 2012;105:336–347). Drawing the wrong conclusions from research that, however unavoidably, is not of high quality, has serious implications for healthcare expenditure, maternal health priorities, and women's health. The conclusion that the 'distribution of oral misoprostol through frontline health workers is effective in reducing the incidence of PPH' is not supported by evidence either in this review or an earlier review of trials (Chu CS, et al. *Journal of the Royal Society of Medicine* 2012;105:336–347). The World Health Organisation should rescind its decision to add misoprostol for the prevention of PPH in low-resource community settings to the Essential Medicines List [WHO (2011), *Unedited report of the 18th expert committee on the selection and use of essential medicines*, Ghana www.who.int]. ■

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