Misoprostol for prevention and treatment of postpartum hemorrhage: A systematic review

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Thesis submitted in partial fulfillment of the requirements for the degree of Masters of Nursing Science in the Faculty of Health Sciences at Stellenbosch University

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Co-supervisor: Doreen KM M'Rithaa
Department of Nursing

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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

December 2011

Abstract

Background: Misoprostol, a prostaglandin E_1 analogue with its uterotonic properties has entered as an integral part of management of the third stage of labour, helping to prevent postpartum haemorrhage (PPH).

Objective: To assess evidence on the effectiveness of misoprostol compared to a placebo for the prevention and treatment of postpartum haemorrhage.

Methods: Databases searched included; MEDLINE, Google Scholar and Cochrane Central Register of Controlled Trials (CENTRAL). Other sources were also searched. All articles were screened for methodological quality by two reviewers independently by standardized instrument. Data was entered in Review Manger 5.1 software for analysis.

Results: Three Misoprostol studies were included (2346 participants), Oral (2 trials) and sublingual (1 trial). Misoprostol has shown not to be effective in reducing PPH (RR 0.65: 95% CI 0.40-1.06). Only one trial reported on need for blood transfusion (RR 0.14; 95% CI 0.02-1.15). Misoprostol use is associated with significant increases in shivering (RR 2.75; 95% CI 2.26-3.34) and pyrexia (RR 5.34; 95% CI 2.86-9.96) than with placebo. No maternal deaths were reported in included trials. Compared to placebo, misoprostol was coupled with less hysterectomies and additional used of uterotonics (RR 0.45; 95%CI 0.21-0.96) compared to placebo.

Conclusion: Results of this review shows that the use of misoprostol in combination with some components of active management was not associated with any significant reduction in incidence of PPH. However oral administration showed a significant reduction in incidence of PPH. For its use for treatment of postpartum haemorrhage, there is a need for research focus in optimal dose and route of administration for a clinically significant effect and acceptable side effects.

Keywords

Misoprostol, prevention, postpartum haemorrhage, randomized controlled trials.

Opsomming

Agtergrond: Misoprostol, 'n prostaglandien E_1 analoog met sy uterotonic eienskappe het ingeskryf as' n integrale deel van die bestuur van die derde stadium van kraam, help postpartum bloeding (PPH) te voorkom.

Doelwit: Om bewyse oor die effektiwiteit van Misoprostol in vergelyking met 'n placebo vir die voorkoming en behandeling van postpartum bloeding te evalueer.

Metodes: Databases gesoek ingesluit, Medline, CINHAL, Google Scholar en Cochrane Sentrale Register van gecontroleerde studies (Sentraal). Ander bronne is ook deursoek. Alle artikels is gekeur vir die metodologiese kwaliteit deur twee beoordelaars onafhanklik deur die gestandaardiseerde instrument. Data is opgeneem in Review Manger 5.1 sagteware vir ontleding.

Hoof Resultate: Drie Misoprostol studies were ingesluit (2346 deelnemers). Mondeling (2 proe) en sublinguale (1 verhoor). Misoprostol het getoon nie doeltreffend te wees in die vermindering van PPH (RR 0,65: 95% CI 0,40-1,06). Slegs een verhoor berig oor die noodsaaklikheid vir 'n bloedoortapping (RR 0,14, 95% CI 0,02-1,15). Misoprostol gebruik word geassosieer met 'n aansienlike toename in bewing (RR 2,75, 95% CI 2,26-3,34) en koors (RR 5,34, 95% CI 2,86-9,96) as met' n placebo. Geen moederlike sterftes is aangemeld in proewe. In vergelyking met placebo, was Misoprostol tesame met minder hysterectomies en addisionele gebruik van uterotonics (RR 0,45, 95% CI,21-,96) in vergelyking met placebo.

Gevolgtrekking: Resultate van hierdie studie toon dat die gebruik van Misoprostol in kombinasie met 'n paar komponente van aktiewe bestuur is wat nie verband hou met' n beduidende afname in die voorkoms van PPH. Vir die gebruik vir die behandeling van postpartum bloeding, daar is 'n behoefte vir navorsing fokus in die optimale dosis en die roete van administrasie vir' n klinies beduidende uitwerking en aanvaarbare newe-effekte.

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- My utmost gratitude goes to my supervisor, Mr Oswell Khondowe, for his expertise, kindness and most of all his patience. With his enthusiasm, inspiration and his great effort in explaining concepts it simply helped me throughout development of this thesis.
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- Lastly, and most importantly, wish to thank my late parents, Mrs. K.Ditshotlo and Mr D. Olefile who raised me, supported my educational path at its menarche, loved and taught me responsibility. To them I dedicate this thesis.

Kabelo Monicah Olefile September 2011

Contents

List of abbreviations

CENTRAL	- Cochrane central Register of controlled trials
CINHAL	- Cumulative Index of Nursing and Allied Health
CI	- confidence interval
KMO	- Kabelo Monicah Olefile
MDGs	- Millennium Development Goals
MEDLINE	- Medical Literature Analysis and Retrieval Systems Online
MESH	- Medical Subject Headings
MMRs	- Maternal Mortality Ratios
OK	- Oswell Khondowe
PPH	- Postpartum haemorrhage
RCT	- Randomised Controlled Trials
RR	- Risk Ratios
RevMan 5.1	- Review Manager 5.1
SA	- South Africa
WHO	- World Health Organization

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- Conclusions are presented in an appropriate fashion and are supported by the data.
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Headings: First headings (normal case, bold and 14pt); Second headings: (normal case, bold and 14pt); Third heading: (normal case, bold and 12pt); Fourth headings: (normal case, bold running in-text and separately by a colon).

Tables, figures and photographs

Tables and figures should be saved and uploaded as separate Excel (.xls) files with no more than 10 figures and tables in the total per table. All personal identifying information should be removed from the supplementary files. All captions should be provided together on a separate page. Tables and figures use numerical numbers.

PART A

MISOPROSTOL FOR PREVENTION AND TREATMENT OF POSTPARTUM HAEMORRHAGE: A SYSTEM REVIEW

MISOPROSTOL FOR PREVENTION AND TREATMENT OF POSTPARTUM HAEMORRHAGE: A SYSTEMATIC REVIEW

Kabelo Monicah Olefile

Oswell Khondowe

Doreen M'Rithaa

Abstract

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there is a need for research focus in optimal dose and route of administration for a clinically significant effect and acceptable side effects.

Background

Maternal mortality continues to be one of the most serious and intractable health problems for women of reproductive age in low-income countries (Tsu & Shane, 2004:83). Reduction of the maternal mortality ratio by three quarters by 2015 is the target for one of the eight Millennium Development Goals (MDGs) set by 189 countries in 2000 (Rosenfield, Maine & Freedman, 2006:1333). Postpartum hemorrhage (PPH), the leading cause of maternal deaths worldwide, has received international attention among medical and research communities for decades. World Health Organization (WHO, 2007) defines PPH as postpartum blood loss of 500ml or more from the genital tract. However in populations with a higher prevalence of anemia, blood loss of less than 500ml has been noted to have several physical consequences (McCormick, Sanghvi, Kinzie & McIntosh, and 2002:267).

Magnitude of the problem: The maternal mortality ratio in developing countries is 450 maternal deaths per 100 000 live births versus nine in developed countries (WHO, 2007). An estimated 358,000 maternal deaths occurred worldwide in 2008 (UNICEF, 2010). According to UNICEF (2010), out of 1000 maternal deaths that occur due to causes including severe bleeding after child birth, 560 deaths occurred in Sub Saharan Africa and 300 in South Asia compared to five in high-income countries. According to the Millennium Development Goals (MDGs) report (2010), there was significant progress in maternal mortality ratios (MMRs) in developing regions, the average annual percentage decline in the global MMR was 2.3%, short of the MDG target of 5.5%. However in year 2008, there was an estimated 1.7 % annual rate of decline in sub-Saharan Africa, where levels of mortality are highest, is slower than in any other region. According to UNICEF (2010) maternal mortality ratio in South Africa was 410 in 100 000 in 2008.

The Saving Mothers reports (2009:12) states that obstetric haemorrhage is the third most common cause of maternal death in South Africa (SA), accounting for 491 (12.4%) of all maternal deaths during the period of 2005 to 2007. In SA, sub-standard care remained a major problem, contributing to over 40% of deaths for every level of care. This includes failure to carry out essential steps of prescribed protocols or serious delays in doing so, and lack of appropriate skills. According to Fawcus and Moodley (2011), it is fundamental that all levels of care are able to deal with the emergency management of PPH and are aware of the factors required to prevent it. This requires sufficient facilities, supplies and skilled staff. Major improvements in the implementation of the health system and appropriate training of doctors and midwives at all levels of care are essential if deaths from this preventable cause of maternal mortality are to be reduced.

Description of the condition

Post partum haemorrhage is defined as excessive vaginal bleeding (blood loss greater than 500 ml) within 24 hours following delivery (WHO, 2005). There is no better or more definitive explanation for PPH. McCormick , Sanghvi, Kinzie and McIntosh (2002) state that, a more accurate definition of PPH is any blood loss that results in a physiological change (e.g., low blood pressure) that threatens the woman's life. Bleeding after delivery is controlled by a combination of contraction of the myometrium, which constricts the blood vessels supplying the placental bed and local decidual hemostatic factors including tissue factor, type-1 plasminogen activator inhibitor and systemic coagulation factors (Lockwood & Schatz, 1996). Major etiologies of and risk factors of PPH include the following: uterine atony, coagulation defects, retained placenta, birth trauma and vaginal or cervical tears (Lockwood, Krikun & Schatz, 1999). Other risk factors include macrosomic baby, twin pregnancy, prolonged or augmented labour and antepartum haemorrhage. Despite the detection of risk factors, primary. PPH often occurs unpredictably in low-risk women.

Complications

The most imperative consequences of PPH include hypovolaemic shock, disseminated intravascular coagulopathy (DIC), fatigue and adult respiratory distress syndrome. In low-income countries, poor nutritional status, deficient access to treatment, inadequate intensive care and blood bank facilities are additional causative factors that lead to the elevated morbidity and mortality rates in some settings.

Description of intervention

Weeks and Faúndes (2007) delineate misoprostol as a prostaglandin E_1-analogue with uterotonic properties that can be administered orally, sublingually, vaginally and rectally. Sublingual administration of misoprostol achieves the uppermost serum peak absorption and takes the shortest time to reach the peak level, in comparison with other routes of administration (Tang, Schweer, Seybert, Lee & Ho, 2002). Initially, misoprostol was introduced as treatment for peptic ulcers. Misoprostol has been used to treat a variety of obstetrical problems, including uterine atony, postpartum haemorrhage, induction of labour, and induction of abortion (Hofmeyr, Walraven, Gülmezoglu, Maholwana, Alfirevic & Villar, 2005). Ng, Chan, Sin, Tang, Cheung and Yuen (2001) observed that misoprostol when given postpartum is known to cause only mild side effects (shivering and pyrexia). However, misoprostol is a sustainable drug for use in developing countries for the treatment of an assortment of obstetrical complications (Winikoff, Dabash, Durocher, Darwish, Nguyen, León, *et al*. 2010).

How misoprostol might work

The key management of PPH involves rapid recognition and diagnosis of the condition, restoration of circulating blood volume with a simultaneous search for the cause. According to WHO (2000), injectable oxytocin and ergometrine have been recommended for routine use in the active management of the third stage of labour. However, administration of an injection requires skills and sterile equipment for safe administration. Oxytocin may be inactivated if exposed to high ambient temperatures and requires cold-chain storage. WHO (2000) regard oxytocin as the gold standard for treatment of post-partum haemorrhage. Mousa and Alfirevic (2007) state that misoprostol is highly effective in inducing uterine contractions and has been proposed as a low-cost, easy-to-use alternative.

Oxytocin is usually the preferred drug where active management of the third stage of labour is practiced (Langenbach, 2006: Gülmezoglu, Villar, Ngoc, Piaggio, Carroli, Adetoro, Abdel-Aleem *et al.* 2001). Zuberi, Durocher, Sikander, Baber, Blum and Walraven (2008), advocated for the availability of misoprostol in community-based settings with limited access to conventional injectable uterotonics. Misoprostol has an important role to play in hospital settings and its adjunct use should continue to be explored for its potential in quick, safe and effective controlling of postpartum bleeding, averting recourse to more invasive procedures and preventing more severe maternal morbidity (Zuberi *et al.* 2008). Ng *et al.* (2001) observed that misoprostol when given postpartum is known to root only mild side effects (shivering and pyrexia) of which are dose dependent.

Significance of this research

Several systematic reviews have been done to assess the effectiveness of misoprostol in the prevention of PPH (Hofmeyer *et al*, 2007; Gülmezoglu, Forna, Villar & Hofmeyr 2011; Mousa & Alfirevic, 2009). In the above mentioned reviews, reviewers looked at the likelihood that misoprostol can be used as first-line of therapy in absence of injectable uterotonics. However some studies have shown that misoprostol promises as an adjunct treatment and its use should continue to be explored for its life-saving potential in the care of women experiencing PPH (Zuberi, 2008). In meta analysis of these previous reviews, studies included compared misoprostol to a placebo in addition to other uterotonics. Does this imply that misoprostol cannot be used alone for management and prevention of PPH? Is the real uterotonic effect of Misoprostol not affected by other uterotonics combined with it? A systematic review is needed to collate and assess the effectiveness of misoprostol compared to a placebo, without additional uterotonics for the prevention and treatment of PPH where other uterotonic agents are not feasible.

Objectives

The objective of this systematic review was to assess evidence on the effectiveness of misoprostol compared to placebo for the prevention and treatment of postpartum haemorrhage.

Specific objectives: The specific objectives were to determine the effectiveness of misoprostol in preventing and treating blood loss of $\geq$ 500ml and to investigate maternal mortality, severe morbidity, pyrexia, shivering, need for additional uterotonics in association with use of misoprostol compared with placebo for prevention of postpartum haemorrhage.

Criteria for considering studies for this review

Type of studies: Randomized controlled trials (RCT) that assessed the effectiveness of misoprostol compared to placebo in the prevention and treatment of postpartum haemorrhage during vaginal delivery were included in this review.

Types of participants: Studies that included women in labour with anticipated vaginal deliveries and women at low risk of postpartum haemorrhage were considered for inclusion. Low risk of PPH was defined as having no history of postpartum haemorrhage, with singleton pregnancies. Studies that included women with caesarean section and women with anaemia were excluded as such participants are considered to be high risk pregnancy and vulnerable to have PPH.

Types of interventions: Intervention considered for this review was Misoprostol versus placebo or non- treatment for prevention and treatment of PPH up to third stage of labour. Active management of third stage of labour (AMTSL) found to be useful and promoted by WHO was included as part of the interventions. AMTSL is defined as use of a uterotonic drug immediately following delivery of the fetus, controlled cord traction and early cord clamping and cutting. All studies irrespective of dose or route (oral, sublingual or rectal) of misoprostol were considered for this review. Studies that compared Misoprostol to a placebo in addition to other uterotonics were excluded.

Types of outcomes measures

Primary outcomes

Outcomes of interest in trials:

- Blood loss of 500ml
- Maternal mortality

Secondary outcomes

- Severe morbidity (hysterectomy/surgery, need for blood transfusion and manual removal of placenta).
- Pyrexia (temperature of more than 38°C or more) and shivering.
- Need for additional use of uterotonics.

For the purpose of this review, maternal morbidity was defined as the need for blood transfusion, manual removal of placenta, hysterectomy and major surgery and pyrexia was defined as temperature of more than 38^{o}C.

Search methods for identification of studies

Electronic search: A thorough comprehensive search for relevant studies was conducted on the following databases: MEDLINE, CINHAL, Google Scholar and Cochrane Central Register of Controlled Trials (CENTRAL). Subsequent MESH (Medical Subject Headings) terms used were; misoprostol, ergot preparations, prevention, postpartum haemorrhage and randomized trials. The search was conducted irrespective of geographical region of the study. Databases were searched from inception till 2011 with no language restrictions.

The following figure (Figure 1) shows the search strategy conducted on the different databases in detail.

2. MEDLINE (Search period inception - 2011)

1.0 Search **randomized controlled trial** Field: Publication type

1.1 Search **controlled clinical trial** Field: Publication type

1.2 Search **randomized** Field: Title or Abstract

1.3 Search **placebo** Field: Title or Abstract

1.4 Search **drug therapy** Field MeSH subheadings
Misoprostol, cytotec, prostaglandins

1.5 Search **randomly** Field: Title or Abstract

1.6 Search **postpartum bleeding or postpartum haemorrhage OR third stage of labour** Field: Title or Abstract

1.7 Search **Normal vaginal delivery** complications

1.8 Search # 1.3,1.4,1.6

1.9 Search # 1.3 # 1.6 # & # 1.7

Figure 1: MEDLINE Database Search Strategy for misoprostol versus placebo citation

Searching other sources: The following journals were hand searched: British Journal of obstetrics and gynaecology, International Journal of Gynaecology and Obstetrics, South African Journal of Obstetrics and Gynaecology and British Medical Journal. Conference reports (17th Expert Committee on the Selection and Use of Essential Medicines Geneva, 2009), The World health report 2005 (WHO, 2005), Route of misoprostol administration: Examining efficacy, side effects and acceptability (Gynuity Health Projects) were identified. Drug administration Guidelines from WHO were also considered. There were no ongoing studies found from Clinical trials register.

Data collection and analysis

Selection of studies: Two reviewers, Kabelo Monicah Olefile (KMO) and Oswell Khondowe (OK) independently assessed all potential studies identified as a result of the search strategy. Disagreements were resolved through discussions. Where consensus was not reached, a third reviewer Doreen M'Rithaa (DM) was available.

Data extraction and management: KMO and OK independently extracted data from eligible studies by using a standardised data extraction form that was adapted from the Cochrane Collaboration website. It was adjusted and refined for the purpose of this review. The refined version was piloted and used in the research process by KMO and OK. Data extracted included characteristics of participants, interventions used, length of follow-up, outcome measures, blood loss and side effects. All data was recorded in a data collection form. Data was entered into Review Manager 5.1 (RevMan 5.1) for analyses.

Assessment of risk of bias in included studies

KMO and OK independently assessed the validity of the studies by using the criteria outlined in Cochrane handbook of systematic reviews of interventions (Higgins, 2006).the following criterions were assessed:

Random sequence generation (assessment for possible selection bias): Method used to generate allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups was assessed as follows:

- Low risk of bias – (any truly random process, e.g. random number table, computer random number generator).
- High risk of bias – (any non-random process, e.g. odd or even date of birth, hospital or clinic number, days of the week, date of admission).
- Unclear risk of bias.

Allocation concealment (assessment for possible selection bias): Quality score for concealment of allocation to study interventions prior to assignment and whether intervention allocation could have been foreseen in advance, during recruitment or changed after assignment was assigned using the following criteria:

- Low risk of bias – (e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes).
- High risk of bias – (open random allocation, unsealed or non-opaque envelopes, alternation, date of birth).
- Unclear risk of bias.

Blinding of participants, personnel and outcome assessors (assessment for possible performance and detection bias): Studies were considered to be low risk of bias if they were blinded. Methods used to blind participants and personnel from knowledge of interventions a participant received were assessed as follows:

- Low, high or unclear risk of bias for participants.
- Low, high or unclear risk of bias for personnel.
- Low, high or unclear risk of bias for outcome assessors.

Incomplete outcome data (checking for possible attrition due to the amount, nature and handling of incomplete outcome data): For each included study and each outcome, the completeness of data including attrition and exclusion from analysis was described. Whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total number of randomised participants), reasons for attrition or exclusion were reported and whether missing data was balanced among groups or related to the outcomes were stated. Loss to follow-up was coded in each outcome as follows:

- Low risk of bias – (no missing outcome data, missing data balanced across groups).
- High risk of bias – (number of reasons for missing outcome data unbalanced across groups).
- Unclear risk of bias.

Selective reporting (checking for reporting bias): Investigation was done on whether there was a possibility of selective outcome reporting bias. Assessment methods were as follows: low risk of bias:

- Low risk of bias – (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review were reported).
- High risk of bias – (where not all the study's pre-specified outcomes have been reported, one or more primary outcomes were not pre-specified or outcomes of interest are reported incompletely and so cannot be used,stuy fails to include results of a key outcome that would have been expected to have been reported).
- Unclear risk of bias.

Other bias (checking for bias due to problems not covered by the above criterions): For each trial, any important concerns about other possible sources of bias were described. Each study was assessed whether it was free from other problems that could put it at risk of bias as follows:

- Low risk of other bias.
- High risk of other bias.

- Unclear risk of other bias.

Overall risk of bias: Explicit judgement was made about whether studies are at high risk of bias, according to the criteria given in the Cochrane handbook. With reference to criterions above, assessment was done on the magnitude and direction of the bias and whether it was considered likely to impact on the findings.

Measures of treatment effect: Results were presented as summary using risk ratios (RR) with 95% confidence interval (CI) as the measurement of effect size for binary outcomes. For continuous data, mean difference was to be used if outcomes were measured in the same way between trials and standardised mean difference to combine trials that measure the same outcome, but used different methods. Random effect (Mantel-Haenszel) meta-analysis was used for were heterogeneous trials. Statistical analyses were done using (RevMan 5.1).

Dealing with missing data: Reviewers proposed to contact original authors in cases where data was missing. However, this was not necessary as all required data was obtainable in included articles.

Assessment of heterogeneity: A test of heterogeneity between trials was applied by using a Chi-square test and I^2. An I^2 describes the percentage of the variability in effect estimates that it is due to heterogeneity rather than sampling error (chance) (Higgins, 2003). If the I^2 was > 30 to < 60 % it represented moderate heterogeneity, > 60 % to < 80% represented substantial heterogeneity and > 80% - 100% was considerable heterogeneity. We regarded heterogeneity as not important when I^2 was less than 30%. We regarded heterogeneity as substantial when I^2 was greater than 30% and either T^2 was greater than zero or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting bias: If there were 10 or more studies in meta analysis, reporting bias (such as publication bias) would have been investigated using funnel plots. Funnel plots would have been assessed for asymmetry visually. If signs of asymmetry were detected visually or formally, exploratory analysis investigations would have been performed.

Data synthesis: Meta analysis was carried out using RevMan 5 software. Meta-analysis combines the results of two or more studies to increase power and precision, to settle controversies arising from conflicting studies and to answer questions which individual studies fail to do (Deeks, Altman & Bradburn, and 2006:102). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Random effects meta-analysis was incorporated to produce an overall summary of effects when sufficient clinical heterogeneity was expected. When random and fixed effects meta analysis was used, summary of results were presented as average treatment effect with 95% confidence interval and I^2. Descriptive analysis of included and excluded studies was also undertaken.

Subgroup analysis and investigation of heterogeneity: When substantial heterogeneity was identified, it was investigated using sub group analysis. Subgroup analysis was done by route of administration of misoprostol (oral and sublingual) based on the incidence of PPH. Differences between subgroups were assessed by inspection of the subgroups' confidence intervals. Non-overlapping confidence intervals indicated a statistically significant difference in treatment effect between the subgroups. If sufficient heterogeneity existed, sensitivity analyses would have been performed

Sensitivity analysis: Sensitivity analyses was planned to incorporate assessment of risk of bias in the review process by plotting intervention effects estimates stratified for risk of bias for each relevant domain. In case of differences in results among studies

with different risks of bias, we planned to perform sensitivity analysis excluding studies with high risk of bias.

Results

Results of the search: The search yielded 339 articles. After carefully reading of the titles, 294 articles were discarded. The abstracts of the remaining 45 articles were read by two reviewers Kabelo Monicah Olefile (KMO) and Oswell Khondowe (OK) independently. Thirty-six articles were excluded as they did not meet the inclusion criteria. Reasons for exclusion were that articles were reviews, editorials, reporting on outcomes not of interest and misoprostol being administered for other obstetrical use and misoprostol being compared to other uterotonic drugs. Full text articles were read in the remaining nine articles by the reviewers independently. This procedure led to further exclusion of 5 articles, reason being that misoprostol was compared to placebo in addition to other uterotonics. One trial was further excluded. This study included three articles. See figure 2 for selection of articles.

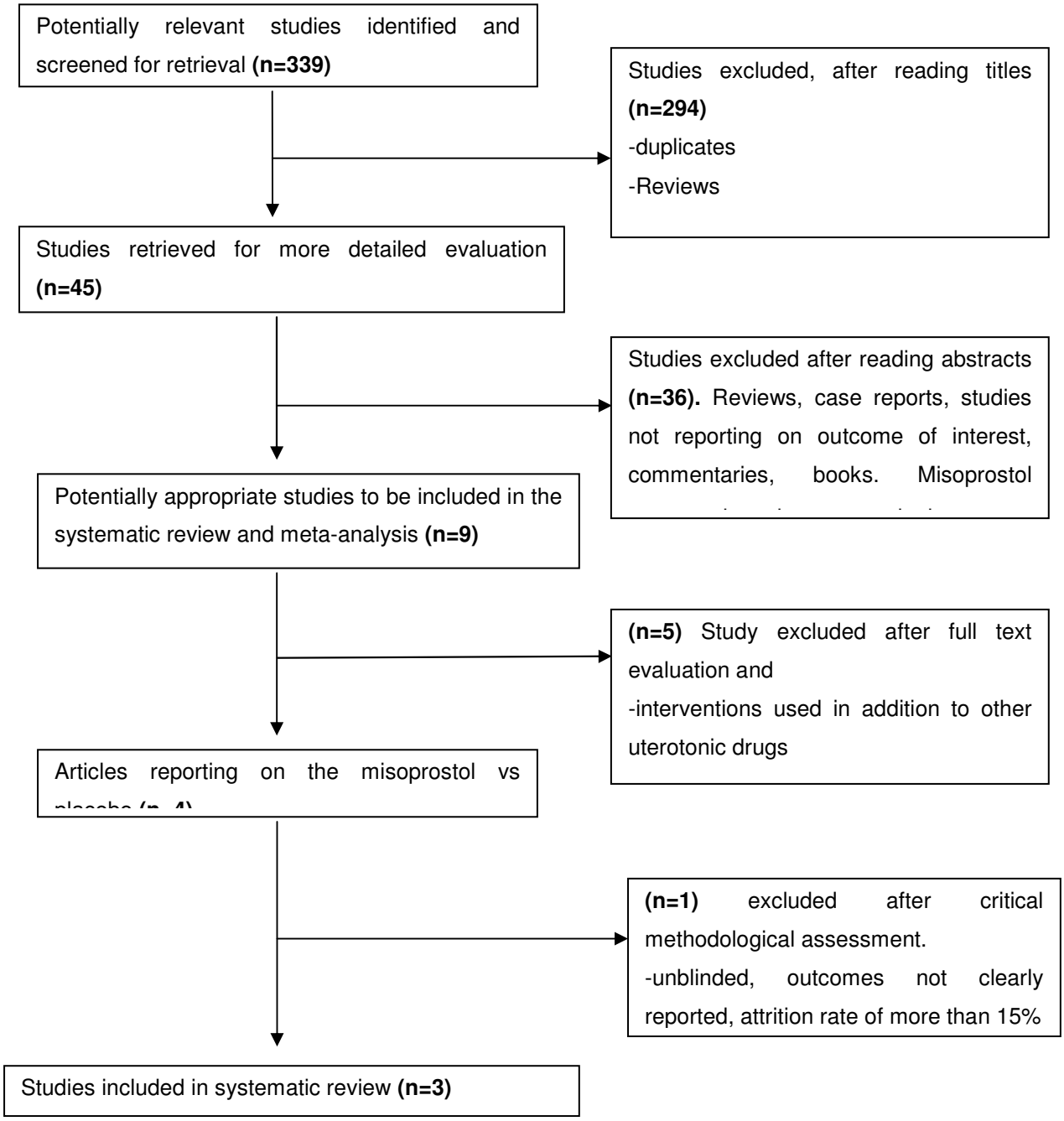

Figure 2: Flow diagram of electronic search

Description of studies: See table 2 for characteristics of included studies and appendix 2 for characteristics excluded studies.

Included studies

Design: All included studies were reported RCTs

Sample size*:* The total number of participants included in the trials contributing data to this review was 2346 pregnant women, and all of them were included in final analyses. The sample size varied from 64 - 1620 participants per trial.

Setting: The 3 trials took place in various countries: India, Guinea Bissau and Switzerland.

Participants*:* This review includes data for 2346 pregnant women. Two trials Derman, (2006) and Hoj (2005) included pregnant women (with a mean age of 23 years) and Suberk (1999) included pregnant women with mean age of 29.3.

Interventions: Trials compared the effectiveness of misoprostol compared to a placebo for management of third stage of labour in pregnant women with vaginal delivery. Active management of third stage of labour was confirmed in two trials (Hoj, 2005: Suberk, 1999). In one trial, Derman (2006) AMTSL components were not fully described. All trials used 600 µg Misoprostol tablets. Two trials, (Derman, 2006; Suberk, 1999) administered Misoprostol orally and in Hoj (2005) Misoprostol was administered sublingually. Treatments interventions were given immediately after the delivery of the baby

Outcomes: The primary outcome of the 3 trials was incidence of postpartum haemorrhage and maternal mortality. Other outcomes of interests that helped in assessment of effectiveness of misoprostol for prevention and treatment of PPH were also presented in the trials.

Excluded studies: Thirty-six of forty-five reports were retrieved for further assessment and were excluded to a placebo in addition to other uterotonics. One trial, Prata, Mbaruku, Campbell, Potts and Vahidnia (2005) was further for the reason that methodological quality was poor, un-blinded, outcomes not clearly after reading abstracts. Nine studies appeared to be eligible for inclusion in this review. However we excluded five trials after full text examination. Reasons being: Misoprostol was compared reported, attrition rate of more than 15%, and randomization was not described. See appendix 2 for excluded trials.

Table 2: Characteristics of included studies

Derman, 2006

Methods	- Randomisation and concealment by computer-generated list with a random block size. - sealed envelopes - double blinding
Design	- Randomised controlled trial
Participants	- 1620 pregnant with anticipated, uncomplicated spontaneous vaginal delivery
Interventions	- 600 µg oral misoprostol versus identical placebo -passive management, delayed cord clamping
Outcomes	- Primary outcome: the incidence of acute postpartum haemorrhage (blood loss ≥500 mℓ). - Secondary outcomes: severe postpartum haemorrhage (blood loss ≥1000 mℓ within 2 hours of delivery) and mean blood loss, need for transfer to a higher level facility, use of additional open-label uterotonic agents, blood transfusion, surgical intervention, maternal death, and drug-related maternal and neonatal side-effects

Hoj, 2005

Methods	- Randomisation by opaque envelopes were consecutively Numbered
Design	- Randomised double blind placebo controlled trial.
Participants	- 661 women undergoing vaginal delivery.
Interventions	- Misoprostol 600 µg or identical placebo administered Sublingually immediately after delivery. -placenta delivered by controlled cord traction (AMTSL).
Outcomes	- Incidence of PPH (blood loss of ≥500mℓ) - decrease in haemoglobin concentration after delivery

Continuation of table 2……..

Surbek, 1999

Methods	- Random allocation with number-generated tables.
Design	- Randomised double masked placebo-controlled trial
Participants	- 65 women with anticipated vaginal deliveries
Interventions	- Oral dose of misoprostol (600 µg) versus identical placebo immediately after cord clamping. - early cord clamping and cord traction (AMTSL).
Outcomes	- Primary outcome: incidence postpartum blood loss (≥500mℓ) and by antepartum and postpartum hematocrit values - Secondary outcomes: side effects, additional use of oxytocics

Risk of bias in included studies

Two Reviewers (KMO & OK) assessed all included trials for risk of bias and were blinded to each other's assessments. The risk of bias in included studies varied. All trials had no missing data. All three studies used methods of sequence generation and allocation concealment which we assessed as being at low risk of bias and overall, the included studies were assessed as low risk of bias for other domains of methodological quality. For an overview of review authors' judgments about each risk of bias item for individual included studies, see Figure 3.

Figure 3 presents trials The "Risk of bias" assessment done in three trials.

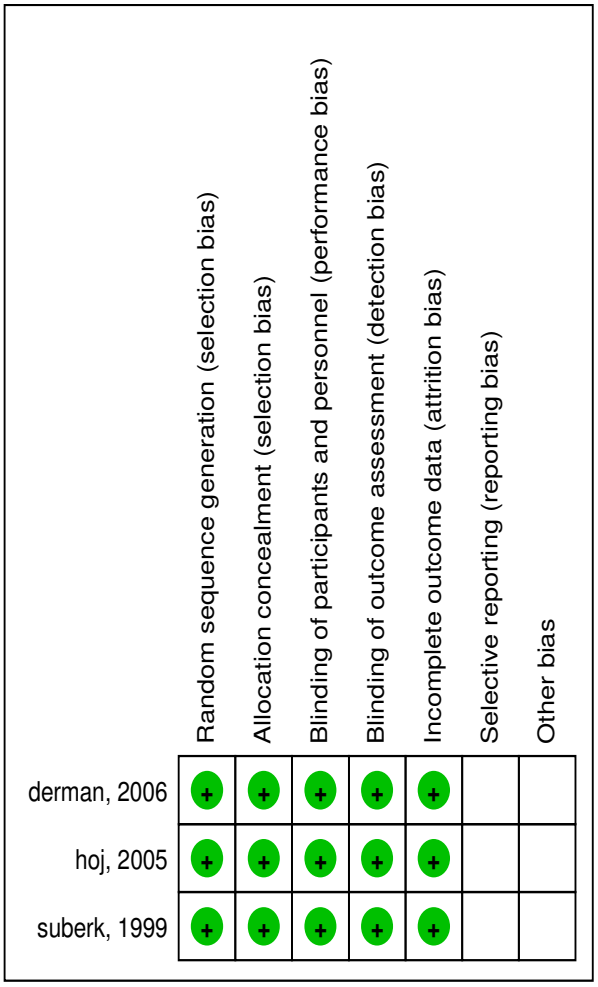

Figure 3: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Key:

Allocation: All studies included in this review were reported as being RCTs. Sample size calculation was clearly stated in all three trials. Adequate sequence generation was performed in all included trials and these were rated as 'low risk of bias' (Derman, 2006, Hoj, 2005 & Suberk, 1999). All included trials had adequate allocation concealment (used sealed opaque envelopes) and were rated as 'low risk of bias').

Blinding: Double-blinding was reported in 3 included trials (Derman, 2006; Hoj, 2005; Suberk, 1999). Personnel and participants were blinded to the intervention given. Identical placebos were used. In Suberk (1999) trial, three identical gelatine capsules, each containing misoprostol (200 mg) (Cytotec) or identical placebo was used. In Hoj (2005) and Derman (2006), three tablets of placebo or three 200mg misoprostol tablets were used and identical to placebo.

Incomplete outcome data: There was no outcome data missing in all included trials. An intention-to-treat analysis was used in all. The rate of losses to follow-up varied from 0% to 0.25%. All trials recruited the pre-calculated sample size.

Selective reporting: All out comes were reported in all included studies and were all rated as low risk of bias.

Other potential sources of bias: None identified.

Effects of interventions

Comparison: The effectiveness of misoprostol versus a placebo in prevention and treatment of postpartum haemorrhage.

Incidence of PPH (Blood loss of ≥500mℓ): Three studies with a total of 2346 participants reported on the primary outcome, incidence of PPH as shown below in figure 4. There was a non-significant tendency of blood loss of ≥500mℓ for those who received Misoprostol. The summary of risk ratios of 3 trials regardless of route of administration of Misoprostol was RR 0.65 and 95% Confidence Interval (CI) 0.40 to 1.06. Misoprostol does not appear to be more effective than a placebo in treatment of PPH. There was a high level of heterogeneity amongst the studies (p=0.008), I^2= 79%. Subgroup analysis on the route of administration was conducted to explore heterogeneity.

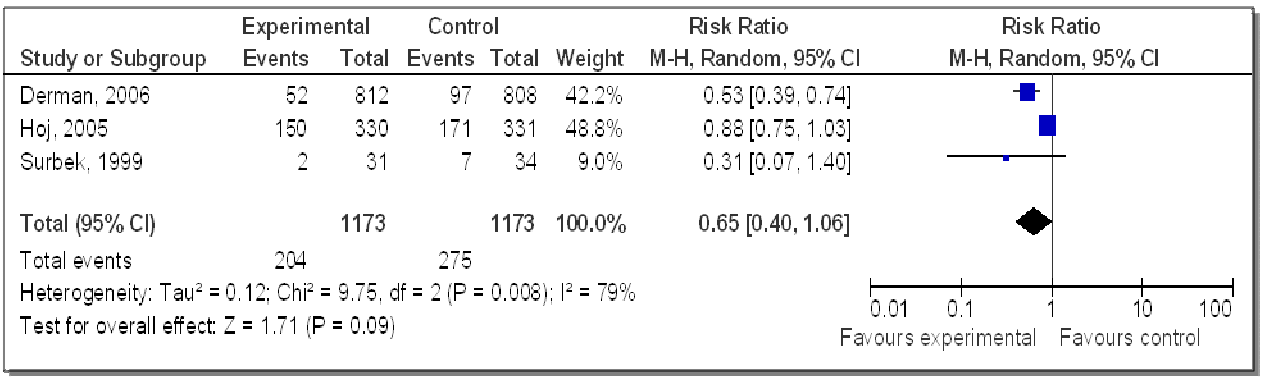

Figure 4: Random effect analysis of Misoprostol versus a placebo in prevention and treatment of PPH on incidence of PPH.

Subgroup analysis was done on the route of administration of misoprostol among trials. Route can be a confounding factor. Although oral and sublingual routes have the advantage of rapid onset of action, sublingual has the most enhanced bioavailability. In comparison of the two routes of administration, oral route was associated with a decreasing the incidence of PPH (RR 0.52, 95%CI 0.38-0.72) compared to sublingual (RR 0.89, 95% CI 0.76-1.04). We did not conduct sensitivity analyses because all included trials for this outcome were rated as 'low risk of bias' for allocation of concealment.

Need for blood transfusion: Only one trial, Derman *et al* (2006) reported on the need for blood transfusion. The study found no significant difference in need for blood transfusion between participants who got Misoprostol and placebo (RR 0.14 CI 95% 0.02 - 1.15). Meta analysis was not performed.

Hysterectomy/surgery: Only one trial (Derman *et al* 2006) reported on hysterectomy or major surgery. The overall effect of misoprostol was coupled with a reduced rate of hysterectomy/surgery compared to a placebo (RR 0.12, CI 95% 0.02-0.99). Meta analysis was not performed.

Pyrexia: Figure 5 below illustrates the occurrence of pyrexia in two trials. There were 1142 women who received Misoprostol and 1139 women who received a placebo. Meta analysis evaluating the occurrence of pyrexia revealed a statistical significant difference between the two groups (summary of RR was 5.34 (95%CI 2.86-9.96). There was evidence of significant heterogeneity among results of studies included for the outcome pyrexia (p=0.19), I^2=42%.

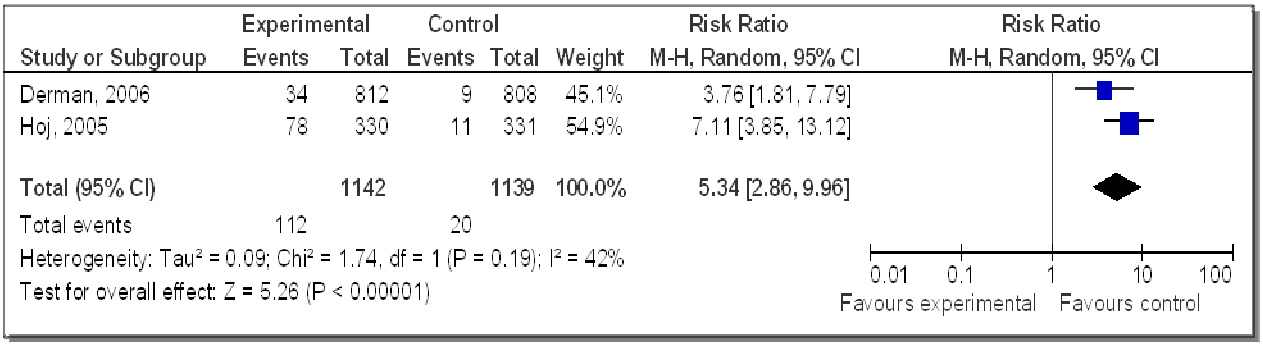

Figure 5: Random effect analysis of Misoprostol versus a placebo in prevention and treatment of PPH on Pyrexia

Shivering: There was no statistically significant difference in shivering between participants who received Misoprostol compared to those who received placebo. Misoprostol was not associated with a significant lessening of shivering RR 2.75 (95%CI 2.26 – 3.34). There was some evidence of statistical heterogeneity detected in studies (p=0.21), I^2=36%.

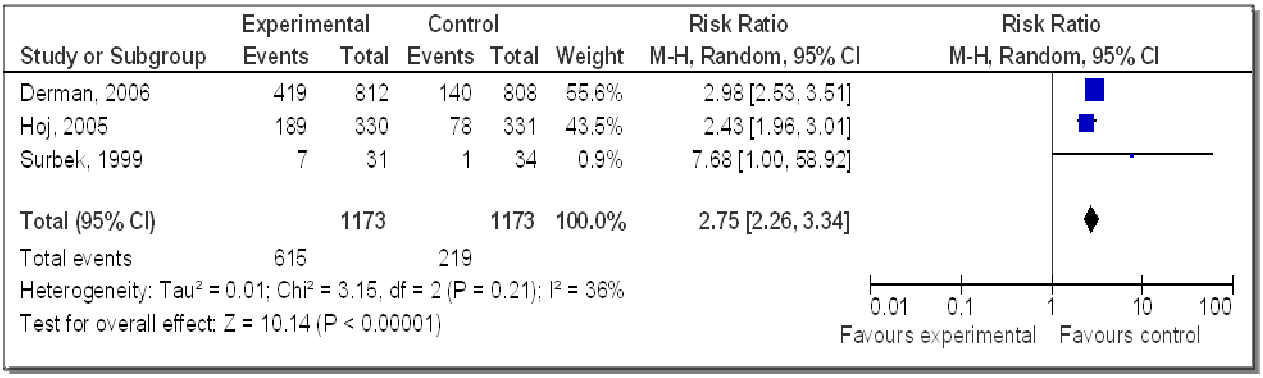

Figure 6: Random effect analysis of Misoprostol versus placebo in prevention and treatment of PPH on shivering.

Need for additional uterotonics: Figure 7 below shows results of two studies. Misoprostol was associated with reduction in need for additional uterotonics compared to a placebo (RR 0.45, 95% CI 0.21- 0.96, p=0.04). The trials were homogeneous (chi²=0.04, I²=0%, p=0.84) and there was a significant difference among all the studies as they strongly favored misoprostol with risk ratio of less than 1.

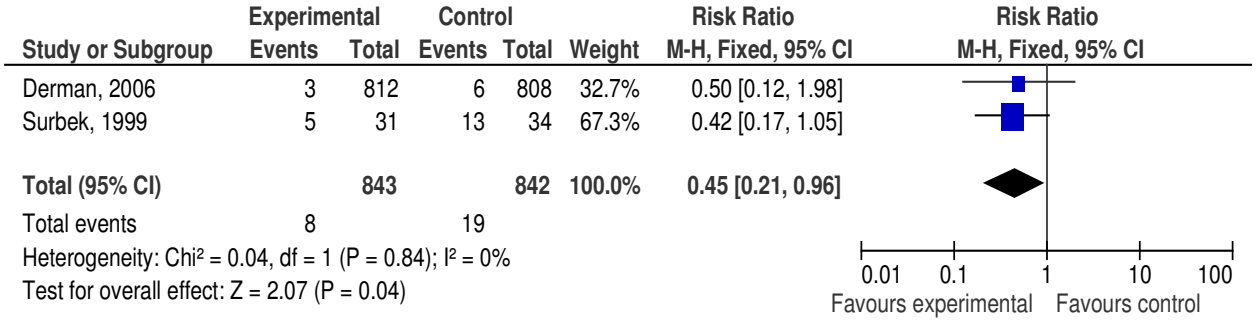

Figure 7: Fixed effect analysis of Misoprostol versus a placebo in prevention and treatment of PPH on need for additional uterotonics.

Conclusion of results

There was significant heterogeneity among results of studies on route of administration. In sub grouping of the two routes, Misoprostol administered orally does show a significant reduction in postpartum blood loss compared to sublingual route. Side effects, pyrexia and shivering were persistent in the Misoprostol group but are dose related. Maternal mortality and manual removal of placenta were not reported in all studies (n=3).

Discussion

Summary of main results

This review included comparison of misoprostol and placebo for management of third stage of labour without additional uterotonics. Meta analysis was done on results of three included studies. Misoprostol was administered orally and sublingually. Most clinically relevant outcomes that this review focused on were the incidence of PPH, occurrence of side effects and additional use of other uterotonics. In overall, Misoprostol did not show a significant reduction of PPH. However there was significant heterogeneity in the results of blood loss. Heterogeneity of results may be because of different route of administration of misoprostol. Most blood loss was shown in Hoj (2005) trial. In sub grouping of these trials by route of administration, oral route showed a significance reduction in incidence of postpartum haemorrhage compared to sublingual route in Hoj (2005) trial.

The incidence of PPH in this review is consistent with results of trial of Hofmeyr *et al* 2007, where misoprostol was associated with a trend of reduced blood loss ≥500 ml, but this dramatic effect couldn't be confirmed as the lower incidence of PPH in placebo group underpowered this result. None of the trials reported on maternal mortality and manual removal of placenta. There was no evidence to support the benefit of misoprostol in reduction of need for blood transfusion as there was only one trial that reported on blood transfusion. There was a consistent increase in pyrexia across two trials (Hoj, 2005; Derman, 2006) mostly in misoprostol arm. Shivering was also consistent among all included trials. These radical rates of side effects are concluded in other trials as been dose related (Amant, Spitz, Timmerman, Corremans and van Assche (1999) and El Refaey, O'Brien, Morafa, Walder and Rodeck (1997).

These side-effects may be related to the rapid absorption of misoprostol given orally, rapid absorption and high bioavailability when given sublingually. There was a significant decrease in need for additional uterotonics with misoprostol use. Studies were homogenous and there was no heterogeneity among them. While there was a statistically significant decrease in cases of hysterectomy with misoprostol use, results for this outcome should be interpreted with caution as heterogeneity could not be measured as only one study that reported on this outcome.

Overall completeness and applicability of evidence

This review was to discover if Misoprostol is more effective than placebo in prevention and treatment of PPH. All relevant literature was retrieved from published journals. There are no ongoing studies at present moment. The included studies concentrated on how effective Misoprostol is and body of evidence does apply to the research question. The three trials were conducted in community hospital settings where deliveries were conducted by midwives. Participants were similar across the trials, which made it more comparable. All main outcomes of interest were presented in trials but not all sub-outcomes were presented. Misoprostol was compared to a placebo in all trials. In two trials (Høj, 2005; Suberk, 1999) active management was done and in Derman (2006), passive management of third stage of labour was confirmed.

Quality of evidence

All of the studies (3 of 3) had good quality evidence (low risk of bias for sequence generation and allocation concealment). Sequence generation, blinding and allocation concealment was clearly explained in all trials. Reviewers could not assess selective reporting; however the primary outcomes of this review were addressed across all the trials. Showing both absolute and relative measures for each outcome is a more transparent evaluation of data, considering the different weight that several variables have on such measures. We accomplished such a need by reporting both RR.

Potential biases in the review process

All relevant studies were identified. A comprehensive search of more than one database for RCTs was implemented to minimize selection bias. Potential bias can result when databases have published only trials that there feel will suit their database. We followed methods set out in the Cochrane Handbook (Higgins 2003) to try to reduce bias in the review process. The review is not able to provide data about the possible biasing effect of protocol violations on the results as we did not have actual protocols of trials. The review only considered published trials hence other trials that are not published that may benefit and alter results of this review may be left out.

Agreements and disagreements with other study reviewers

A Cochrane review by Gulmezoglu *et al* (2011) entitled "prostaglandins for preventing Postpartum haemorrhage" also carried out meta analysis on the effectiveness of misoprostol compared to a placebo. The results of this review are in agreement with the above mentioned review on the incidence of PPH when misoprostol is administered orally. However, in their review, they compared studies that used misoprostol in addition to other uterotonics unlike in this review where meta analysis was done only in studies that compared misoprostol without additional uterotonics. The true benefit of misoprostol in prevention and treatment of third stage of labour can only be revealed when misoprostol is used alone not combined with the effect of other uterotonics.

Authors' conclusions

Implications to research

Future randomized controlled trials are required to identify the best route, and dose of misoprostol, for the treatment of primary PPH. Side effects (pyrexia and shivering) associated with Misoprostol are dose related and should be watched carefully. Home deliveries in some communities are still evident. It is vital to investigate on interventions to control of PPH following home deliveries. More importantly, trials must be large enough to assess maternal morbidity and mortality. There has being a lack of research linking management of the third stage of labour to what has occurred in the first and second stages of labour. It may be timely to assess possible effects of current strategies for management of labour on rates of PPH. None of the included trials has addressed the women's preferences, associated with uterotonic options. It would be of interest to embrace this aspect of care in future research on trials of uterotonic choice.

Limitations

The review focused mainly on studies that compared misoprostol to a placebo, not in addition to other uterotonics, hence only three trials included for analysis. This may result in other studies that tested misoprostol to a placebo to be left out, which could have benefitted on the findings of this review.

Conclusion

The overall use of misoprostol was not associated with any significant reduction in amount of blood loss. Studies included in the review were not large enough to evaluate the effects of misoprostol on maternal mortality, in women with primary PPH. Because of the enormous potential impact of PPH on maternal health in poor countries, further research aiming to evaluate effects of misoprostol on substantive health outcomes, its safety and the optimal route and dosage is of the utmost urgency. Misoprostol is relatively cheap easy to administer compared to injectable uterotonics (oxytocin, ergometrine) of which are considered first line of treatment by WHO. Ergometrine and syntometrine are contraindicated in hypertensive pregnant women as they stimulate vasoconstriction and causes hypertension. Injectable uterotonics need skill to administer, sterile syringes, alcohol swabs, unstable in tropical conditions and requires special storage facilities to maintain efficacy, whereas Misoprostol is devoid of these constraints and may therefore be an alternative treatment of in developing countries where storage facilities and resources are limited.

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PART B

APPENDICES

Appendix 1 : Data extraction form 01

1. Source

Study ID	Derman, 2006
Reviewer	Kabelo Monicah Olefile; Oswell Khondowe
Author & year	Derman, R.J, Kodkany, B.S., Goudar, S.S., Geller, S.E., Naik, V.A., Bellad, M. B., Patted, S.S., Patel, A., Edlavitch, S.A., Hartwell, T., Chakraborty, H. & Moss,N., 2006
Journal	Lancet; 368: 1248–53.,
Title	Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial
Country	India

2. Eligibility

(Tick in the appropriate spaces)

2.1 Types of studies

RCT	√
Quasi-experimental	**-**
Published study	√

2.2 Types of participants

Term pregnancy	√
Spontaneous vaginal deliveries	√
Caesarean section	**-**

2.3 Types of intervention

(Tick in the appropriate spaces and provide details of treatment given)

Treatment		Details
Misoprostol vs placebo	√	600µg orally
Misoprostol vs placebo in addition to other uterotonics	-	-

2.4 Types of outcomes

Incidence of PPH (blood loss ≥500mℓ)	√
Maternal mortality	√
Need for Blood transfusion	√
Hysterectomy/Surgery	√
Manual removal of placenta	
Pyrexia	√
Shivering	√
Need for Additional uterotonics	√

2.5 Participants lost to follow-up <15%

Total number of participants	Total number lost	% lost
1620	4	0.25%

2.5.1 Reasons for loss to follow-up

3 participants did not receive misoprostol **Reasons:** patient transferred, twin delivery, and excess bleeding
1 did not receive placebo **Reason:** stillbirth

2.5.2 Other reasons for exclusion

None.

Methodology

3.1 Study design

RCT	√	**Multi centre**	√
Quasi-experimental	**-**	**Single centre**	

3.2 Duration of Study

Months	39 months

3.3 Eligibility Criteria

-pregnant women with uncomplicated spontaneous vaginal delivery.
-more than 28 weeks pregnant.
-no chronic diseases.

Methodological quality/ risk of bias assessment

(Answer the domain question with **"LR"** signifying low risk of bias, **"HR"** signifying high risk of bias, **"U"** signifying lack of information or unknown risk of bias).

3.4 Cochrane collaboration "Risk of bias" Tool

Entry	**Judgement**	**description**
Adequate sequence generation?	**LR**	Computer generated randomization
Allocation concealment?	**LR**	Non-distinguishable envelops with drug of same appearance.
Blinding of participants, personnel and outcome assessors?	**LR**	Preparation of envelops by independent pharmacist. Personnel & participants blinded.
Incomplete outcome data addressed?	**LR**	No data was missing
Selective outcome reporting?	**LR**	Reported on all outcomes
Other bias?	**LR**	Conflict of interest declared

3.5 Participants

Total number	1620
Total number analyzed	1620
Single or twin pregnancy	Single
Mode of delivery	Vaginal delivery
High risk or low risk	Low risk
Study setting	Sub centre of health.
Age of participants (mean)	23.2
Sex	Females
Country	India

3.6 Interventions

Experimental group			
Type	**Route**	**Dose**	**Time given**
Misoprostol	orally	600µg	Within 5 minutes of clamping and cutting of the umbilical cord
Control group			
Type	**Route**	**Dose**	**Time given**
Placebo	Orally	600µg	Within 5 minutes of clamping and cutting of the umbilical cord

3.7 Outcomes relevant to this review

(Tick where appropriate)

Incidence of PPH (blood loss ≥500mℓ)	**YES√**	**NO**
Maternal mortality	**YES√**	**NO**
Need for Blood transfusion	**YES√**	**NO**
Hysterectomy/Surgery	**YES√**	**NO**
Manual removal of placenta	**YES√**	**NO**
Pyrexia	**YES√**	**NO**
Shivering	**YES√**	**NO**
Need for Additional uterotonics	**YES√**	**NO**

4. Results

Total number of participants		
	Total Randomised	**Total included in analysis**
Experimental arm	812	812
Control arm	808	808
Total	1620	1620

4.1 summary data for each intervention group

Outcomes	**Intervention groups**			
	E		**C**	
	E	**T**	**E**	**T**
Incidence of PPH (blood loss ≥500mℓ)	52	812	97	808
Maternal mortality	0	812	0	808
Need for Blood transfusion	1	812	7	808
Hysterectomy/Surgery	1	812	8	808
Manual removal of placenta	0	812	0	808
Pyrexia	34	812	9	808
Shivering	419	812	140	808
Need for Additional uterotonics	3	812	6	808

4.2 Continuous data: N/A

4.3 Subgroup analysis

Appendix 2: Data extraction form 02

1. Source

Study ID	Suberk,1999
Reviewer	Kabelo Monicah Olefile, Oswell Khondowe
Author & year	Suberk, D.V., Fehr, P.M., Hösli, I. & Holzgreve, W. 1999.
Journal	Elsevier Science Incorporation; 92: 255-258.
Title	Oral Misoprostol for Third Stage of Labor: A Randomized Placebo-Controlled Trial
Country	Switzerland

2. Eligibility

(Tick in the appropriate spaces)

2.1 Types of studies

RCT	√
Quasi-experimental	**-**
Published study	√

2.2 Types of participants

Term pregnancy	√
Spontaneous vaginal deliveries	√
Caesarean section	**-**

2.3 Types of intervention

(Tick in the appropriate spaces and provide details of treatment given)

Treatment		Details
Misoprostol vs placebo	√	600µg orally
Misoprostol vs placebo in addition to other uterotonics	-	-

2.4 Types of outcomes

Incidence of PPH (blood loss ≥500mℓ)	√
Maternal mortality	√
Need for Blood transfusion	**-**
Hysterectomy/Surgery	**-**
Manual removal of placenta	**-**
Pyrexia	**-**
Shivering	**-**
Need for Additional uterotonics	√

2.5 Participants lost to follow-up <15%

Total number of participants	Total number lost	% lost
65	0	0%

2.5.1 Reasons for loss to follow-up

None applicable

Methodology

3.1 Study design

RCT	√	**Multi centre**	**-**
Quasi-experimental	**-**	**Single centre**	√

3.2 Duration of Study

Months	11 months

3.3 Eligibility Criteria

Women with anticipated vaginal deliveries.

Methodological quality/ risk of bias assessment

(Answer the domain question with **"LR"** signifying low risk of bias, **"HR"** signifying high risk of bias, **"U"** signifying lack of information or unknown risk of bias).

3.4 Cochrane collaboration "Risk of bias" Tool

Entry	Judgement	description
Adequate sequence generation?	**LR**	Random generated tables
Allocation concealment?	**LR**	Study drugs allocation prepared by hospital pharmacy. Identical drug capsules.
Blinding of participants, personnel and outcome assessors?	**LR**	Randomisation code not broken till completion of study. Participants and midwives unaware of treatment allocation.
Incomplete outcome data addressed?	**LR**	No missing data

Selective outcome reporting?	**LR**	Reported on all outcomes
Other bias?	**Unclear**	None

3.5 Participants

Total number	65
Total number analyzed	65
Single or twin pregnancy	single
Mode of delivery	Vaginal delivery
High risk or low risk	Low risk
Study setting	Hospital setting
Age of participants (mean)	29.3
Sex	Female
Country	Switzerland

3.6 Interventions

Experimental group			
Type	**Route**	**Dose**	**Time given**
Misoprostol	Orally	600 mg	Immediately after cord clamping
Control group			
Type	**Route**	**Dose**	**Time given**
Placebo	Orally	600 mg	Immediately after cord clamping

3.7 Outcomes relevant to this review

(Tick where appropriate)

Incidence of PPH (blood loss ≥500mℓ)	**YES√**	**NO**
Maternal mortality	**YES√**	**NO**
Need for Blood transfusion	**YES**	**NO**
Hysterectomy/Surgery	**YES**	**NO**
Manual removal of placenta	**YES**	**NO**
Pyrexia	**YES**	**NO**
Shivering	**YES**	**NO**
Need for Additional uterotonics	**YES√**	**NO**

4. Results

Total number of participants		
	Total Randomised	**Total included in analysis**
Experimental arm	31	31
Control arm	34	34
Total	65	65

4.1 summary data for each intervention group

Outcomes	**Intervention groups**			
	E		**C**	
	E	**T**	**E**	**T**
Incidence of PPH (blood loss ≥500mℓ)	2	31	7	34
Maternal mortality	0	31	0	34
Need for additional uterotonics	5	31	13	34

4.2 Continuous data: N/A

4.4 Subgroup analysis: N/A

Appendix 3: Data extraction 03

1. Source

Study ID	Hoj,2005
Reviewer	Kabelo Monicah Olefile: Oswell Khondowe
Author & year	Hoj, L., Cardoso, P., Nielsen, B.B., Hvidman, L., Nielsen, J. & Aaby, P. 2005.
Journal	*British Medical Journal;* 331: 723.
Title	Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomised double blind clinical trial
Country	Guinea-Bissau

2. Eligibility

(Tick in the appropriate spaces)

2.1 Types of studies

RCT	√
Quasi-experimental	**-**
Published study	√

2.2 Types of participants

Term pregnancy	**-**
vaginal deliveries	√
Caesarean section	**-**

2.3 Types of intervention

(Tick in the appropriate spaces and provide details of treatment given)

Treatment		Details
Misoprostol vs placebo	√	600µg misoprostol
Misoprostol vs placebo in addition to other uterotonics	-	-

2.4 Types of outcomes

Incidence of PPH (blood loss ≥500mℓ)	√
Maternal mortality	√
Need for Blood transfusion	**-**
Hysterectomy/Surgery	**-**
Manual removal of placenta	**-**
Pyrexia	√
Shivering	√
Need for Additional uterotonics	**-**

2.5 Participants lost to follow-up <15%

Total number of participants	**Total number lost**	**% lost**
661	0	0%

Methodology

3.1 Study design

RCT	√	**Multi centre**	**-**
Quasi-experimental	**-**	**Single centre**	√

3.2 Duration of Study

Months	17 months

Methodological quality/ risk of bias assessment

(Answer the domain question with **"LR"** signifying low risk of bias, **"HR"** signifying high risk of bias, **"U"** signifying lack of information or unknown risk of bias).

3.4 Cochrane collaboration "Risk of bias" Tool

Entry	Judgement	description
Adequate sequence generation?	**LR**	Random blocked sizes were used. (computer-generated Randomisation)
Allocation concealment?	**LR**	Pharmacy controlled randomization, opaque envelopes. Identical tablets in form, size and color.
Blinding of participants, personnel and outcome assessors?	**LR**	Double blinding
Incomplete outcome data addressed?	**LR**	No data missing.
Selective outcome reporting?	**LR**	Reported on all mentioned outcomes.
Other bias?	**LR**	Conflict of interest declared.

3.5 Participants

Total number	661
Total number analyzed	661
Single or twin pregnancy	Single
Mode of delivery	Vaginal delivery
High risk or low risk	Low risk
Study setting	Local health centre
Age of participants (mean)	23yrs
Sex	Females
Country	Guinea-Bissau

3.6 Interventions

Experimental group			
Type	**Route**	**Dose**	**Time given**
Misoprostol	sublingually	600µg	immediately after delivery
Control group			
Type	**Route**	**Dose**	**Time given**
Placebo	sublingually	600µg	immediately after delivery

3.7 Outcomes relevant to this review

(Tick where appropriate)

Incidence of PPH (blood loss ≥500mℓ)	**YES√**	**NO**
Maternal mortality	**YES√**	**NO**
Need for Blood transfusion	**YES**	**NO√**
Hysterectomy/Surgery	**YES**	**NO√**
Manual removal of placenta	**YES**	**NO√**
Pyrexia	**YES√**	**NO**
Shivering	**YES√**	**NO**
Need for Additional uterotonics	**YES**	**NO√**

4. Results

Total number of participants		
	Total Randomised	**Total included in analysis**
Experimental arm	**330**	**330**
Control arm	**331**	**331**
Total	**661**	**661**

4.1 summary data for each intervention group

Outcomes	**Intervention groups**			
	E		**C**	
	E	**T**	**E**	**T**
Incidence of PPH (blood loss ≥500mℓ)	150	330	170	331
Maternal mortality	0	330	0	330
pyrexia	78	330	11	331
Shivering	189	330	78	331

4.2 Continuous data: N/A

4.3 Subgroup analysis

Appendix 4: Table of excluded studies

Citation	Reasons for exclusion
Abdel-Aleem, H., El-Nashar, I. & Abdel-Aleem, A. 2001. Management of severe postpartum hemorrhage with misoprostol. *International Journal of Gynecology & Obstetrics*; 72: 75-76.	Short brief.
Adekanmi, O.A., Purmessur, S., Edwards, G. & Barrington, J.W. 2001. Intrauterine misoprostol for the treatment of severe recurrent atonic secondary postpartum haemorrhage. *British Journal of Obstetrics and Gynaecology;* 108: 541-542.	Case report.
Afolabi, E.O., Kuti, O., Orji, E. O. & Ogunniyi, S. O. 2010. Oral misoprostol versus intramuscular oxytocin in the active management of the third stage of labour. *Singapore Medical Journal;* 51: 207-211.	Interventions not of interest.
Ahmed, N., Ahmed, Y., Shahin, A. M., Elsamman, M.S. Zakherah, O. & Shaaban, O. 2009. Rectal misoprostol versus intravenous oxytocin for prevention of postpartum hemorrhage. *International Journal of Gynecology and Obstetrics* 105: 244–247.	Interventions not of interest.
Amant, F., Spitz, B., Timmerman, D., Corremans, A. & van Assche, F.A. 1999. Misoprostol compared with methylergometrine for the prevention of postpartum haemorrhage: A double-blind randomized trial. *British Journal of Obstetrics and Gynaecology*; 106(10):1066–70.	Misoprostol compared to ergometrine.
Blum, J., Winikoff, B., Raghavan, S., Dabash, R., Ramadan, M.R., Dilbaz, B., Dao, B., Durocher, J., Yalvac, S., Diop, A., Dzuba, I.G. & Ngoc, N.T.	Misoprostol compared to oxytocin, not placebo.

2010. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. *Lancet*; 375: 217–23.	
Blum, J., Alfirevic, Z., Walraven, G., Weeks, A. & Winikoff, B. 2007. Treatment of postpartum Haemorrhage with Misoprostol. *International Journal of Gynecology & Obstetrics*; 99: 202-205.	A systematic review.
Bugalho, A., Daniel, A., Faundes, A. & Cunha, M. Misoprostol for prevention of postpartum hemorrhage. *International Journal of Gynaecology Obstetrics*; 73: 1–6.	Misoprostol compared to oxytocin, not placebo
Campbell, M.R. & Graham, W.J. 2006. Strategies for reducing maternal mortality: Getting on with what works. *Lancet*; 368: 1284–99.	A comment.
Carroli, G. 2002. Side effects of oral misoprostol during the first 24 hours after administration in the third stage of labour. *British Journal of Obstetrics & Gynaecology;* 109:1222–26.	Outcomes not of interest.
Cook, C.M., Spurrett, B. & Murray, H. 1999. A randomized clinical trial comparing oral misoprostol with synthetic oxytocin or syntometrine in the third stage of labour. Australia and New Zealand Journal of Obstetrics & Gynaecology; 39:414–9.	Misoprostol compared to oxytocin, not placebo
El-Refaey, H., O'Brien, P., Morafa, W., Walder, J. & Rodeck, C. 1997. Use of oral misoprostol in the prevention of postpartum haemorrhage. *British Journal of Obstetrics & Gynaecology;* 104:336 –9.	Misoprostol
El-Refaey, H., Nooh, R., O'Brien, P., et al. 2000.The misoprostol third stage	Misoprostol compared to standard treatment.

of labour study: A randomised controlled comparison between orally administered misoprostol and standard management *British Journal of Obstetrics and Gynaecology*; 107: 1104–10.	
Fawcus, F. & Moodley, J. 2011. Management of postpartum haemorrhage. *South African Journal of Obstetrics & Gynaecology;* 17: 1-2.	An editorial.
Fawole, A.O., Sotiloye, O.S., Hunyinbo, K.I., Umezulike, A.C., Okunlola, M.A., Adekanle, D.A., et al 2010. Misoprostol and routine uterotonics for prevention of postpartum hemorrhage: A double-blind, randomized, placebo controlled trial. *International Journal of Gynecolology & Obstetrics;* 112:107–111.	Misoprostol compared to routine uterotonics.
Hofmeyr, G.J., Fawole, B., Mugerwa, K., Godi, P., Blignaut, Q., Mangesi, L, Singata, M., Brady, L., Blum, J. 2010. Administration of 400 µg of misoprostol to augment routine active management of the third stage of labor. *International Journal of Gynecology and Obstetrics;* 112: 98–102.	Misoprostol compared to routine management of PPH.
Hofmeyr, G.J., Ferreira, S. & Nikodem, V.C. 2004. Misoprostol for treating postpartum haemorrhage: A randomized controlled trial. *BioMedical Centre Pregnancy Childbirth*. 4: 16	Misoprostol compared to a placebo in addition to other uterotonics.
Hofmeyr, G. J., Walraven, G. & Gülmezoglu, A.M. 2007. Misoprostol to treat postpartum haemorrhage: A systematic review. *Journal of Obstetrics& Gynecology*. 112: 547–553.	A systematic review.
Hofmeyr, G.J., Nikodem, V.C., de Jager, M. & Drakely, A. 2001. Side-effects of oral misoprostol in the third stage of labour—a randomised placebo-	Misoprostol compared to a placebo in addition to other uterotonics

controlled trial. *South African Medical Journal*; 91: 432–35.	
Hofmeyr, G.J., Nikodem, V.C., de Jager, M. & Gelbart, B.R. 1998. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. *British Journal of Obstetrics & Gynaecology*; 105:971–5.	Misoprostol compared to a placebo in addition to other uterotonics.
Kundodyiwa, T.W., Majoko, F. & Rusakaniko S. 2001. Misoprostol versus oxytocin in the third stage of labor. *International Journal of Gynaecology and Obstetrics*; 75: 235–41.	A preliminary report.
Langenbach C. 2006. Misoprostol in preventing postpartum hemorrhage: A meta-analysis. *International Journal of Gynaecology and Obstetrics*; 92: 10–18.	A systematic review.
Lokugamage, A. U., Sullivan, K.R., Niculescu, O., Tigere, P., Onyangunga, F., El- Refaey, H., Moodley, J. & Rodeck, C. 2001. A randomized study comparing rectally administered misoprostol *versus* Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. *Acta Obstetrics & Gynecology Scandinavica;* 80: 835–839.	Misoprostol compared to other uterotonics.
Lombaard, H., & Pattison, R.C. (2009). Common errors and remedies in managing Postpartum Haemorrhage*: Maternal and Fetal Medicine Unit, Department of obstetrics & Gynecology,* University of Pretoria, 1-10.	Irrelevant and does not report on outcomes of interest.
Miller, S., Lester, F. & Hensleigh, P., (2004). Prevention and treatment of postpartum hemorrhage: New advances for low-resource settings. *Journal of Midwifery Women's Health*, 49: 283-92.	Does not report on outcomes of interest.
McCormick, M. L., Sanghvi, H.C., Kinzie, B., & McIntosh, N. 2002.	Review article.

Preventing postpartum haemorrhage in low-resource settings. *International Journal of Gynecology and Obstetrics*; 77: 267–75.	
Mousa, H. A., Cording, V., & Alfirevic, Z. 2008. Risk factors and interventions associated with major primary postpartum hemorrhage unresponsive to first-line conventional therapy. *Acta Obstetric Gynecology*, 87: 652–661.	Does not report on outcomes of interest.
Ng, P.S., Chan, A.S., Sin, W.K., Tang, L.C., Cheung, K.B., & Yuen, P.M. 2001.A multicentre randomized controlled trial of oral misoprostol and intramuscular syntometrine in the management of the third stage of labour. *Human Reproduction*; 16: 31–35.	Misoprostol compared to syntometrine.
Prendiville, W.J., Elbourne, D. & McDonald, S. 2000. Active versus expectant management in the third stage of labour. *Cochrane Database Systematic Review*; Issue (3):CD000007.	Interventions not of interest.
Prendiville, W.J. 1996. The prevention of postpartum haemorrhage: Optimizing routine management of the third stage of labour. *European Journal of Obstetrics, Gynecology & Reproductive Biology*, 69: 19-24.	Interventions not of interest.
Sadiq, S.S., Hasmi, U., Aman, Q. & Zareen, N. 2008.Prophylactic use of oxytocin (syntoncinon) vs oxytocin plus ergometrine (syntometrine) for prevention of postpartum haemorrhage. *Pakistan Journal of Surgery,* 24: 235- 239.	Interventions not of interest
Singh, G., Radhakrishnan, G. & Guleria, K. 2009. Comparison of sublingual misoprostol, intravenous oxytocin, and intravenous methylergometrine in active management of the third stage of labor. *International Journal of*	Misoprostol compared to other uterotonics.

Gynecology and Obstetrics; 107: 130–134.	
Tang, O.S., Schweer, H., Seyberth, H.W., Lee, S.W.H. & Ho, P.C. 2002. Pharmacokinetics of different routes of administration of misoprostol. *Human Reproduction; 17:332*-336.	Systematic Review.
Vimala, N., Mittal, S. & Kunar, S. 2006. Sublingual misoprostol versus oxytocin infusion to reduce blood loss at cesarean section. *International Journal of Gynecology* and Obstetrics; 92: 106–10.	Misoprostol compared to oxytocin.
Walley, R.L., Wilson, J.B., Crane, J.M., Matthews, K., Sawyer, E. & Hutchens, D. 2000. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. *British Journal of Obstetrics and Gynaecology*; 107: 1111–15.	Misoprostol compared to oxytocin.
Walraven, G., Dampha, Y., Bittaye, B., Sowe, M. & Hofmeyr, J. 2004. Misoprostol in the treatment of postpartum haemorrhage in addition to routine management: A placebo randomized controlled trial. *British Journal of Obstetrics and Gynaecology*; 111: 1014–17.	Misoprostol compared to a placebo combined to routine management.
Weeks, A. 2006. Oral misoprostol for postpartum haemorrhage. *Lancet*; 368: 2123.	Editorial.
Widmer, M., Blum, J., Hofmeyr, G.J, Carroli, G., Abdel-Aleem, H., Lumbiganon, P., et al. 2010. Misoprostol as an adjunct to standard uterotonics for treatment of post-partum hemorrhage: A multicentre, double-blind randomized trial. *Lancet;* 375:1808–13.	Misoprostol compared to a placebo in addition to other uterotonics.
Winikoff, B., Dabash, R., Durocher, J., Darwish, E., Nguyen, T.N. & Leon, W.	Misoprostol compared to oxytocin.

2007. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: A double-blind, randomised, non-inferiority trial. *The Lancet*; 375: 210-6.	
Zieman, M., Fong, S.K., Benowitz, N.L., Banskter, D. & Darney, P.D. 1997. Absorption kinetics of misoprostol with oral or vaginal administration. *International Journal of Gynaecology Obstetrics*; 90: 88–92.	Outcomes not of interest.
Zuberi, N., Durocher, J., Sikander, R., Baber, N., Blum, J. & Walraven, G. 2008. Misoprostol in addition to routine treatment of postpartum hemorrhage: A hospital-based randomized controlled-trial in Karachi, Pakistan. *BioMedical Centre Pregnancy Childbirth*; 8: 40.	Misoprostol compared to a placebo in addition to routine management.

Appendix 4: Prisma Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	41
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this	23

		information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	14
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	14
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	23
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	15
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8,20
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	23
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12,23,35
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	20,36
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	25
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	23
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	34
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	34
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	33
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data);	N/A

		role of funders for the systematic review.	