A Pill to Save Bleeding Mothers: a Meta-analysis of Misoprostol's Effectiveness, Safety, and Dosage for the Prevention of Postpartum Hemorrhage in Resource-Poor Communities.

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Thesis Abstract

Objective

Postpartum hemorrhage (PPH) is a major cause of maternal mortality world-wide; misoprostol is a relatively cheap, easily administered, and an efficient medication to be given after the delivery of the baby to prevent PPH, thus posing it as a first choice in resource-poor communities. The aim of this study is to answer questions regarding the most appropriate dose (400 µg versus 600 µg), effect of labour settings (community or clinical), and management of labour on misoprostol effectiveness and safety in preventing PPH.

Methods

We developed a search strategy and conducted a search within five key databases. Two reviewers screened the articles for predefined inclusion/exclusion criteria, quality, and performed data extraction. Discrepancy was dealt with by reaching consensus. In article 1, we only included randomized controlled trials, we performed a random-effects Bayesian network meta-analysis comparing 400 µg to 600 µg misoprostol over five outcomes of interest: blood loss ≥500 ml, blood loss ≥1000 ml, using additional uterotonics, shivering, and pyrexia. In article 2, we included any experimental trial, we performed a random effects model meta-analysis, pooling the incidence of PPH from each misoprostol arm. Subsequently, a meta-regression model was performed on identified potential effect-modifiers, including clinical settings and labour management.

Results

Of 444 identified records, 46 trials met the inclusion/exclusion criteria in article 1, and 56 trials in article 2. The odds ratio (OR) of misoprostol 400 µg vs. 600 µg for bleeding ≥ 500 ml is 0.86 [95% Credible Intervals: 0.46 − 1.54], for bleeding ≥ 1000 ml the OR is 0.83 [95% CrI 0.54 – 1.26], for additional uterotonics is 0.75 [95% CrI 0.40 – 1.40], for pyrexia and shivering an OR of 0.57 [95% CrI 0.15 – 2.18] and 0.63 [95% CrI 0.29 – 1.31] respectively. The overall incidence of PPH was 6.62 per 100 pregnancies (95%CI 4.71 per 100 – 8.53 per 100). Labour settings and other aspects of active management of labour had no statistically significant effect on the incidence of post-partum hemorrhage.

Conclusion

We found no difference between the administration of misoprostol 400 µg or 600 µg for the prevention of PPH and side effects of misoprostol, as well as no effect of labour settings and management of labour on misoprostol effectiveness.

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Preface

Ghayath Janoudi led the protocol development, co-ordinated the research efforts, developed the search strategy with a consultation of a medical librarian, performed the literature search, screened the articles as the first reviewer, extracted data as the first reviewer, assessed biases as the first reviewer, analysed data, wrote the manuscript, and performed necessary revisions. Laura Mesana helped in developing the protocol, screened the articles as a second reviewer, extracted date as a second reviewer, and assessed biases as a second reviewer. Mark Walker provided clinical guidance and expertise, reviewed the protocol, reviewed the manuscript, and provided revisions. Edward Mills provided methodological guidance and expertise, acted as a third reviewer in cases of discrepancy among the first two reviewers, provided training in evidence synthesis practice, reviewed the protocol, reviewed the manuscript, and provided revisions.

Introduction

Dying as a result of childbirth should not be accepted. Giving birth is a physiologic process that could expose the mother to certain vulnerabilities, which, with the right care, should not lead to such a tragic outcome as death. Unfortunately, in the year 2013, an estimated 292,982 [95% uncertainty interval (UI) 261 017–327 792] maternal deaths occurred worldwide (1), 99% of which happened in developing countries (1). Postpartum hemorrhage (PPH) is a globally leading cause of maternal mortality (1).

Postpartum haemorrhage (PPH) is defined as any bleeding in excess of 500mL within 24 hours of vaginal delivery (2). The majority of cases of PPH are due to loss of the ability of the uterus to contract and compress the bleeding vessels (uterine atony)(2). PPH usually has a dramatic presentation and can quickly lead to signs of hypovolemic shock which, if not treated abruptly, can cause the death of the mother(3). However, the frequency of PPH can be significantly reduced with the right methods of care and management of labour, these include active management of labour (umbilical cord traction and early clamping), and administering an uterotonic agent such as oxytocin, ergometrine, or a combination of both (4-6).

Misoprostol has been recommended as a valid option for the prevention of PPH when oxytocin or ergometrine are not available (7). With the advantages of misoprostol being relatively inexpensive, thermally stable, and administered orally, all make it a very attractive candidate for developing countries and resource poor communities.

There is no general consensus, however, on the least effective dosage of misoprostol for the prevention of PPH. In addition, it is unknown to what extent certain environmental and clinical conditions that are present in randomised controlled trials (RCT) affect the outcome of PPH and thus the generalisability of the protective effect of misoprostol on PPH to the community settings.

Literature review

Misoprostol has been extensively used “off-label” in obstetrics and gynaecology. It is a synthetic prostaglandin E1 analog that has been long recognized for its ability to inhibit gastric acid secretions (8) and was introduced as a medication for the prevention and treatment of gastro-duodenal

ulcers(9). In 1991, misoprostol's ability to act as a potent utero-contractive agent was made use of in the field of medical abortion (10) and it quickly gained influence as the drug of choice in medical abortions (11). The discovery of misoprostol as a potent contracting agent for the uterus led to the hypothesis that it is able to treat and prevent uterine atony, a major etiology of PPH. In addition, misoprostol has a relative low cost, is thermal stability, and its availability to be administered orally, sublingually, vaginally, or rectally have all led to a great interest in misoprostol to treat and prevent postpartum haemorrhage in developing countries (12).

A series of systematic reviews have shown that misoprostol has a protective effect against PPH when compared to placebo, but might not be as efficient as oxytocin (12-16). However, under the setting of a resource poor community, misoprostol has advantages over the other conventional therapies; being relatively inexpensive, thermally stable, and, since it can be taken orally, would not require special training for administration. These factors have led the WHO to recommend misoprostol 600 µg for the prevention of PPH in areas where access to oxytocin or ergometrine is not possible (7).

Despite its shown benefits, misoprostol is not without side effects. It is, though, considered to be a generally safe drug (17). The most common side effect would be diarrhea that would cease in two to six hours (17). Other side effects emphasized by clinical trials that investigated misoprostol in the setting of postpartum haemorrhage; they have reported chills and fever that are dose dependent and would manifest the most in doses > 600µg (17). A Cochrane review in 2013 examined the effect of misoprostol on maternal mortality and morbidity (16); the review included 78 studies with a total 59,216 participants and had a primary objective of reviewing maternal deaths and sever morbidity in the RCTs of misoprostol. There was no statistically significant difference in maternal mortality when misoprostol was compared against all control groups (placebo and other uterotonic agents) (16).

The recommendation provided by the WHO was largely based on randomised controlled trials that took place under a clinical environment (7). As such, the issue of generalisability of these results into a mass PPH prevention campaign in peripheral community settings come into question. In addition, while the dosage of 600 µg has been recommended, a lower dosage might have a similar protective effect with a possible lower profile of side-effects. A synthesis of the available evidence to address these points remain largely unachieved.

To shed light on the previous points, we conducted two systematic reviews, one with a network meta-analysis, and the other with a classic meta-analysis using a mixed-effect model.

Research questions

A) In labouring mothers receiving 400µg misoprostol, compared to labouring mothers receiving 600µg misoprostol, is the incidence of postpartum haemorrhage higher?
B) In deliveries outside healthcare facilities, would administering misoprostol to labouring mothers, compared to deliveries inside healthcare facilities, be more protective against postpartum haemorrhage?
C) In labouring mothers who receive misoprostol alone, compared to labouring mothers who receive misoprostol as part of the active management of the third stage of labour, is the incidence of postpartum haemorrhage higher?

Methods

Each of the articles presented have a separate methods section. While they both share the same search strategy, the same population, intervention, and comparison; article one restricts the studies inclusion to randomised controlled trials, while article two allows the inclusion of non-randomised and quasi-experimental trials. In addition, each article have a different approach to data analysis.

Article one will address question "A" and will also include an analysis of the comparative side-effect profile of misoprostol 400 µg vs 600 µg. This will be achieved through employing a network meta-analysis model under a Bayesian statistics framework. Article two will address questions "B" and "C" through employing a mixed effect model by introducing the settings and management of labour as a potential treatment effect-modifiers that may influence the incidence of PPH in mothers taking misoprostol for prevention purposes.

A detailed methodology is presented in each article. Thus the reader is advised to consult the methodology section in each of the articles separately.

Discussion of Bayesian approach network meta-analysis

The research employed two methods; Bayesian network meta-analysis to establish a comparative effectiveness between the two most commonly used misoprostol doses (400 µg and 600 µg), and a frequentist meta-regression model to assess for the effect of possible treatment effect-modifiers, both analytical methods were used to analyze evidence derived from a systematic review of published literature. We will focus this discussion on the Bayesian network meta-analysis, since as the meta-regression model is a commonly used method derived from regression statistics and applied to handle studies instead of individual data, which adds the component of intra-study variability into the model (18).

Network meta-analysis (NMA) is a method used to combine direct and indirect evidence comparing two or more health interventions (19). The advantages of this method is the utilization of all available evidence and its ability to compare several interventions simultaneously (20). With the use of NMA, evidence can be reached, or strengthened, for comparisons of health interventions without the need for expensive and time consuming primary research. In addition, NMA results allow the reader to pick up the best intervention from all that have been analyzed (20). Using NMA as a method for providing evidence for health policy makers have been adopted since the 2004, and the uptake f this method has been ever increasing (21).

The main difference between Bayesian statistics and frequentist statistics is the concept in Bayesian statistics that prior evidence, outside the experiment observation, should be included when reaching a final decision regarding the true effect and result of said experiment (22). This concept provides NMA using Bayesian statistics with several advantages over a frequentists approach, most important of which is the flexibility in handling variability between studies (20). Using a Bayesian approach under a Markov-Chain Monte-Carlo hierarchical model to conduct NMA is considered to be the mainstream method (21), and offers several advantages over other frequentists approaches for indirect comparisons; including: borrowing strength from the transitivity assumption leading to more precise intervals, allowing for uncertainty in all parameters, allowing for introduction of other sources of evidence, allowing for exact likelihoods to be calculated, allowing for direct probability statements,

and providing a ranking of interventions based on the probability of each being the most effective (21).

Perhaps one of the most distinguishing features between Bayesian statistics and frequentist statistics is the use of the Credible Interval (CrI) to measure precision in the Bayesian statistics as opposed to the conventional Confidence Interval (CI) used in the frequentist statistics. Mathematically, the confidence interval is determined by the standard error of the estimator, while the CrI is determined by the standard deviation of the posterior (22). However, the interpretation of these methods should be more meaningful; conventionally, a 95% CrI is where there is 95% probability that the true estimator lies, a 95% CI is where, in a long series of repeating the observations, 95% of them should contain the parameter value (22). This conventional explanation might not be very intuitive, and in practice, CrI and CI both have been mainly used to assess the significance and the magnitude of health intervention, rather than speculating on the experimental interpretation of both. Perhaps with the possible advancement of statistical methods to support individualized health intervention, there will be more emphasis on sampling out of the probability distribution of the CrI rather than the long-run CI, this remains purely hypothetical, however.

There are three major assumptions used in any Bayesian NMA: transitivity, consistency, and homogeneity. Transitivity generally means that if A is greater than B in one trial, and B is greater than C in a different trial, then we can safely deduct that A is greater than C; to make such deduction, we need to assume that B is sufficiently similar across both trials. This assumption is hard to test in a statistical method, and would largely depend on clinical judgement. Consistency is the assumption that direct evidence would be equal to indirect evidence; this assumption is statistically tested through comparing these two types of evidence in a closed loop of the network, or through running an inconsistency model. Homogeneity is the assumption that the included trials are of sufficient similarity to be compared to one another; this has three component: clinical homogeneity, methodological homogeneity, and statistical homogeneity, and each have a different method of assessment (20, 21).

Interdisciplinary aspect of the thesis

Broadly, there are four fields that, together, drove the idea and the execution of this research, namely: clinical medicine, health policy, epidemiology, and statistics.

The basic issue that this research handles is a clinical problem that is encountered frequently and is a major cause of maternal mortality; namely, postpartum hemorrhage. Childbirth is a physiological process that carries certain risks (23). A normal aspect of childbirth process is bleeding from the uterus after the delivery of the placenta (23, 24). This happens as the separation of the placenta from the uterus leaves behind a bleeding area not so much different from a deep skin abrasion wound, in which capillaries and arterioles are exposed. Under normal conditions this uterine wound should stop bleeding profoundly in a short time, this is due to the uterus contracting on its own and closing the wound by exerting pressure on the bleeding capillaries and arterioles (25-29).

In many cases, however, the uterus fails to stop this bleeding. There are three major etiologies behind this: uterine atony, retained placental fragments, and trauma. By far, uterine atony is the most common cause of PPH (25, 26). Uterine atony indicates that the uterus has lost its ability to contract

and exert pressure to stop bleeding; this in turn will lead the blood to pour into the uterine cavity, expanding the uterus, and making it even more difficult for the uterus to contract (25-29).

The results of this bleeding can be abrupt and life-threatening. The continuous bleeding can develop to a hypovolemic shock, threatening the life of the new mother (24, 30, 31). Another dire consequence would be disseminated intravascular coagulation (DIC) caused by uncontrolled activation of the coagulation cascade as the body tries to stop the bleeding (32). DIC is a life-threatening medical emergency where blood starts to coagulate inside the vessels (32). Even if the body manages to stop the excessive bleeding, the acute depletion of the blood volume can leave the new mother with serious morbidities, including renal failure (33, 34) and Sheehan syndrome (35).

Medically, PPH can be prevented through the administration of one of different drugs that would act to encourage the uterus to contract, called a uterotonic (23, 25, 28, 30). These include oxytocin, ergometrine, and misoprostol to name few.

The health policy aspect plays an important role in tackling the plight of PPH. Pregnancy, childbirth, and maternal care are cornerstones for the growth of any society. It is arguable that the rate of maternal morbidity and mortality is a good indicator of the level of a society's development, cohesiveness, and overall health. Since the importance of maternal care cannot be over emphasized, many governments and non-government-organizations are highly invested in this field. With the main question being: How to reduce maternal and neonatal morbidity and mortality? Developed countries have an expanded infrastructure, political and societal stability, hygienic maternity wards, professionally trained birth attendants, and, above all, unrestricted access to unlimited quantities of oxytocin. In contrast, many developing countries do not have many of the aforementioned factors; they lack transportation infrastructure, childbirth take place at home in most cases, they have traditional birth attendants, and they are unable to maintain a stockpile of oxytocin due to its price, cold temperature storage requirement, and the need for intravenous administration.

Due to the amount of challenges in developing countries, misoprostol can be an appropriate choice in the fight against PPH. Misoprostol costs around $1.5 a tablet, does not need special storage requirements, can withstand heat, and can be administered as a pill through the mouth with no need for special training or extra equipment that are associated with IV injections. However, the questions that many health policy experts would want to know are: How much misoprostol should be given? How many cases of PPH should we expect with misoprostol? Does misoprostol need the birth attendant to practice active management of labour? Can it be given at home? And is the route of administration a factor to consider?

To shed a light on those questions we need to look at the epidemiological basis of PPH. It affects roughly 10 women out of a 100 (36). It is the cause of maternal death in 25% of maternal mortality cases (27).

Also to answer these questions we need to employ an array of epidemiological methods and tools. Systematic review will be needed to capture all available evidence on misoprostol, critical appraisal of the evidence is essential to ensure good quality, using odds ratio as a measure to compare different doses of misoprostol, and looking at the incidence rate of PPH under different factors in a meta-regression as a measure of the effect of many different variables.

Biostatistics is an integral part in the process of conducting our research; as we set forward to answer these questions with the epidemiological measures we chose, we need to decide on the best approach to handle all the data from the evidence we collected. We decided to move forward with a Bayesian-model network meta-analysis in answering the appropriate dose, and to use frequentist mixed-effects meta-regression to look at the effect of treatment-modifiers. Both aspects required the incorporation of advanced knowledge and utilization of statistical concepts; including prior distribution, variability measure, Marcov-Chain-Monte-Carlo decision modelling, model consistency, heterogeneity, and meta-regression.

These four fields coming together in this research paint a picture of scientific inquiry at its essence. An individual problem that is observed and described biologically, affecting many individuals in a society that warrant it to be a concern to policy makers, the extent of the problem is defined on a mass population level and the answers are needed to be on the same level, using math and statistics to utilize mass data to give these answers.

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Article 1: Misoprostol Dosage and Side-effects for the Prevention of Postpartum Haemorrhage: A systematic review and network meta-analysis on 400 µg misoprostol vs. 600 µg misoprostol.

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Abstract:

Objectives:

To compare the efficacy and safety of 400 µg misoprostol versus 600 µg misoprostol for the prevention of postpartum hemorrhage (PPH).

Methods:

We developed a search strategy and conducted a search within five key databases. Two reviewers screened the articles for predefined inclusion/exclusion criteria, quality, and performed data extraction. Discrepancy was dealt with by reaching consensus. We performed a random-effects Bayesian network meta-analysis over five outcomes of interest: blood loss ≥500 ml, blood loss ≥1000 ml, using additional uterotonics, shivering, and pyrexia.

Results:

Of 444 identified records, 46 trials met the inclusion/exclusion criteria. One trial, with four arms, directly assessed misoprostol 400 µg against 600 µg. In our analysis, the odds ratio (OR) of misoprostol 400 µg vs. 600 µg for bleeding ≥ 500 ml is 0.86 [95% Credible Intervals: 0.46 − 1.54], for bleeding ≥ 1000 ml the OR is 0.83 [95% CrI 0.54 – 1.26], and the OR of additional uterotonics is 0.75 [95% CrI 0.40 – 1.40], while pyrexia and shivering have an OR of 0.57 [95% CrI 0.15 – 2.18] and 0.63 [95% CrI 0.29 – 1.31] respectively. These results are supported by a sensitivity analysis for study blinding and they show similar results in blinded trials.

Conclusion:

We found no difference between the administration of misoprostol 400 µg and 600 µg for the prevention of PPH. Only one trial assessed the evidence directly, pointing to the need for more direct research. This evidence can prevent unnecessary extra-medication and can help reduce costs.

Introduction:

Postpartum haemorrhage (PPH) is the second leading cause of maternal mortality worldwide (1). In the year 2010, an estimated 287,000 maternal deaths occurred worldwide, 99% of these deaths took place in developing countries (2). With the right care and management, death due to PPH can be largely reduced. This is evident in developed countries in which PPH accounts for 16.3% of maternal deaths compared to 27.1% in developing countries. This fact is also reflected in the incidence of PPH; the US has an incidence rate of 2.9% (3), while developing countries, depending on the method used to measure blood loss, have incident rates between 5% and up to 20% (4).

Misoprostol has shown to be superior to placebo in PPH prevention (5-8), while considered inferior to oxytocin (7, 8), the mainstream drug that is recommended by World Health Organisation (WHO) (9). Unlike oxytocin, however, misoprostol is readily available, does not require cold storage, and does not require special training as it can be administered orally as a pill. These qualities make misoprostol especially important in remote, underserved, and resource-poor communities. Considering that up to 50% of all births take place without a trained birth attendant (10), and the general hardships in accessing logistic, financial, and human resources in developing countries (11), misoprostol is an important and practical intervention that can save the lives of many mothers that have no access to a dedicated maternal care services.

WHO recommends the use of 600 µg Misoprostol in cases where other injectable uterotonics (e.g. oxytocin, syntometrin) are not available (12). The choice of 600 µg can be considered as the safer option in regard to ensuring effectiveness in PPH prevention. However, there is some evidence showing that a dose of 400 µg can also be effective in PPH prevention, with less exposure to possible adverse effects (13). In this study, we aim to compare 400 µg to 600 µg in terms of effectiveness in PPH prevention and safety.

Methods:

Eligibility criteria

For this study we included open label and blinded randomised clinical trials (RCT) of misoprostol 600 µg or 400 µg administered orally, sublingually, or rectally against control, placebo, or any other uterotonic for the purposes of PPH prevention in vaginal deliveries. We excluded studies that looked at a combination of misoprostol plus any other uterotonic, studies with vaginal administration of misoprostol, studies with treatment and management purposes rather than prevention, non-RCT design, and studies published in languages other than English or French.

Study end-points

The primary outcomes were bleeding ≥ 500 ml, bleeding ≥ 1000 ml, and the need for additional uterotonic. Bleeding over 500 ml reflects the commonly agreed upon definition of PPH, while bleeding over 1000 ml is considered severe PPH. The need for additional uterotonic reflects the clinical judgement of the attending physician on the effectiveness of the first-line prevention, such outcome can be very useful in deciding on the economical effectiveness of an intervention.

Shivering and pyrexia were the two safety outcomes analysed in this study, since these side effect are most commonly associated with misoprostol administration. Maternal death are collected but not analysed as we expect very few cases for a meaningful analysis.

Search strategy

We established a search strategy in consultation with a medical librarian specialist. On 25 September, 2014, each of the following five databases were searched independently: MEDLINE (Ovid), EMBASE (Ovid), Cochrane CENTRAL (Ovid), CINAHL, (Ovid), and CAB Direct Global Health. The specific Ovid search strategy is provided in appendix A.

Study selection

According to the predefined inclusion and exclusion criteria, two investigators (G.J., L.M.) independently and in duplicate screened all titles and abstracts. Studies that passed the initial abstract screening were further screened by their full-text independently by the two investigators. Any discrepancy between the two investigators were solved through discussion and reaching a consensus. If a consensus could not be reached, a third investigator (E.M.) served to arbitrate.

Data extraction

Using a preformed data extraction spreadsheet (appendix B), two investigator (G.J., L.M.) independently and in duplicate performed data extraction on all included studies. Information collected included data on study characteristics (year, design, allocation, blinding, setting, geographic area), methods used to estimate blood loss, population characteristics (age, parity, gestational age, weight, BMI, previous PPH), treatment characteristics (type, dosage, route), labour characteristics (induction of labour, augmentation of labour, instrumental delivery, episiotomy, tears), and outcomes of each study (mean blood loss, blood loss ≥ 500 ml, blood loss ≥ 1000 ml, additional uterotonics needed, blood transfusion, referral, safety population, death, pyrexia ≥ 38 C, shivering, diarrhea, headache).

The need for additional uterotonic would imply that, clinically, after the first uterotonic was used to prevent PPH, in the opinion of the birth attendant, this was not enough to prevent or stop the bleeding, and more uterotonics, same as the initial or different, should be administered. The principle nature of this outcome is administering more uterotonics after the first one. This outcome is not necessary defined literally as such in the trials where we are extracting data, but this definition would be implied by the nature of the methodology used in the trial, and this outcome is extracted as reported in the trial. The side effects chosen were the most frequently reported with misoprostol use for PPPH prevention (13).

Data analysis

Data for the number of events and population were derived from the intent-to-treat (ITT) analysis of individual studies. In the case where ITT was not specified, the randomised population was used for the calculation of odds ratio (OR). Zero cells were adjusted by adding a 0.5 adjusted continuity correction factor(14). A Bayesian network meta-analysis (NMA) using Markov chain Monte Carlo (MCMC) modelling was employed to evaluate the comparative effectiveness of the intervention under a random effect model (15). A random effects model was chosen as we expect to encounter a degree of heterogeneity in our studies, in such circumstances choosing a random effects model would allow for a better model fit. Three chains were initiated from different, randomly chosen, and non-

informative (vague) priori. Each chain went through 50,000 iterations and 50,000 burn-ins. Chains were monitored through the Gelmen Rubin statistic (16), they achieved convergence after 20,000 burn-ins. Monte Carlo error was calculated for each node in order to evaluate the accuracy of the posterior distribution.

Results of the posterior distribution are presented as OR with a corresponding 95% credible interval (CrI). Model fit was assessed using the Deviance Information Criterion (DIC) (17), different models would be generated and the difference in the DIC between the models should be small, otherwise the model with the least DIC should be chosen to derive inferences. Inconsistency was assessed for each node that had a direct and an indirect comparison. Subgroup analysis was conducted on open label and blinded studies.

NMA data were entered in NetMetXL; a freely available, Microsoft Excel macro that generates and runs the model, retrieves the results, and facilitates conducting NMA in WinBUGS from within Microsoft Excel (18), the code generated by the macro is available in appendix C. Network diagram, league tables, forest plots, and inconsistency diagrams have all been generated by NetMetaXL. WinBUGS version 1.4 (Medical Research Council Biostatistics Unit, Cambridge) was used for conducting the network meta-analysis. R version 3.2.0 was used for descriptive statistics.

This study is part of a systematic review and meta-analysis project that has been registered with PROSPERO under PROSPERO 2014:CRD42014013802. Available from

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013802

Results

Our search strategy, conducted in September 24th, 2014, identified 444 records. Of these, 46 trials met our inclusion and exclusion criteria (Figure 1). These 46 trials represented a total of 44,874 participants (19-64). The mean age of the participants was 26.2 [Standard deviation (SD) 2.12], with a range of 22.1 to 31.0 years. Twenty nine trials reported on the number of nulliparous women (20, 22-25, 27-32, 35, 38, 39, 41-44, 46, 49-51, 54-56, 59, 60, 62, 63), with a mean percentage of 39.3% (SD 14.88) and a median of 45.8% (range 9.3% to 67.9%). We identified six different methods used in the trials to estimate blood loss; 12 used calibrated collection instruments (funnel shaped plastic bag, kidney dish, etc.) that are situated underneath the labouring mother immediately after the delivery of the placenta (19, 21, 22, 26, 31, 34, 37, 44, 47, 53, 56, 61), 5 trials used the weight of the absorbed blood on different fabric (gauze, pad, bed linen, etc) as means to estimate blood loss (29, 51, 52, 54, 60), 12 trials used both previous methods (24, 27, 28, 35, 36, 38-41, 46, 57, 58), 7 trials depended on the attending health professional's (physician, nurse, midwife, etc.) subjective clinical estimate (43, 45, 48-50, 55, 63), 4 trials relied on both a subjective clinical estimate and a calibrated measurement (23, 25, 30, 42), 1 trial used a subjective clinical estimate and weight measurement (32), and 5 trials did not specify the method of blood estimation (20, 33, 59, 62, 64). Thirty trials reported on the duration of blood collection (21-24, 27-29, 31, 32, 35-40, 43-48, 51-54, 56-58, 60, 63), with an overall mean of 3.3 hours (SD 6.79) and a median of 1.0 hour (range 0.1 to 24.0 hours). Study characters are displayed in (Table 1).

Quality of included trials

All trials, except eight (25, 26, 36, 45, 47, 48, 62, 64), adequately reported on methods employed in generating randomisation. Twenty five of the trials were blinded (20, 23, 24, 26-29, 31, 34-36, 38-41, 44-46, 50, 52, 54, 55, 59, 60, 63). Since this was a one-time intervention with immediate observation, loss of follow up was not an issue.

A detailed quality assessment Using the The Cochrane Collaboration's tool for assessing risk of bias in randomised trials (65) is provided in Table 2. The overall assessment shows good quality of studies as is represented in Figure 2.

Bleeding 500 ml or over

Forty trials reported on the outcome of bleeding loss of 500 ml or greater (19-21, 24, 26-37, 40-61, 63, 64), representing 42,001 participants with a total of 5,337 events. These trials compared misoprostol (400 and 600 µg) to twelve different interventions. Only one multi-arm trial directly compared misoprostol 400 µg to 600µg (54). The network is visually represented in Figure 3.

The result of the Monte Carlo error was below 5% of the SD of individual effect size and between study variance, suggesting satisfactory convergence. Due to the large number of interventions, we have witnessed a high DIC value. This value, however, did not differ much when alternative models were tested, suggesting good data fit of the current used random effect model with vague priors. Inconsistency modeling showed largely equivocal results, indicating good reliability of the consistency model. Figure 4 provides a visual interpretation of the results of inconsistency versus consistency modelling.

Despite the observation of large residual variance, we can observe a consistent trend in which misoprostol 400 µg shows no statistical difference to misoprostol 600 µg in comparative effect and shows similar ORs with when compared individually with other interventions. In our analysis, the OR of ≥500 ml bleeding in 400 vs 600 µg misoprostol is 0.86 (95% CrI 0.46 – 1.54). This direction also appears in the results of calculating the surface under the cumulative ranking curve (SUCRA), a measure of the probability of a specific treatment being ranked the highest in a list of treatments. In our analysis, the SUCRA for misoprostol 400 µg is equal to 0.62 (95% CrI 0.31 – 0.92), while the SUCRA for misoprostol 600 µg is equal to 0.52 (95% CrI 0.23 – 0.85). A league table showing the results of all comparisons is provided in Figure 5, it is important to note that only comparisons between misoprostol and another intervention can be considered systematic, as we only included trial with at least one arm with either misoprostol 400 or 600 µg.

Subgroup analysis was conducted on basis of study deign, blinded and open label trials were analysed separately. Analysis of the twenty two included blinded trials (20, 24, 26-29, 31, 34-36, 40, 41, 44-46, 50, 52, 54, 55, 59, 60, 63) showed an OR of 0.54 (95%CrI 0.15 – 1.20) for misoprostol 400 µg to misoprostol 600 µg. The same comparison in the analysis of the included eighteen open label trials (19, 21, 25, 30, 32, 33, 37, 42, 47-49, 51, 53, 56-58, 61, 64) showed an OR of 1.55 (95%CrI 0.36 – 6.46). Network diagrams, League tables, and inconsistency models for the subgroup analysis is presented in appendix D.

Bleeding 1000 ml or over

Thirty nine trials reported on the outcome of bleeding loss of 1000 ml or greater (19-32, 34-44, 46, 48-56, 58-61, 63), representing 42,862 participants with a total of 1,198 events. These trials compared misoprostol (400 and 600 µg) to eleven different interventions. Only one multi-arm trial compared misoprostol 400 µg to 600µg directly (54). The network is visually represented in Figure 6.

As with the previous outcome, the result of the Monte Carlo error was below 5% of the SD of individual effect size and between study variance. DIC value did not differ much when alternative models were tested. Inconsistency results are presented in Figure 7.

Here also, misoprostol 400 µg shows no statistical difference to misoprostol 600 µg in comparative effect. In our analysis, the OR of ≥1000 ml bleeding in 400 vs 600 µg misoprostol is 0.83 (95% CrI 0.54 – 1.26). In this outcome, the SUCRA for misoprostol 400 µg is equal to 0.54 (95% CrI 0.25 – 0.75), while the SUCRA for misoprostol 600 µg is equal to 0.40 (95% CrI 0.17 – 0.67). A league table showing the results of all comparisons is provided in Figure 8. It is important to note that only comparisons between misoprostol and another intervention can be considered systematic, as we only included trial with at least one arm with either misoprostol 400 or 600 µg.

Subgroup analysis was conducted on basis of study deign, blinded and open label trials were analysed separately. Analysis of the twenty four included blinded trials (20, 23, 24, 26-29, 31, 34-36, 38-41, 44, 46, 50, 52, 54, 55, 59, 60, 63) showed an OR of 0.83 (95%CrI 0.48 – 1.55) for misoprostol 400 µg to misoprostol 600 µg. The same comparison in the analysis of the included fifteen open label trials (19, 21, 22, 25, 30, 32, 37, 42, 48, 49, 51, 53, 56, 58, 61) showed an OR of 0.50 (95%CrI 0.06 – 3.11). Network diagrams, League tables, and inconsistency results for the subgroup analysis is presented in appendix E.

Need for additional uterotonics

Forty trials reported on the outcome of additional uterotonics (19-24, 26-39, 41-45, 47-52, 54-59, 61-64). These trials represent 38,717 participants with a total of 4,568 events. These trials compared misoprostol (400 and 600 µg) to twelve different interventions. Only one multi-arm trial directly compared misoprostol 400 µg to 600µg (54). The network is visually represented in Figure 9. Monte Carlo error was below 5% of the SD of individual effect size and between study variance. DIC value did not differ much when alternative models were tested. Inconsistency results is presented in Figure 10.

Misoprostol 400 µg shows no statistical difference to misoprostol 600 µg. In our analysis, the OR of additional uterotonic in 400 vs 600 µg misoprostol is 0.75 (95% CrI 0.40 – 1.40). In this outcome, the SUCRA for misoprostol 400 µg is equal to 0.54 (95% CrI 0.31 – 0.77), while the SUCRA for misoprostol 600 µg is equal to 0.37 (95% CrI 0.15 – 0.69). A league table showing the results of all comparisons is provided in Figure 11. It is important to note that only comparisons between misoprostol and another intervention can be considered systematic, as we only included trial with at least one arm with either misoprostol 400 or 600 µg.

Subgroup analysis was conducted on basis of study deign, as blinded trials were analysed separately. Analysis of the twenty two included blinded trials (20, 23, 24, 26-29, 31, 34-36, 38, 39, 41, 44, 45, 50, 52, 54, 55, 59, 63) showed an OR of 0.68 (95%CrI 0.26 – 1.74) for misoprostol 400 µg to misoprostol 600 µg. The same comparison in the analysis of the included fifteen open label trials (19, 21, 22, 30,

32, 33, 37, 42, 47-49, 51, 56-58, 61, 62, 64) showed an OR of 0.96 (95%CrI 0.31 – 2.37). Network diagrams, League tables, and inconsistency results for the subgroup analysis is presented in appendix F.

Pyrexia

Thirty three trials reported on the outcome of pyrexia (19, 23-26, 28, 29, 31-33, 35, 36, 39-47, 49, 50, 52-54, 56-59, 61-63), representing 37,359 participants with a total of 1,529 events. These trials compared misoprostol (400 and 600 µg) to twelve different interventions. Only one multi-arm trial directly compared misoprostol 400 µg to 600µg (54). The network is visually represented in Figure 12. Monte Carlo error was below 5% of the SD of individual effect size and between study variance. DIC value did not differ much when alternative models were tested. Inconsistency results is presented in Figure 13.

Misoprostol 400 µg shows no statistical difference to misoprostol 600 µg. In our analysis, the OR of pyrexia in 400 vs 600 µg misoprostol is 0.57 (95% CrI 0.15 – 2.18). In this outcome, the SUCRA for misoprostol 400 µg is equal to 0.16 (95% CrI 0.00 – 0.38), while the SUCRA for misoprostol 600 µg is equal to 0.06 (95% CrI 0.00 – 0.31). A league table showing the results of all comparisons is provided in Figure 14. It is important to note that only comparisons between misoprostol and another intervention can be considered systematic, as we only included trial with at least one arm with either misoprostol 400 or 600 µg

Subgroup analysis was conducted on basis of study deign, blinded and open label trials were analysed separately. Analysis of the nineteen included blinded trials (23, 24, 26, 28, 29, 31, 35, 36, 39-41, 44-46, 50, 52, 54, 59, 63) showed an OR of 0.56 (95%CrI 0.11 – 2.87) for misoprostol 400 µg to misoprostol 600 µg. The same comparison in the analysis of the included fourteen open label trials (19, 25, 30, 32, 33, 37, 42, 47, 49, 56-58, 61, 62) showed an OR of 0.78 (95%CrI 0.06 – 9.63). Network diagrams, League tables, and inconsistency results for the subgroup analysis is presented in appendix G.

Shivering

Forty one trials reported on the outcome of shivering (19, 20, 22-26, 28, 29, 31-50, 52, 54-64), representing 40,891 participants with a total of 5,596 events. These trials compared misoprostol (400 and 600 µg) to twelve different interventions. Only one multi-arm trial directly compared misoprostol 400 µg to 600µg (54). The network is visually represented in Figure 15. Monte Carlo error was below 5% of the SD of individual effect size and between study variance. DIC value did not differ much when alternative models were tested. Inconsistency results is presented in Figure 16.

Misoprostol 400 µg shows no statistical difference to misoprostol 600 µg. In our analysis, the OR of shivering in 400 vs 600 µg misoprostol is 0.63 (95% CrI 0.29 – 1.31). In this outcome, the SUCRA for misoprostol 400 µg is equal to 0.21 (95% CrI 0.08 – 0.38), while the SUCRA for misoprostol 600 µg is equal to 0.09 (95% CrI 0.00 – 0.31). A league table showing the results of all comparisons is provided in Figure 17. It is important to note that only comparisons between misoprostol and another intervention can be considered systematic, as we only included trial with at least one arm with either misoprostol 400 or 600 µg.

Subgroup analysis was conducted on basis of study deign, blinded and open label trials were analysed separately. Analysis of the twenty four included blinded trials (20, 23, 24, 26, 28, 29, 31, 34-36, 38-41, 44-46, 50, 52, 54, 55, 59, 60, 63) showed an OR of 0.98 (95%CrI 0.36 – 2.55) for misoprostol 400 µg to

misoprostol 600 µg. The same comparison in the analysis of the included seventeen open label trials (19, 22, 25, 30, 32, 33, 37, 42, 47-49, 56-58, 61, 62, 64) showed an OR of 0.30 (95%CrI 0.04 – 1.65). Network diagrams, League tables, and inconsistency results for the subgroup analysis is presented in appendix H.

Discussion:

Our analysis included over forty thousand participants from forty six different trials. Of these trials only one assessed misoprostol 400 µg directly to misoprostol 600 µg. Throughout the five outcomes we have chosen in this analysis, misoprostol 400 µg has constantly shown no statistically significant differences when compared to 600 µg, in terms of both efficacy in prevention PPH, and possible side effects. Despite having shown no statistical significance improvement over 600 µg, the point estimates of the comparisons between misoproatol 400 µg to misoprostol 600 µg were consistently in favour of misoprostol 400 µg. The results of the comparison of misoprostol 400 µg to 600 µg across the five outcomes are visually represented as a forest plot in Figure 18.

Although this analysis uses the results of 46 trials with a collective population of 44,874 participants, the statistical reliability of the indirect comparison between misoprostol 400 µg and 600 µg could not be assessed in a satisfactory way due to the lack of sufficiently large and high quality RCTs comparing the two interventions directly. The one multi-arm trial that carried this comparison suffered from low power and methodological limitations (54). Another limitation of this analysis is the finding of large total residual variance. Although in our subgroup analysis we saw a decrease in such variance, indicating that the blinding of a trial has an effect on the measurement of outcomes, this alone did not account for all observed heterogeneity. This finding might reflects the partial subjectivity in measuring and estimating blood loss, the lack of thorough reporting in the trials on many possible population based effect modifiers; including previous PPH, body mass index (BMI), induction of labour, labour augmentation, perineal tears, episiotomies, and large for gestational age (LGA). The time since the literature search is another limitation. However, and due to the large number of trials included, representing a large population, new RCTs are unlikely to exert any significant influence on the results obtained.

Despite the above mentioned limitations, this study has synthesised all of the available evidence for a comparison that has very little direct evidence behind it. The large number of participants and the heterogeneity of the analysis might reassure policy and decision makers on the external validity of these findings. Our finding that misoprostol 400 µg is not statistically different than 600 µg have the potential to reduce harms that might be associated with possible side effects of higher dose misoprostol. Considering that the generic misoprostol pill comes in a dose of 200 µg, our finding have the potential of reducing costs associated with mass campaigns to prevent PPH using misoprostol, as only two pills of misoprostol is required to infer the same protection from three pills.

Funding and conflict of interest

No funding has been received for this study. All authors declare no conflict of interest.

GJ Led the protocol development, co-ordinated the research efforts, developed the search strategy with a consultation of a medical librarian, performed the literature search, screened the articles as the first reviewer, extracted data as the first reviewer, assessed biases as the first reviewer, analysed data, wrote the manuscript, and performed necessary revisions. LM helped in developing the protocol, screened the articles as a second reviewer, extracted date as a second reviewer, and assessed biases as a second reviewer. MW provided clinical guidance and expertise, reviewed the protocol, reviewed the manuscript, and provided revisions. EM provided methodological guidance and expertise, acted as a third reviewer in cases of discrepancy among the first two reviewers, provided training in evidence synthesis practice, reviewed the protocol, reviewed the manuscript, and provided revisions.

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Figures and tables

Figure 1: Flowchart of identified and included studies

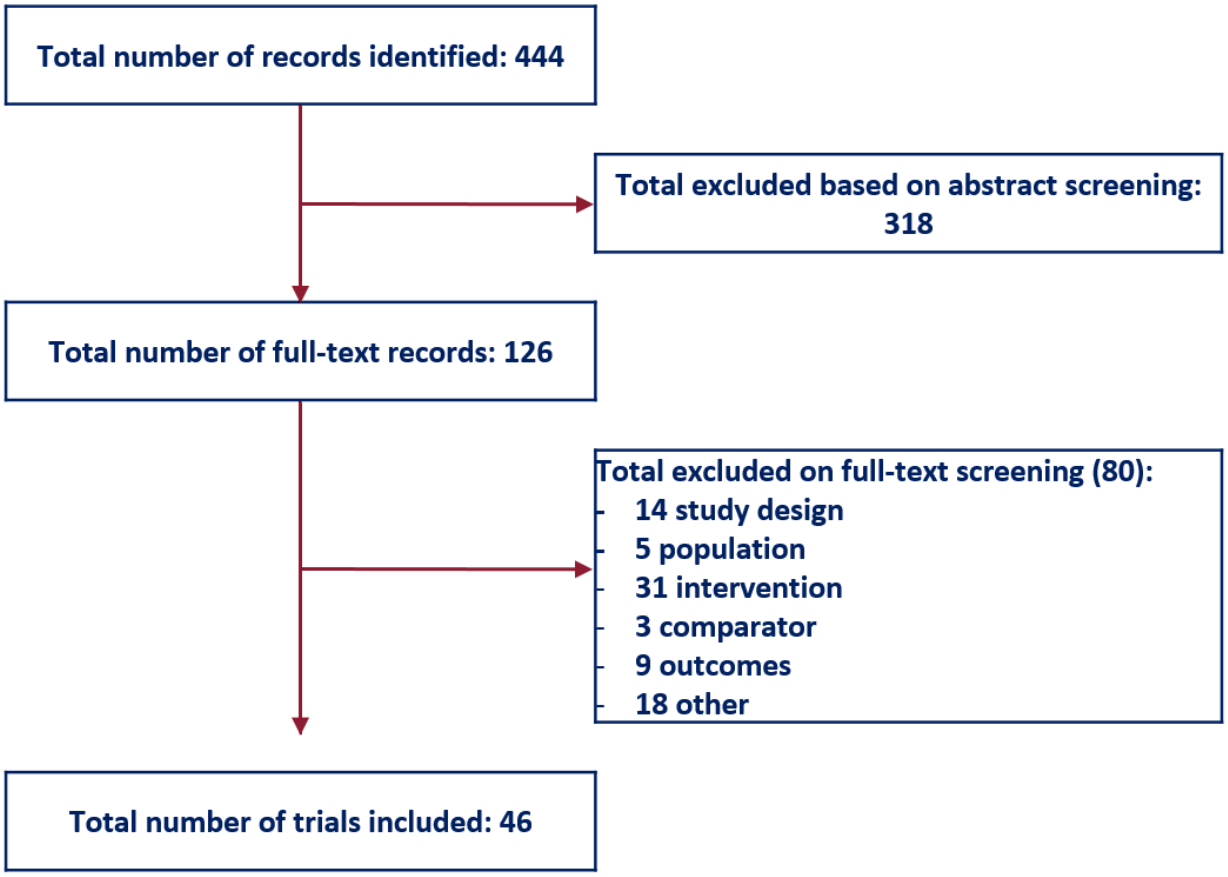


Table 1: Characteristics of included trials

Author, year	Setting	Comparison	Blinding	Region	Intervention	Dosage	Route	Randomised population	Age	Gestational age	Induction of labour	Augmentation of labour	Episiotomy	Instrumental deliveries	Previous PPH
								N	Mean year (SD)	Mean year (SD)	(%)	(%)	(%)	(%)	(%)
Afolabi, E.O. 2010	Clinical	Misoprostol vs Oxytocin	Open label	Nigeria	Misoprostol	400 µg	Oral	100	27.1 (3.4)	39.1 (1.2)	NA	15	NA	NA	NA
Afolabi, E.O. 2010	Clinical	Misoprostol vs Oxytocin	Open label	Nigeria	Oxytocin	10 IU	IM	100	27.5 (3.5)	39 (1.1)	NA	12	NA	NA	NA
Amant, F. 1999	Clinical	Misoprostol vs Methylergometrine	Double blind	Belgium	Misoprostol	600 µg	Oral	100	29.8 (4.1)	39.4 (1.3)	37	NA	79	15	NA
Amant, F. 1999	Clinical	Misoprostol vs Methylergometrine	Double blind	Belgium	Methylergometrine	200 µg	IV	100	29.9 (4.1)	39.6 (1.1)	39	NA	80	17	NA
Bamigboye, A.A. 1998a	Clinical	Misoprostol vs Placebo	Open label	South Africa	Misoprostol	400 µg	Rectal	271	26.3 (5.8)	NA (NA)	NA	NA	60	NA	NA
Bamigboye, A.A. 1998a	Clinical	Misoprostol vs Placebo	Open label	South Africa	Placebo		Rectal	275	27.3 (6)	NA (NA)	NA	NA	60	NA	NA
Bamigboye, A.A. 1998b	Clinical	Misoprostol vs Syntometrine	Open label	South Africa	Misoprostol	400 µg	Rectal	241	25 (5.8)	NA (NA)	NA	NA	73	NA	NA
Bamigboye, A.A. 1998b	Clinical	Misoprostol vs Syntometrine	Open label	South Africa	Syntometrine	Oxytocin 5 IU & ergometrine 0.5 g	IM	250	25 (6.4)	NA (NA)	NA	NA	70	NA	NA
Baskett, T.F 2007	Clinical	Misoprostol vs Oxytocin	Double blind	Canada	Misoprostol	400 µg	Oral	311	28.6 (5.27)	NA (NA)	49.5	NA	21.9	10.6	NA
Baskett, T.F 2007	Clinical	Misoprostol vs Oxytocin	Double blind	Canada	Oxytocin	5 IU	IV	311	29.3 (5.49)	NA (NA)	46.9	NA	20.9	13.5	NA
Bellad, M. 2012	Clinical	Misoprostol vs Oxytocin	Double blind	India	Misoprostol	400 µg	Sublingual	321	23 (3.1)	38.8 (1.6)	NA	NA	53.3	0	NA

Bellad, M. 2012	Clinical	Misoprostol vs Oxytocin	Double blind	India	Oxytocin	10 IU	IM	331	22.8 (3)	38.9 (1.5)	NA	NA	48.6	0	NA
Benchimol, M. 2001	Clinical	Misoprostol vs Oxytocin vs Control	Open label	France	Misoprostol	600 µg	Oral	186	27.3 (NA)	NA (NA)	NA	NA	34.4	NA	NA
Benchimol, M. 2001	Clinical	Misoprostol vs Oxytocin vs Control	Open label	France	Oxytocin	2.5 IU	IV	196	28.3 (NA)	NA (NA)	NA	NA	35.71	NA	NA
Benchimol, M. 2001	Clinical	Misoprostol vs Oxytocin vs Control	Open label	France	Control			220	28.16 (NA)	NA (NA)	NA	NA	34.54	NA	NA
Bugalho, A. 2001	Clinical	Misoprostol vs Oxytocin	Double blind	Mozambique	Misoprostol	400 µg	Rectal	324	25.4 (7.7)	38.73 ()	NA	NA	NA	NA	NA
Bugalho, A. 2001	Clinical	Misoprostol vs Oxytocin	Double blind	Mozambique	Oxytocin	10 IU	IM	339	25.8 (8.04)	38.81 ()	NA	NA	NA	NA	NA
Çaliskan, E. 2003	Clinical	Misoprostol vs Oxytocin	Double blind	Turkey	Misoprostol	400 µg	Oral	388	24.4 (4.7)	39.43 (1.56)	9.7	68.8	74.4	2	NA
Çaliskan, E. 2003	Clinical	Misoprostol vs Oxytocin	Double blind	Turkey	Oxytocin	10 IU	IV	384	25 (5.1)	39.29 (1.59)	9.3	69.2	74.5	1	NA
Çaliskan, E. 2002	Clinical	Misoprostol vs Oxytocin	Double blind	Turkey	Misoprostol	400 µg	Rectal	396	25.3 (5.1)	39.29 (1.9)	10.1	68.6	72.4	3.5	NA
Çaliskan, E. 2002	Clinical	Misoprostol vs Oxytocin	Double blind	Turkey	Oxytocin	10 IU	IV	407	25 (5.1)	39.29 (1.59)	8.8	65.3	70.2	3.6	NA
Chaudhuri, P. 2012	Clinical	Misoprostol vs Oxytocin	Double blind	India	Misoprostol	400 µg	Sublingual	265	22.07 (3.6)	37.69 (1.99)	0	0	72.5	0	0
Chaudhuri, P. 2012	Clinical	Misoprostol vs Oxytocin	Double blind	India	Oxytocin	10 IU	IM	265	22.35 (2.97)	37.84 (1.9)	0	0	68.3	0	0
Cook, C.M. 1999	Clinical	Misoprostol vs Oxytocin vs Syntometrine	Open label	Multi-National	Misoprostol	400 µg	Oral	425	26 (5.3)	39.6 (1.4)	NA	NA	NA	4	NA
Cook, C.M. 1999	Clinical	Misoprostol vs Oxytocin vs Syntometrine	Open label	Multi-National	Oxytocin/Syntometrine	10 IU/0.5 mg ergometrine + 5 IU Oxytocin)	IM	439	25.5 (5.2)	39.5 (1.5)	NA	NA	NA	4	NA
Derman, R.J. 2006	Community	Misoprostol vs Placebo	Double blind	India	Misoprostol	600 µg	Oral	812	23.3 (3.3)	NA (NA)	0	0	NA	0	0

Derman, R.J. 2006	Community	Misoprostol vs Placebo	Double blind	India	Placebo		Oral	808	23.2 (3.1)	NA (NA)	0	0	NA	0	0
Enakpene, C.A. 2007	Clinical	Misoprostol vs Methylergometrine	Open label	Nigeria	Misoprostol	400 µg	Oral	432	26.8 (5.4)	38.7 (1.5)	0	0	NA	NA	0
Enakpene, C.A. 2007	Clinical	Misoprostol vs Methylergometrine	Open label	Nigeria	Ergometrine	500 µg	IM	432	28.2 (5.4)	39.5 (1.3)	0	0	NA	NA	0
Garg, P. 2005	Clinical	Misoprostol vs Methylergometrine	Open label	India	Misoprostol	600 µg	Oral	100	22.86 (NA)	NA (NA)	NA	NA	NA	NA	NA
Garg, P. 2005	Clinical	Misoprostol vs Methylergometrine	Open label	India	Methylergometrine	0.2 mg	IV	100	22.07 (NA)	NA (NA)	NA	NA	NA	NA	NA
Gerstenfeld, T.S. 2001	Clinical	Misoprostol vs Oxytocin	Double blind	USA	Misoprostol	400 µg	Rectal	159	27.8 (0.5)	39 (0.1)	41.7910447 8	35.32338308	NA	NA	1.3
Gerstenfeld, T.S. 2001	Clinical	Misoprostol vs Oxytocin	Double blind	USA	Oxytocin	20 IU	IV	166	27 (0.5)	39.2 (0.1)	37.185929 65	33.16582915	NA	NA	0.6
Gulmezoglu, A.M. 2001	Clinical	Misoprostol vs Oxytocin	Double blind	Multi-National	Misoprostol	600 µg	Oral	9264	26.5 (5.5)	38.7 (2.3)	NA	NA	NA	9	NA
Gulmezoglu, A.M. 2001	Clinical	Misoprostol vs Oxytocin	Double blind	Multi-National	Oxytocin	10 IU	IV/IM	9266	26.3 (5.4)	38.7 (2.2)	NA	NA	NA	8	NA
Gupta, B. 2006	Clinical	Misoprostol vs Oxytocin	Double blind	India	Misoprostol	600 µg	Rectal	100	NA (NA)	NA (NA)	NA	NA	NA	NA	NA
Gupta, B. 2006	Clinical	Misoprostol vs Oxytocin	Double blind	India	Oxytocin	10 IU	IM	100	NA (NA)	NA (NA)	NA	NA	NA	NA	NA
Harriott, J. 2009	Clinical	Misoprostol vs Syntometrine	Open label	Jamaica	Misoprostol	400 µg	Rectal	70	28 (5.9)	39.2 (1.2)	NA	NA	NA	4.285714286	0
Harriott, J. 2009	Clinical	Misoprostol vs Syntometrine	Open label	Jamaica	Syntometrine	Oxytocin 5 IU & ergometrine 0.5 g	IM	70	27.4 (6.1)	39.1 (1.8)	NA	NA	NA	1.428571429	0
Hofmeyr, G.J. 2001	Clinical	Misoprostol vs Placebo	Double blind	South Africa	Misoprostol	600 µg	Oral	300	26.6 (5.6)	NA (NA)	NA	NA	NA	NA	NA

Hofmeyr, G.J. 2001	Clinical	Misoprostol vs Placebo	Double blind	South Africa	Placebo		Oral	300	27.4 (5.8)	NA (NA)	NA	NA	NA	NA	NA
Hofmeyr, G.J. 1998	Clinical	Misoprostol vs Placebo	Double blind	South Africa	Misoprostol	400 µg	Oral	250	26.3 (5.9)	NA (NA)	NA	NA	NA	NA	NA
Hofmeyr, G.J. 1998	Clinical	Misoprostol vs Placebo	Double blind	South Africa	Placebo		Oral	250	26 (5.5)	NA (NA)	NA	NA	NA	NA	NA
Hoj, L. 2005	Clinical	Misoprostol vs Placebo	Double blind	Guinea-Bissau	Misoprostol	600 µg	Sublingual	330	23 (19-26)	NA (NA)	NA	NA	NA	NA	6.1
Hoj, L. 2005	Clinical	Misoprostol vs Placebo	Double blind	Guinea-Bissau	Placebo		Sublingual	331	24 (20-28)	NA (NA)	NA	NA	NA	NA	9.7
Kundodyiwa, T.W. 2001	Clinical	Misoprostol vs Oxytocin	Double blind	Zimbabwe	Misoprostol	400 µg	Oral	243	24.4 (5.6)	39.3 (1.9)	NA	NA	37.4	0	0
Kundodyiwa, T.W. 2001	Clinical	Misoprostol vs Oxytocin	Double blind	Zimbabwe	Oxytocin	10 IU	IM	256	23.8 (5.3)	39.2 (2)	NA	NA	45.7	0	0
Lam, H. 2004	Clinical	Misoprostol vs Syntometrine	Open label	Hong Kong SAR, China	Misoprostol	600 µg	Sublingual	30	29.6 (4)	NA (NA)	0	0	NA	0	0
Lam, H. 2004	Clinical	Misoprostol vs Syntometrine	Open label	Hong Kong SAR, China	Syntometrine	Oxytocin 5 IU & ergometrine 0.5 g	IV	30	31 (5)	NA (NA)	0	0	NA	0	0
Mansouri, H.A. 2011	Clinical	Misoprostol vs Misoprostol	Open label	Saudi Arabia	Misoprostol	600 µg	Oral	331	26.76 (5.3)	39.9 (1.8)	NA	NA	NA	NA	NA
Mansouri, H.A. 2011	Clinical	Misoprostol vs Misoprostol	Open label	Saudi Arabia	Misoprostol	600 µg	Rectal	327	27.48 (6.1)	39.7 (1.4)	NA	NA	NA	NA	NA
Miller, S. 2009	Clinical	Misoprostol vs ZB11	Double blind	Tibet	Misoprostol	600 µg	Oral	484	27 (4.6)	NA (NA)	NA	NA	50.4	NA	NA
Miller, S. 2009	Clinical	Misoprostol vs ZB11	Double blind	Tibet	ZB11		Oral	476	26.9 (4.6)	NA (NA)	NA	NA	48.3	NA	NA
Mirteimouri, M. 2013	Clinical	Misoprostol vs Oxytocin	Double blind	Iran	Misoprostol	400 µg	Rectal	200	29.7 (9.3)	NA (NA)	NA	NA		NA	0
Mirteimouri, M. 2013	Clinical	Misoprostol vs Oxytocin	Double blind	Iran	Oxytocin	3 IU	IV	200	28.8 (5.6)	NA (NA)	NA	NA		NA	0
Mobeen, N. 2011	Community	Misoprostol vs Placebo	Double blind	Pakistan	Misoprostol	600 µg	Oral	533	28 (5)	NA (NA)	0	0		NA	NA

Mobeen, N. 2011	Community	Misoprostol vs Placebo	Double blind	Pakistan	Placebo		Oral	583	27 (4)	NA (NA)	0	0		NA	NA
Mukta, M. 2013	Clinical	Misoprostol vs Oxytocin	Open label	India	Misoprostol	600 µg	Oral	100	NA (NA)	NA (NA)	NA	NA		NA	NA
Mukta, M. 2013	Clinical	Misoprostol vs Oxytocin	Open label	India	Oxytocin	10 IU	IM	100	NA (NA)	NA (NA)	NA	NA		NA	NA
Nellore, V. 2006	Clinical	Misoprostol vs 15-methyl prostaglandin F2α	Open label	India	Misoprostol	400 µg	Rectal	60	NA (NA)	NA (NA)	0	0		NA	NA
Nellore, V. 2006	Clinical	Misoprostol vs 15-methyl prostaglandin F2α	Open label	India	15-methyl prostaglandin F2α	125 µg	IM	60	NA (NA)	NA (NA)	0	0		NA	NA
Ng, P.S. 2001	Clinical	Misoprostol vs Syntometrine	Open label	Hong Kong SAR, China	Misoprostol	600 µg	Oral	1026	28.1 (5.1)	39.4 (1.4)	16.08 1871 35	15.8	88.7	NA	1.1
Ng, P.S. 2001	Clinical	Misoprostol vs Syntometrine	Open label	Hong Kong SAR, China	Syntometrine	Oxytocin 5 IU & ergometrine 0.5 g	IM	1032	28.4 (5)	39.4 (1.4)	19.08 9147 29	18.1	89.3	NA	1.2
Oboro, V.O. 2003	Clinical	Misoprostol vs Oxytocin	Double blind	Nigeria	Misoprostol	600 µg	Oral	247	23.6 (5.2)	39.7 (2.8)	0	0	28	NA	0
Oboro, V.O. 2003	Clinical	Misoprostol vs Oxytocin	Double blind	Nigeria	Oxytocin	10 IU	IM	249	23.9 (4.8)	39.1 (3.3)	0	0	30	NA	0
Ozkaya, O. 2005	Clinical	Misoprostol vs Placebo	Open label	Turkey	Misoprostol	400 µg	Rectal	48	26.2 (4.1)	38.2 (3.11)	NA	NA	83	NA	NA
Ozkaya, O. 2005	Clinical	Misoprostol vs Placebo	Open label	Turkey	Placebo		Rectal	44	27.4 (6.2)	38.1 (2.58)	NA	NA	86	NA	NA
Rajaei, M. 2014	Clinical	Misoprostol vs Oxytocin	Double blind	Iran	Misoprostol	400 µg	Oral	200	NA (NA)	NA (NA)	NA	NA	NA	NA	NA
Rajaei, M. 2014	Clinical	Misoprostol vs Oxytocin	Double blind	Iran	Oxytocin	20 IU	IV	200	NA (NA)	NA (NA)	NA	NA	NA	NA	NA
Sadiq, U.G. 2011	Clinical	Misoprostol vs Oxytocin	Open label	Nigeria	Misoprostol	600 µg	Oral	900	NA (NA)	NA (NA)	NA	NA	NA	NA	NA
Sadiq, U.G. 2011	Clinical	Misoprostol vs Oxytocin	Open label	Nigeria	Oxytocin	10 IU	IV	900	NA (NA)	NA (NA)	NA	NA	NA	NA	NA

Singh, G. 2009	Clinical	Misoprostol vs Oxytocin vs Methylergometrine	Double blind	India	Misoprostol	400 µg	Sublingual	75	24.17 (2.57)	38.52 (1.42)	NA	NA	NA	NA	NA
Singh, G. 2009	Clinical	Misoprostol vs Oxytocin vs Methylergometrine	Double blind	India	Misoprostol	600 µg	Sublingual	75	23.83 (2.92)	38.76 (1.76)	NA	NA	NA	NA	NA
Singh, G. 2009	Clinical	Misoprostol vs Oxytocin vs Methylergometrine	Double blind	India	Oxytocin	5 IU	IV	75	24.27 (2.67)	38.65 (1.08)	NA	NA	NA	NA	NA
Singh, G. 2009	Clinical	Misoprostol vs Oxytocin vs Methylergometrine	Double blind	India	Methylergometrine	0.2 mg	IV	75	24.41 (2.64)	38.58 (1.36)	NA	NA	NA	NA	NA
Surbek, D.V. 1999	Clinical	Misoprostol vs Placebo	Double blind	Switzerland	Misoprostol	600 µg	Oral	31	29.3 (1.1)	40 (0.3)	23	58		13	0
Surbek, D.V. 1999	Clinical	Misoprostol vs Placebo	Double blind	Switzerland	Placebo		Oral	34	30.8 (1)	40 (0.1)	21	47		24	0
Tewatia, R. 2014	Clinical	Misoprostol vs Oxytocin	Open label	India	Misoprostol	600 µg	Sublingual	50	25.1 (3.3)	38.6 (1)	NA	NA	NA	NA	0
Tewatia, R. 2014	Clinical	Misoprostol vs Oxytocin	Open label	India	Oxytocin	10 IU	IV	50	25.2 (3.5)	38.5 (1.1)	NA	NA	NA	NA	0
Vaid, A. 2009	Clinical	Misoprostol vs Methylergometrine vs 15-methyl PGF2α	Open label	India	Misoprostol	400 µg	Sublingual	66	26.04 (3.36)	38.53 (1.21)	NA	NA	66.67	10.61	NA
Vaid, A. 2009	Clinical	Misoprostol vs Methylergometrine vs 15-methyl PGF2α	Open label	India	Methylergometrine	0.2 mg	IM	67	25.74 (3.45)	38.67 (1.21)	NA	NA	70.15	13.43	NA
Vaid, A. 2009	Clinical	Misoprostol vs Methylergometrine vs 15-methyl PGF2α	Open label	India	15-methyl PGF2α	125 µg	IM	67	25.71 (3.79)	38.47 (1.29)	NA	NA	79.1	5.97	NA
Vimala, N. 2004	Clinical	Misoprostol vs Methylergometrine	Open label	India	Misoprostol	400 µg	Sublingual	60	26 (2.4)	39.2 (1.3)	0	0	60	3.3	NA

Vimala, N. 2004	Clinical	Misoprostol vs Methylergometrine	Open label	India	Methylergometrine	0.2 mg	IV	60	24 (4.2)	38.6 (1.6)	0	0	53.3	5	NA
Walley, R.L. 2000	Clinical	Misoprostol vs Oxytocin	Double blind	Ghana	Misoprostol	400 µg	Oral	203	25.7 (5)	38 (2)	0	0	36.5	NA	0
Walley, R.L. 2000	Clinical	Misoprostol vs Oxytocin	Double blind	Ghana	Oxytocin	10 IU	IM	198	26.1 (5.5)	38 (1.9)	0	0	42.4	NA	0
Walraven, G. 2005	Community	Misoprostol vs Ergometrine	Double blind	Gambia	Misoprostol	600 µg	Oral	630	25.9 (5.3)	NA (NA)	0	0	NA	0	NA
Walraven, G. 2005	Community	Misoprostol vs Ergometrine	Double blind	Gambia	Ergometrine	2.0 mg	Oral	599	25.8 (5.3)	NA (NA)	0	0	NA	0	NA
Zachariah, E.S. 2006	Clinical	Misoprostol vs Oxytocin vs Ergometrine	Open label	India	Misoprostol	400 µg	Oral	730	24.4 (3.9)	39.2 (14)	NA	NA	NA	7.7	NA
Zachariah, E.S. 2006	Clinical	Misoprostol vs Oxytocin vs Ergometrine	Open label	India	Oxytocin	10 IU	IM	617	24.6 (3.8)	39.3 (11.5)	NA	NA	NA	8	NA
Zachariah, E.S. 2006	Clinical	Misoprostol vs Oxytocin vs Ergometrine	Open label	India	Ergometrine	2.0 mg	IV	676	24.8 (4)	39.1 (11)	NA	NA	NA	7.7	NA
Karkanis S.G. 2002	Clinical	Misoprostol vs Oxytocin	Open label	Canada	Misoprostol	400 µg	Rectal	110	NA (NA)	39.3 (1.1)	NA	NA	NA	20	NA
Karkanis S.G. 2002	Clinical	Misoprostol vs Oxytocin	Open label	Canada	Oxytocin	5 or 10 IU	IV/IM	113	NA (NA)	39.6 (1.1)	NA	NA	NA	22	NA
Ng P.S. 2007	Clinical	Misoprostol vs Oxytocin	Double blind	Hong Kong SAR, China	Misoprostol	400 µg	Oral	178	28.8 (4.9)	39.5 (1.5)	NA	19.7	93.8	NA	1.7
Ng P.S. 2007	Clinical	Misoprostol vs Oxytocin	Double blind	Hong Kong SAR, China	Oxytocin	5 IU	IM	177	28.4 (4.9)	39.3 (1.6)	NA	18.6	94.4	NA	1.7
Wangwe, P. 2009	Clinical	Misoprostol vs Oxytocin	Open label	Tanzania	Misoprostol	400 µg	Rectal	210	NA (NA)	39 (2.52)	0	NA	NA	NA	NA
Wangwe, P. 2009	Clinical	Misoprostol vs Oxytocin	Open label	Tanzania	Oxytocin	5 IU	IM	204	NA (NA)	38.9 (2.5)	0	NA	NA	NA	NA

Table 2: Risk of bias assessment

	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other bias**
Afolabi, E.O.	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk
Amant, F.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Bamigboye, A.A.	Low risk	Low risk	High risk	High risk	Low risk	Unclear risk	Low risk
Bamigboye, A.A.	Low risk	Low risk	High risk	High risk	Low risk	Unclear risk	Low risk
Baskett, T.F	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Bellad, M.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Benchimol, M.	Unclear risk	Low risk	High risk	High risk	Low risk	Unclear risk	Low risk
Bugalho, A.	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Çaliskan, E.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Çaliskan, E.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Chaudhuri, P.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cook, C.M.	Low risk	Low risk	High risk	High risk	Low risk	Unclear risk	Low risk
Derman, R.J.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Enakpene, C.A.	Low risk	Low risk	High risk	High risk	Low risk	Unclear risk	Low risk

Garg, P.	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Unclear risk
Gerstenfeld, T.S.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Gulmezoglu, A.M.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Gupta, B.	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Harriott, J.	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk
Hofmeyr, G.J.	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Hofmeyr, G.J.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Hoj, L.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Kundodyiwa, T.W.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Lam, H.	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk
Mansouri, H.A.	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk
Miller, S.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mirteimouri, M.	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Mobeen, N.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mukta, M.	Unclear risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Unclear risk
Nellore, V.	Unclear risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk
Ng, P.S.	Low risk	Low risk	High risk	High risk	Low risk	Unclear risk	Low risk
Oboro, V.O.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Ozkaya, O.	Low risk	Low risk	High risk	High risk	Low risk	Unclear risk	Low risk
Rajaei, M.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Sadiq, U.G.	Low risk	Low risk	High risk	High risk	Low risk	Unclear risk	Low risk
Singh, G.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Surbek, D.V.	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Tewatia, R.	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk
Vaid, A.	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk
Vimala, N.	Low risk	Low risk	High risk	High risk	Low risk	Unclear risk	Low risk
Walley, R.L.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Walraven, G.	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Zachariah, E.S.	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk
Karkanis S.G.	Unclear risk	Low risk	High risk	High risk	Low risk	Unclear risk	Low risk
Ng P.S.	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Wangwe, P.	Unclear risk	Low risk	High risk	High risk	Low risk	Unclear risk	Low risk

Figure 2: Overall assessment of risk of bias

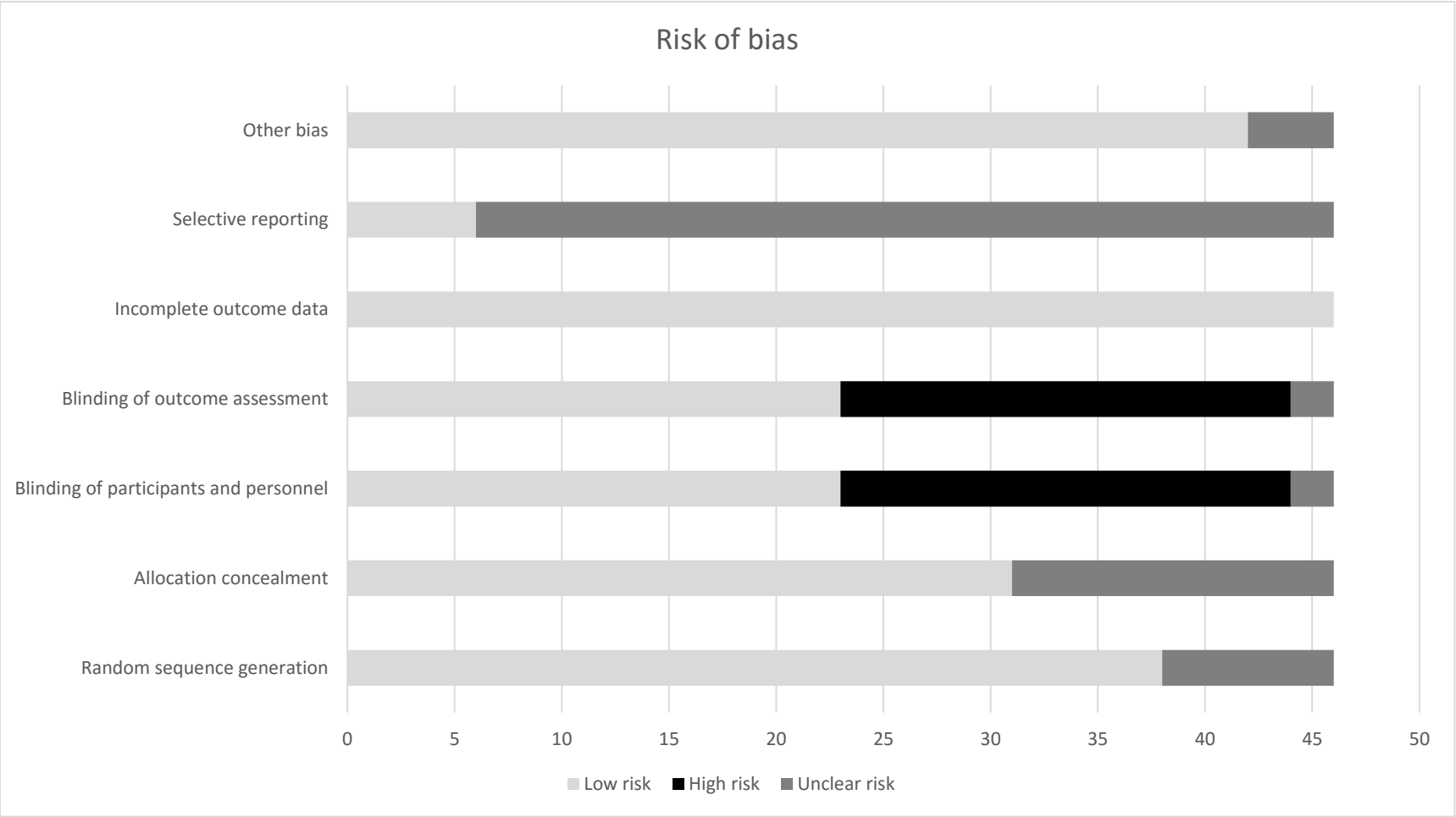


Figure 3: Network diagram for the outcome “bleeding 500 ml or over”

Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Placebo / Control	D
Oxytocin 5 IU	E
Oxytocin 20 IU	F
Methylergometrin 0.2 mg	G
Oxytocin 3 / 2.5 IU	H
Ergometrin 2.0 mg	I
ZB11	J
15-methyl PGF2α 125 µg	K
Syntometrine	L
Ergometrine 0.5 mg	M
Oxytocin/Syntometrine	N

Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

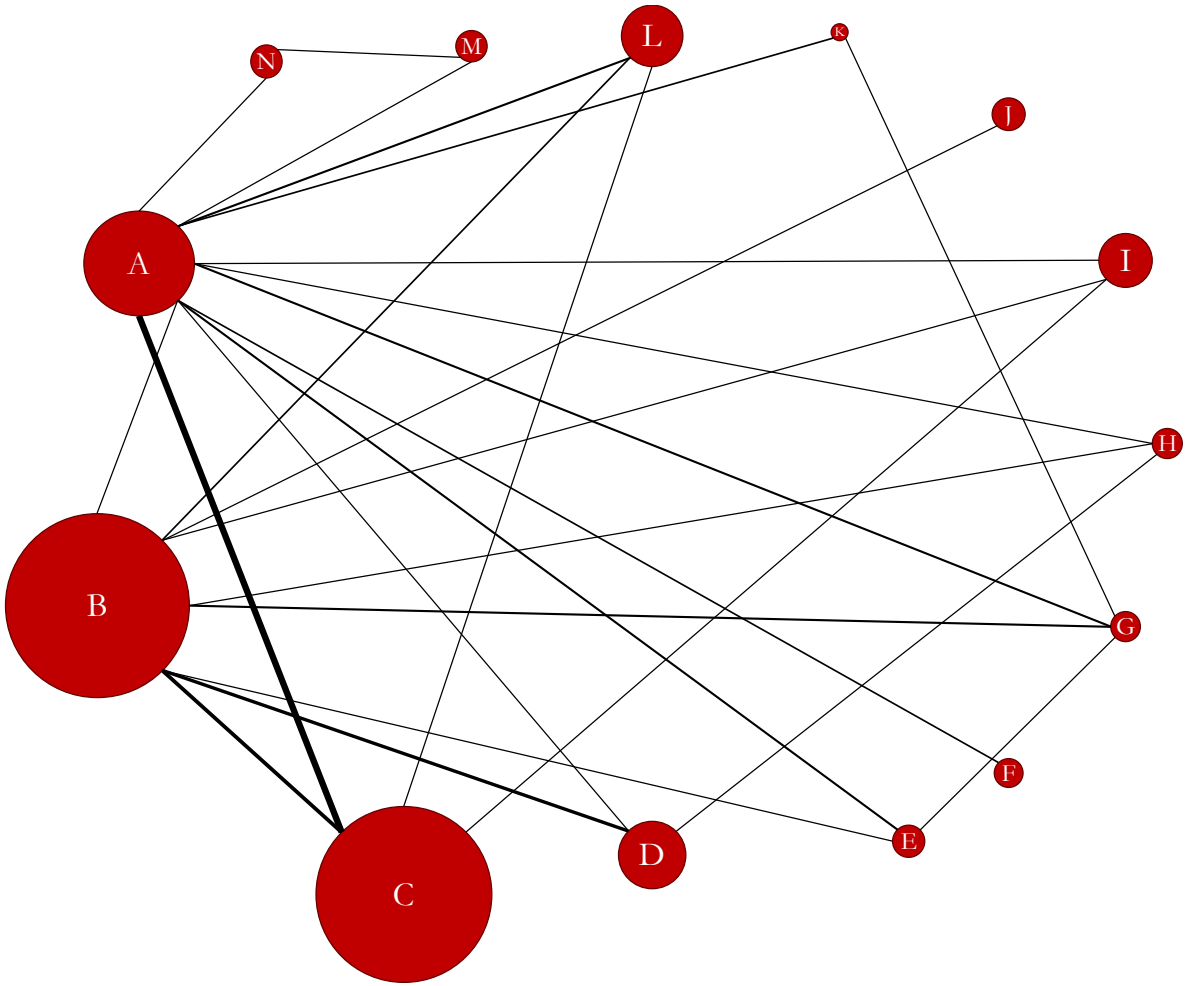


Figure 4: Inconsistency results for the outcome “bleeding 500 ml or greater”

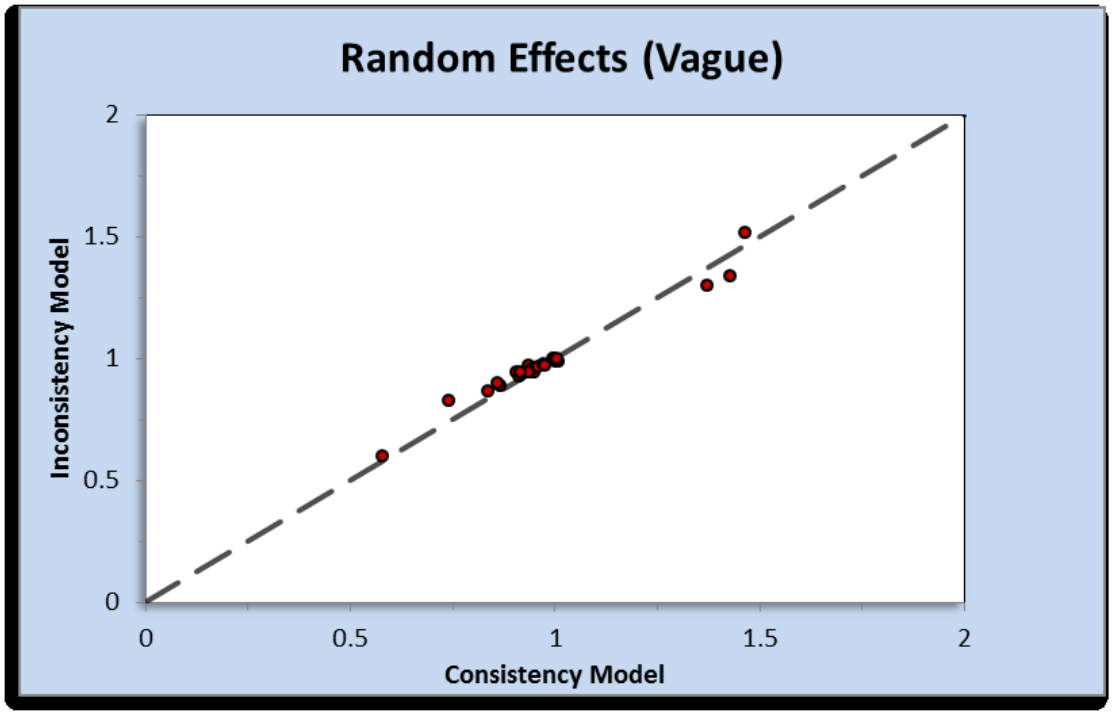


Figure 5: League table for the outcome “bleeding 500 ml or greater”

Oxytocin 5 IU													
0.75 (0.19 – 3.01)	**Methylergometrin 0.2 mg**												
0.68 (0.18 – 2.42)	0.91 (0.28 – 2.70)	**Syntometrine**											
0.65 (0.21 – 2.00)	0.87 (0.33 – 2.26)	0.96 (0.44 – 2.25)	**Oxytocin 10 IU**										
0.62 (0.13 – 3.08)	0.84 (0.18 – 3.80)	0.92 (0.23 – 4.05)	0.96 (0.26 – 3.47)	**Oxytocin 20 IU**									
0.60 (0.21 – 1.70)	0.81 (0.32 – 2.01)	0.89 (0.42 – 2.02)	0.92 (0.58 – 1.45)	0.96 (0.29 – 3.24)	**Misoprostol 400 µg**								
0.57 (0.12 – 2.66)	0.76 (0.22 – 2.60)	0.84 (0.23 – 3.38)	0.87 (0.27 – 2.89)	0.91 (0.18 – 4.78)	0.95 (0.31 – 2.92)	**15-methyl PGF2α 125 µg**							
0.52 (0.15 – 1.67)	0.70 (0.27 – 1.69)	0.77 (0.35 – 1.70)	0.80 (0.45 – 1.35)	0.83 (0.21 – 3.10)	0.86 (0.46 – 1.54)	0.91 (0.26 – 2.98)	**Misoprostol 600 µg**						
0.48 (0.12 – 1.89)	0.64 (0.19 – 2.14)	0.71 (0.24 – 2.23)	0.74 (0.29 – 1.81)	0.77 (0.17 – 3.46)	0.80 (0.32 – 1.98)	0.84 (0.20 – 3.42)	0.92 (0.38 – 2.31)	**Ergometrin 2.0 mg**					
0.40 (0.10 – 1.63)	0.53 (0.15 – 1.83)	0.59 (0.19 – 1.92)	0.61 (0.23 – 1.63)	0.64 (0.14 – 2.94)	0.66 (0.26 – 1.71)	0.70 (0.16 – 2.94)	0.77 (0.30 – 2.04)	0.83 (0.24 – 2.89)	**Oxytocin 3 / 2.5 IU**				
0.35 (0.06 – 1.89)	0.47 (0.10 – 2.09)	0.51 (0.12 – 2.25)	0.54 (0.13 – 2.01)	0.56 (0.09 – 3.41)	0.58 (0.14 – 2.23)	0.61 (0.10 – 3.35)	0.67 (0.19 – 2.30)	0.72 (0.15 – 3.29)	0.87 (0.18 – 4.05)	**ZB11**			
0.37 (0.10 – 1.35)	0.49 (0.16 – 1.41)	0.54 (0.21 – 1.46)	0.57 (0.25 – 1.22)	0.59 (0.13 – 2.48)	0.61 (0.27 – 1.35)	0.65 (0.17 – 2.39)	0.71 (0.39 – 1.29)	0.77 (0.26 – 2.20)	0.93 (0.33 – 2.53)	1.06 (0.27 – 4.19)	**Placebo / Control**		
0.07 (0.01 – 0.44)	0.10 (0.02 – 0.54)	0.11 (0.02 – 0.59)	0.11 (0.02 – 0.51)	0.12 (0.02 – 0.79)	0.12 (0.03 – 0.52)	0.13 (0.02 – 0.80)	0.14 (0.03 – 0.70)	0.15 (0.03 – 0.87)	0.18 (0.03 – 1.04)	0.21 (0.03 – 1.60)	0.20 (0.04 – 1.07)	**Oxytocin/Syntometrine**	
0.07 (0.01 – 0.44)	0.10 (0.02 – 0.54)	0.11 (0.02 – 0.59)	0.11 (0.02 – 0.51)	0.12 (0.02 – 0.78)	0.12 (0.03 – 0.52)	0.13 (0.02 – 0.79)	0.14 (0.03 – 0.70)	0.15 (0.03 – 0.86)	0.18 (0.03 – 1.04)	0.21 (0.03 – 1.60)	0.20 (0.04 – 1.07)	1.00 (0.28 – 3.56)	**Ergometrine 0.5 mg**

Figure 6: Network diagram for the outcome "bleeding 1000 ml or over"

Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Placebo / Control	D
Oxytocin 5 IU	E
Oxytocin 20 IU	F
Methylergometrin 0.2 mg	G
Ergometrin 2.0 mg	H
ZB11	I
Syntometrine	J
15-methyl PGF2α 125 µg	K
Oxytocin 2.5 IU	L
Oxytocin/Syntometrine	M
	N
	O

Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

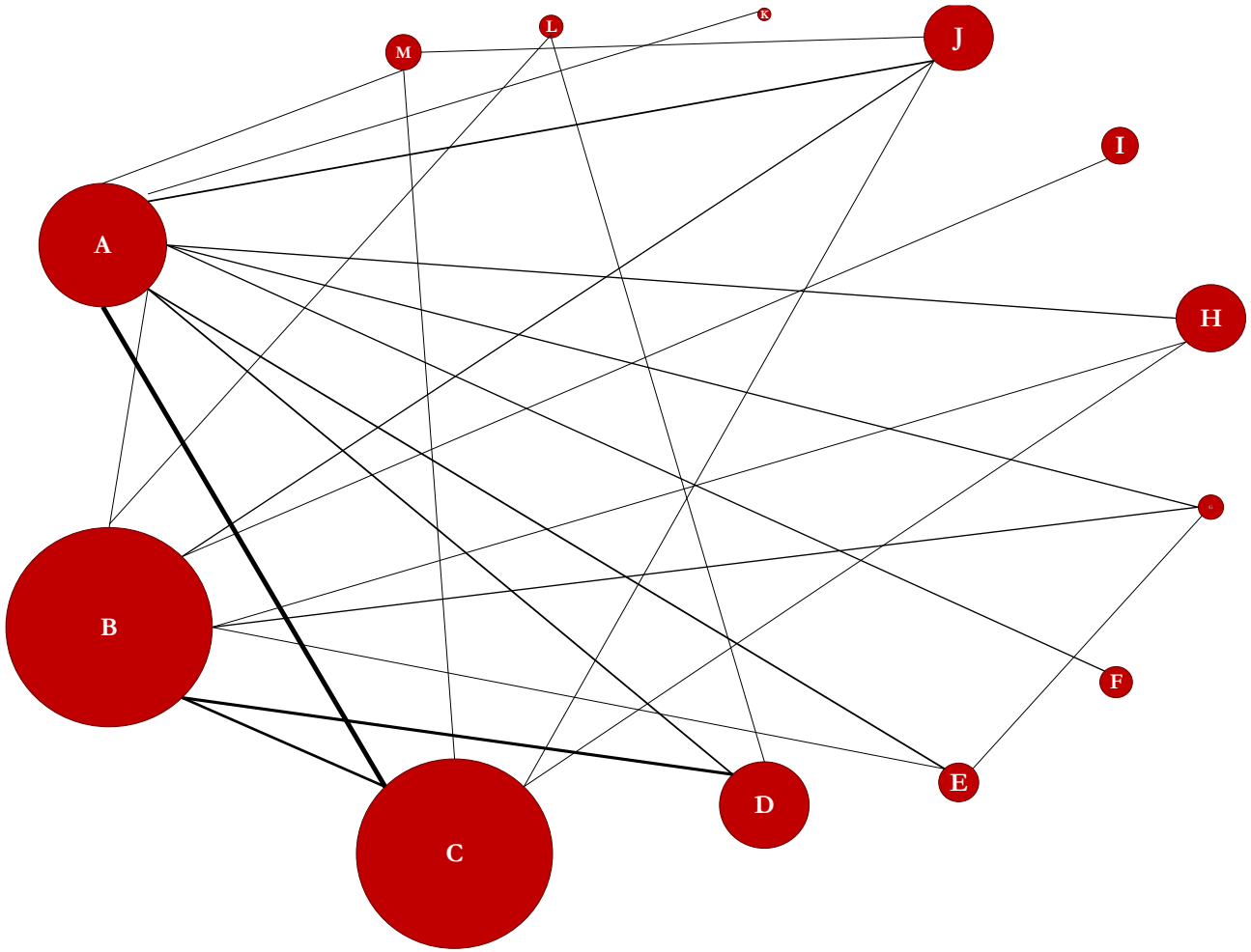


Figure 7: Inconsistency results for the outcome “bleeding 1000 ml or over”

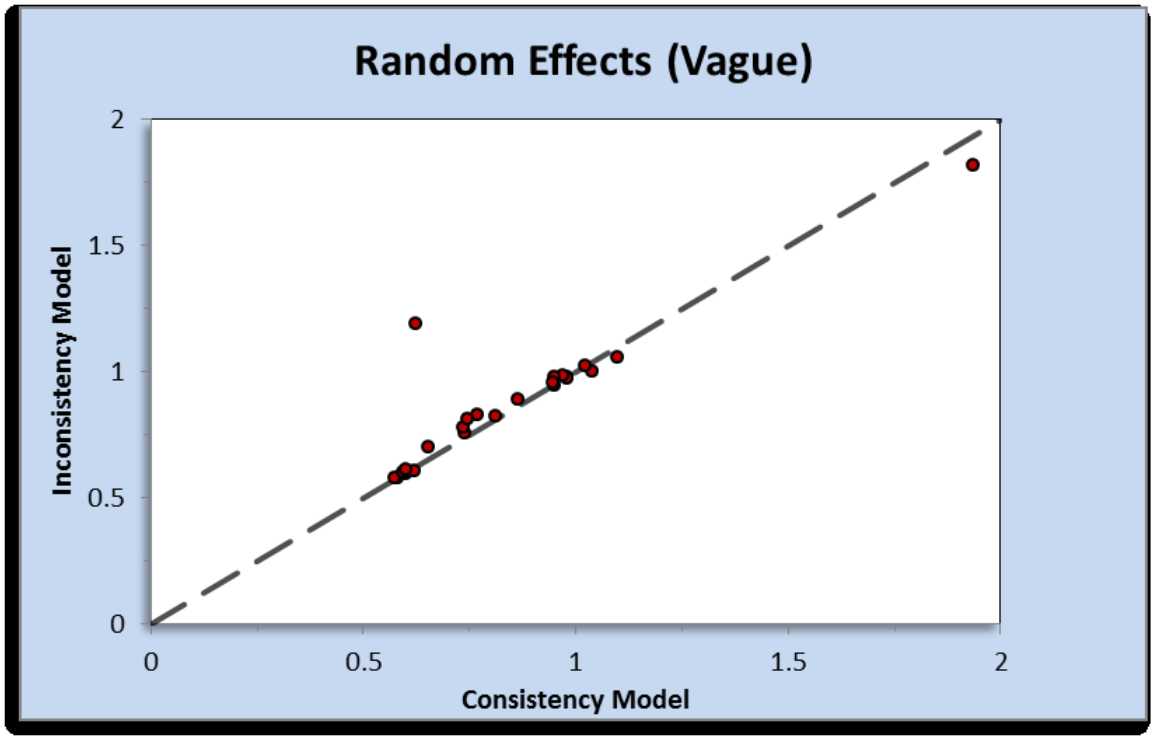
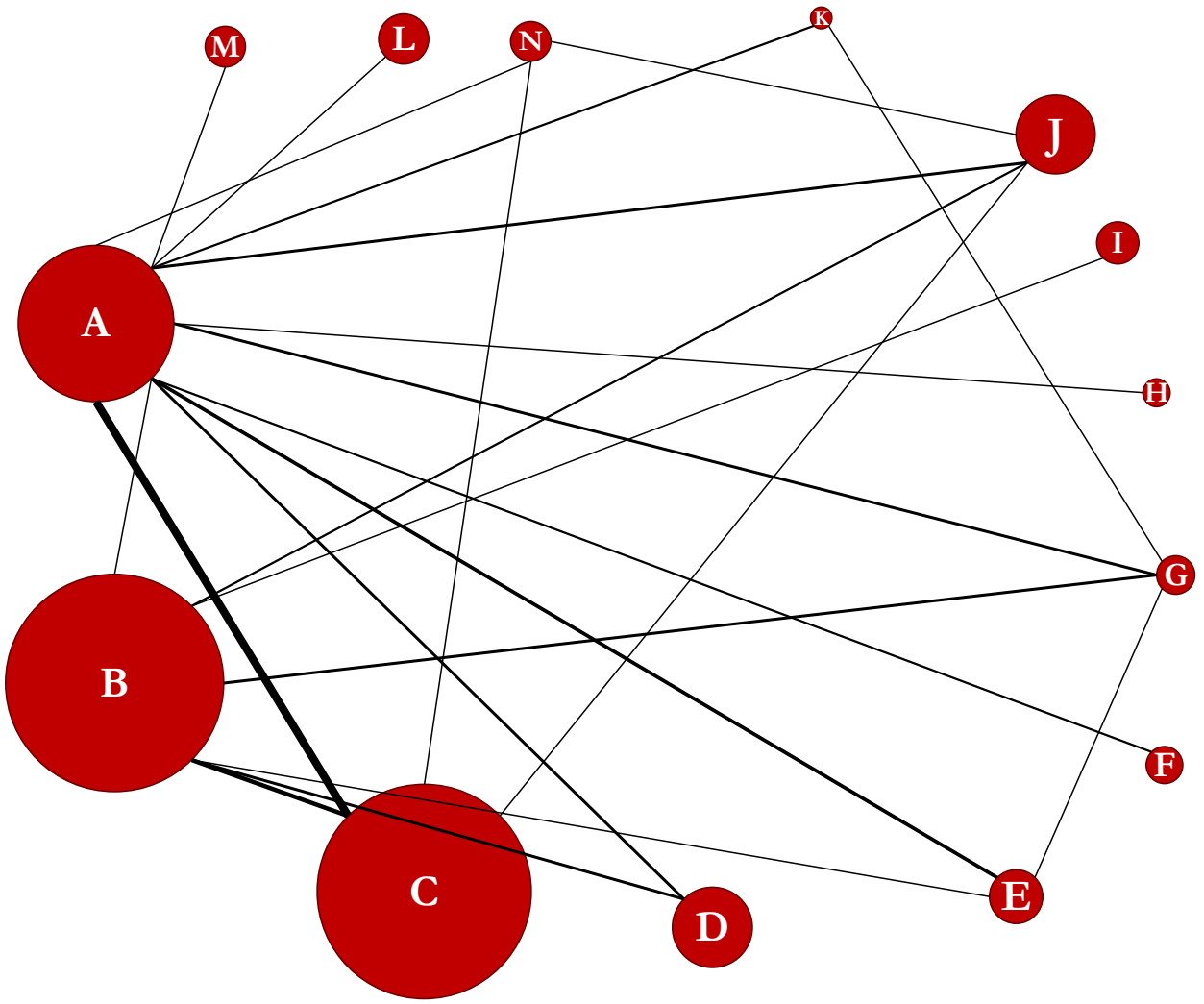


Figure 8: League table for the outcome “bleeding 1000 ml or greater”

Oxytocin 5 IU												
0.74 (0.19 – 2.92)	**Oxytocin/Syntometrine**											
0.85 (0.07 – 15.87)	1.20 (0.10 – 20.97)	**Methylergometrin 0.2 mg**										
0.55 (0.20 – 1.45)	0.75 (0.26 – 2.11)	0.65 (0.04 – 6.73)	**Oxytocin 10 IU**									
0.57 (0.15 – 1.98)	0.75 (0.20 – 2.88)	0.66 (0.03 – 7.78)	1.01 (0.40 – 2.51)	**Oxytocin 20 IU**								
0.51 (0.15 – 1.70)	0.70 (0.23 – 2.04)	0.60 (0.03 – 6.97)	0.93 (0.41 – 1.99)	0.91 (0.29 – 2.98)	**Syntometrine**							
0.49 (0.18 – 1.21)	0.66 (0.24 – 1.81)	0.56 (0.03 – 5.91)	0.87 (0.62 – 1.25)	0.87 (0.37 – 2.08)	0.95 (0.45 – 2.08)	**Misoprostol 400 µg**						
0.37 (0.00 – 785.55)	0.52 (0.00 – 902.60)	0.44 (0.00 – 1225.19)	0.68 (0.00 – 1124.48)	0.66 (0.00 – 1159.82)	0.74 (0.00 – 1281.56)	0.77 (0.00 – 1312.68)	**15-methyl PGF2α 125 µg**					
0.41 (0.11 – 1.51)	0.54 (0.15 – 2.09)	0.49 (0.02 – 5.33)	0.74 (0.31 – 1.82)	0.73 (0.21 – 2.56)	0.79 (0.26 – 2.48)	0.84 (0.34 – 2.09)	1.11 (0.00 – 2555.58)	**Oxytocin 2.5 IU**				
0.40 (0.14 – 1.08)	0.54 (0.19 – 1.58)	0.47 (0.03 – 4.78)	0.72 (0.51 – 1.06)	0.72 (0.28 – 1.91)	0.78 (0.36 – 1.77)	0.83 (0.54 – 1.26)	1.05 (0.00 – 2801.00)	0.98 (0.42 – 2.24)	**Misoprostol 600 µg**			
0.26 (0.06 – 1.02)	0.35 (0.08 – 1.38)	0.31 (0.01 – 3.64)	0.47 (0.17 – 1.25)	0.46 (0.12 – 1.73)	0.50 (0.14 – 1.74)	0.54 (0.18 – 1.45)	0.67 (0.00 – 1905.00)	0.63 (0.18 – 2.26)	0.64 (0.25 – 1.60)	**ZB11**		
0.30 (0.10 – 0.81)	0.40 (0.14 – 1.17)	0.35 (0.02 – 3.61)	0.53 (0.35 – 0.83)	0.53 (0.21 – 1.39)	0.57 (0.25 – 1.35)	0.61 (0.39 – 0.93)	0.76 (0.00 – 1992.00)	0.73 (0.31 – 1.62)	0.74 (0.54 – 1.01)	1.14 (0.43 – 3.23)	**Placebo / Control**	
0.21 (0.05 – 0.84)	0.29 (0.06 – 1.14)	0.25 (0.01 – 2.84)	0.38 (0.13 – 1.04)	0.38 (0.10 – 1.41)	0.41 (0.10 – 1.49)	0.44 (0.14 – 1.17)	0.58 (0.00 – 1396.00)	0.53 (0.13 – 1.86)	0.53 (0.17 – 1.43)	0.82 (0.19 – 3.32)	0.72 (0.22 – 2.00)	**Ergometrin 2.0 mg**

Figure 9: Network diagram for the outcome “need for additional uterotonics”.

Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Placebo / Control	D
Oxytocin 5 IU	E
Oxytocin 20 IU	F
Methylergometrin 0.2 mg	G
Oxytocin 3 IU	H
ZB11	I
Syntometrine	J
15-methyl PGF2α 125 µg	K
Ergometrine 2 mg	L
Ergometrine 0.5 mg	M
Oxytocin/Syntometrine	N
	O



Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

Figure 10: Inconsistency results for the outcome “need for additional uterotonics”.

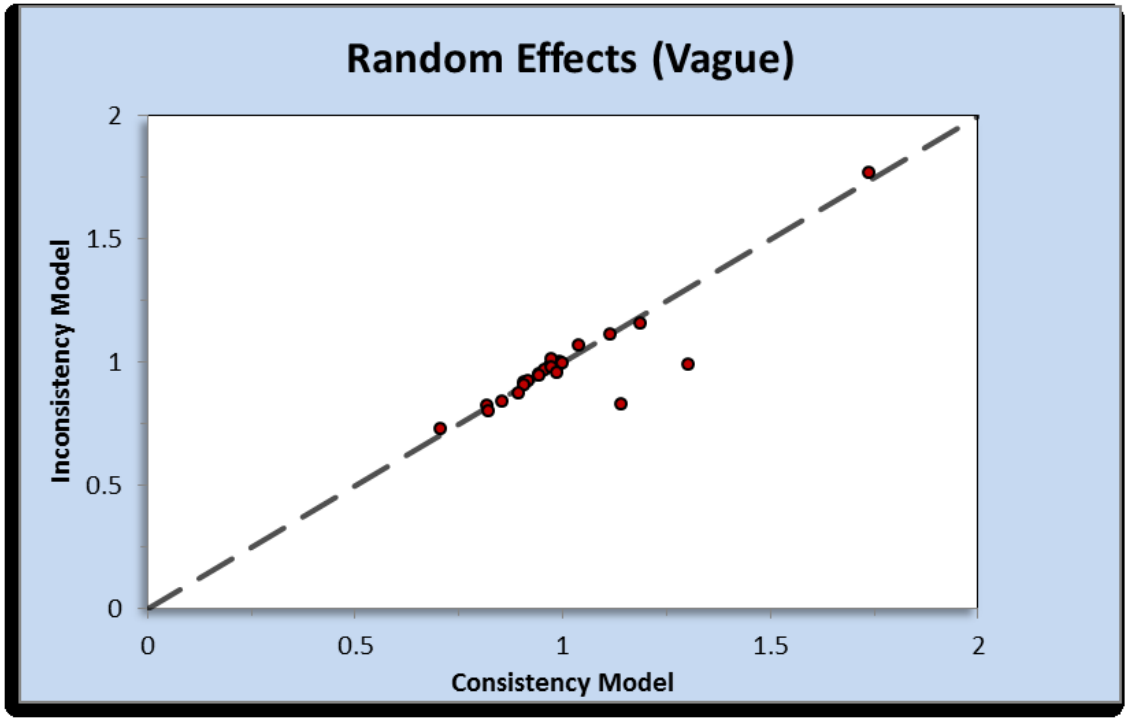
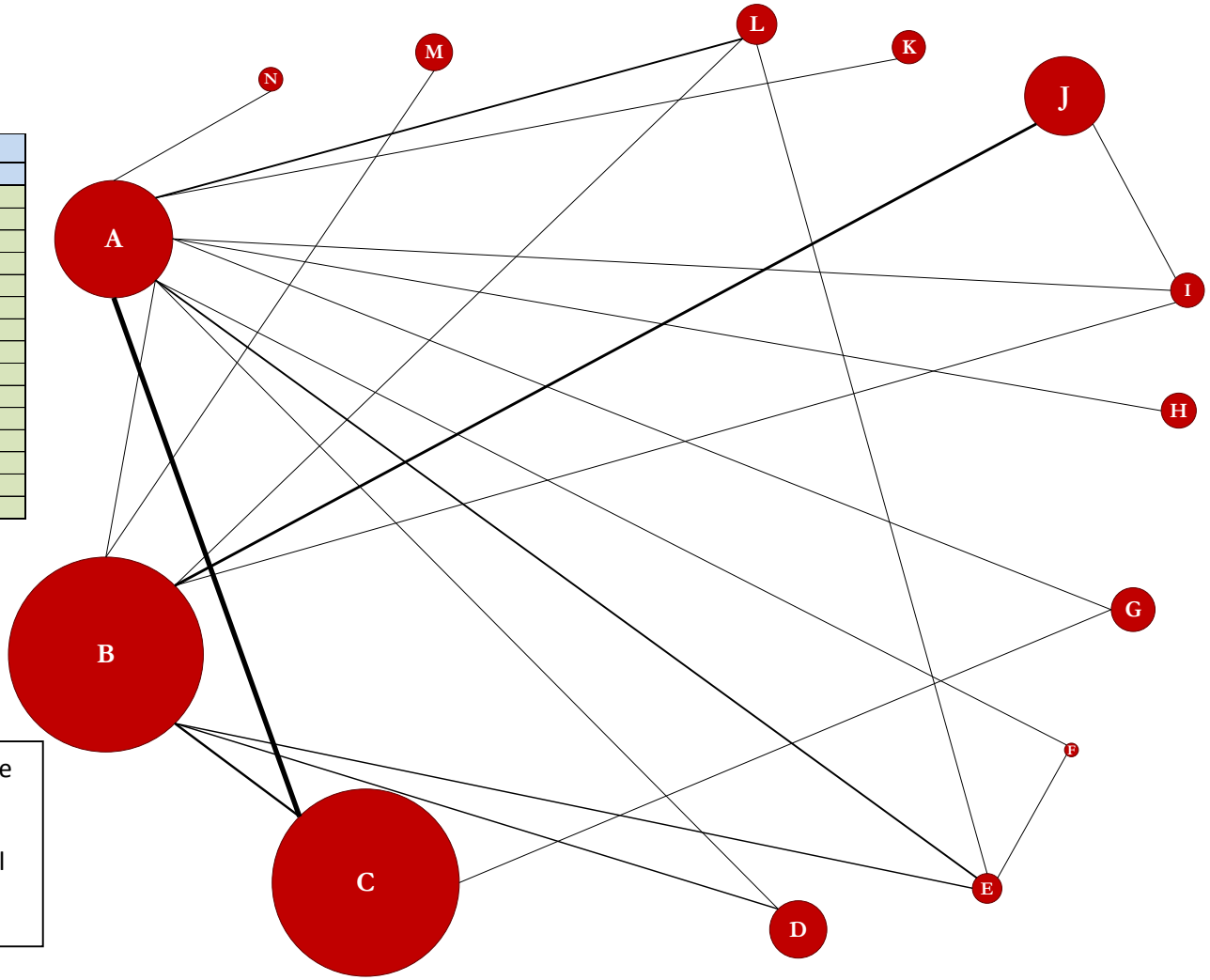


Figure 11: League table for the outcome “need for additional uterotonics”.

15-methyl PGF2α 125 µg													
0.84 (0.19 – 3.72)	Syntometrine												
0.94 (0.15 – 5.35)	1.11 (0.27 – 4.23)	Oxytocin/Syntometrine											
0.59 (0.15 – 2.16)	0.71 (0.29 – 1.67)	0.63 (0.17 – 2.46)	Oxytocin 10 IU										
0.54 (0.12 – 2.30)	0.64 (0.19 – 2.03)	0.58 (0.13 – 2.73)	0.92 (0.36 – 2.33)	Oxytocin 5 IU									
0.56 (0.08 – 4.00)	0.68 (0.12 – 3.73)	0.60 (0.09 – 4.49)	0.96 (0.20 – 4.55)	1.04 (0.20 – 5.76)	Ergometrine 2 mg								
0.50 (0.09 – 2.65)	0.60 (0.14 – 2.37)	0.54 (0.10 – 3.02)	0.85 (0.24 – 2.87)	0.93 (0.23 – 3.71)	0.88 (0.14 – 5.53)	Oxytocin 20 IU							
0.49 (0.14 – 1.67)	0.58 (0.25 – 1.31)	0.52 (0.14 – 1.99)	0.82 (0.51 – 1.34)	0.89 (0.40 – 2.05)	0.86 (0.20 – 3.79)	0.97 (0.32 – 3.08)	Misoprostol 400 µg						
0.37 (0.09 – 1.39)	0.44 (0.17 – 1.04)	0.39 (0.10 – 1.59)	0.62 (0.34 – 1.12)	0.68 (0.25 – 1.84)	0.65 (0.12 – 3.18)	0.73 (0.20 – 2.67)	0.75 (0.40 – 1.40)	Misoprostol 600 µg					
0.35 (0.09 – 1.29)	0.41 (0.13 – 1.24)	0.38 (0.08 – 1.71)	0.59 (0.24 – 1.45)	0.64 (0.21 – 1.90)	0.62 (0.11 – 3.30)	0.70 (0.17 – 2.89)	0.72 (0.30 – 1.63)	0.95 (0.41 – 2.24)	Methylergometrin 0.2 mg				
0.28 (0.04 – 2.13)	0.34 (0.06 – 1.84)	0.30 (0.04 – 2.34)	0.48 (0.09 – 2.36)	0.52 (0.09 – 3.10)	0.50 (0.05 – 4.37)	0.56 (0.08 – 4.17)	0.58 (0.11 – 2.85)	0.77 (0.17 – 3.43)	0.81 (0.14 – 4.56)	ZB11			
0.24 (0.03 – 1.61)	0.28 (0.05 – 1.52)	0.25 (0.03 – 1.89)	0.39 (0.08 – 1.93)	0.43 (0.08 – 2.41)	0.41 (0.05 – 3.39)	0.47 (0.07 – 3.11)	0.48 (0.11 – 2.20)	0.64 (0.13 – 3.32)	0.67 (0.13 – 3.78)	0.83 (0.09 – 7.69)	Oxytocin 3 IU		
0.18 (0.02 – 1.23)	0.21 (0.04 – 1.15)	0.19 (0.03 – 1.39)	0.30 (0.06 – 1.45)	0.32 (0.06 – 1.82)	0.31 (0.04 – 2.57)	0.35 (0.05 – 2.37)	0.36 (0.08 – 1.61)	0.48 (0.10 – 2.51)	0.50 (0.09 – 2.83)	0.62 (0.07 – 5.62)	0.75 (0.09 – 6.41)	Ergometrine 0.5 mg	
0.21 (0.05 – 0.87)	0.25 (0.08 – 0.72)	0.23 (0.05 – 1.00)	0.36 (0.15 – 0.82)	0.39 (0.13 – 1.18)	0.38 (0.07 – 1.97)	0.42 (0.10 – 1.64)	0.44 (0.19 – 0.93)	0.58 (0.26 – 1.24)	0.61 (0.21 – 1.72)	0.76 (0.13 – 4.03)	0.91 (0.16 – 4.85)	1.21 (0.21 – 6.35)	Placebo / Control

Figure 12: Network diagram for the outcome "pyrexia"

Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Syntometrine	D
Methylergometrine 0.2 mg	E
15-methyl PGF2α 125 µg	F
Ergometrine 2 mg	G
Ergometrine 0.5 mg	H
Oxytocin 3 / 2.5 IU	I
Placebo / Control	J
Oxytocin/Syntometrine	K
Oxytocin 5 IU	L
ZB11	M
Oxytocin 20 IU	N
	O



Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

Figure 13: Inconsistency results for the outcome “pyrexia”

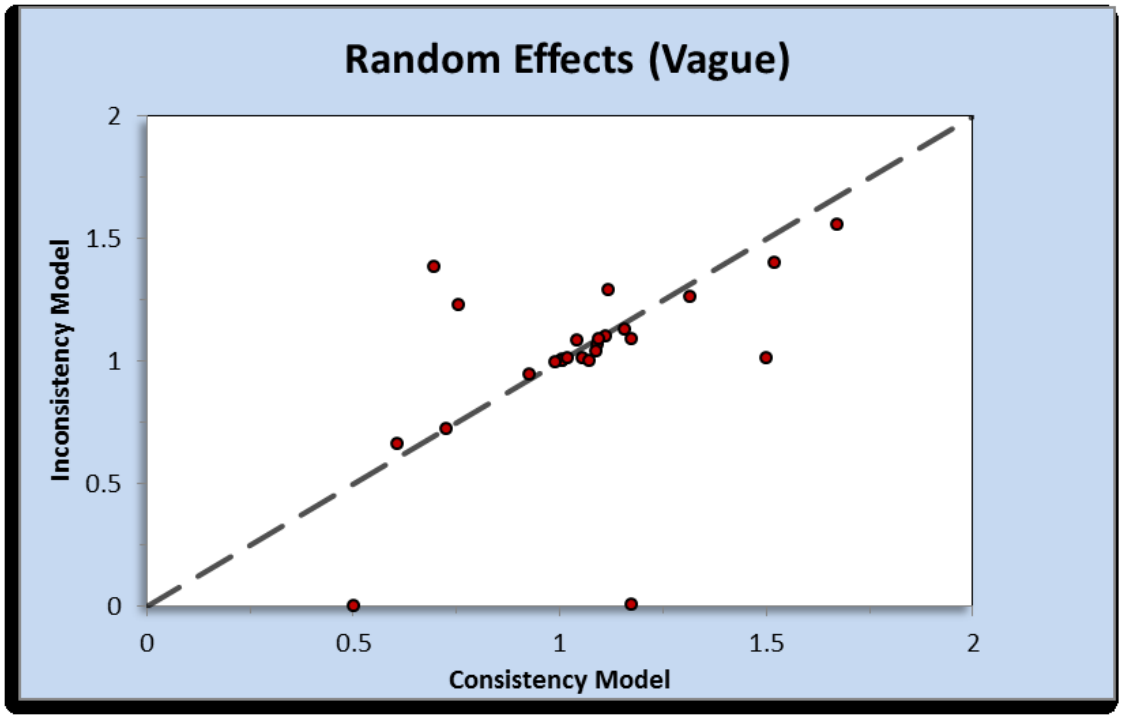


Figure 14: League table for the outcome “pyrexia”

Oxytocin 5 IU													
0.16 (0.00 – 4.26)	**Methylergometrine 0.2 mg**												
0.12 (0.00 – 11.70)	0.80 (0.02 – 44.50)	**15-methyl PGF2α 125 µg**											
0.07 (0.00 – 2.47)	0.44 (0.01 – 9.59)	0.53 (0.01 – 32.62)	**Oxytocin 20 IU**										
0.06 (0.00 – 1.57)	0.37 (0.02 – 4.49)	0.45 (0.01 – 22.41)	0.84 (0.03 – 29.64)	**Syntometrine**									
0.05 (0.00 – 8.36)	0.31 (0.01 – 38.54)	0.40 (0.00 – 89.21)	0.75 (0.01 – 137.70)	0.86 (0.02 – 107.62)	**Oxytocin 3 / 2.5 IU**								
0.04 (0.00 – 0.56)	0.27 (0.02 – 1.68)	0.34 (0.01 – 8.83)	0.62 (0.04 – 10.45)	0.73 (0.07 – 6.71)	0.87 (0.01 – 22.17)	**Oxytocin 10 IU**							
0.04 (0.00 – 1.24)	0.24 (0.01 – 4.67)	0.29 (0.00 – 16.96)	0.55 (0.01 – 21.39)	0.65 (0.02 – 17.71)	0.73 (0.00 – 45.98)	0.88 (0.05 – 13.04)	**Ergometrine 0.5 mg**						
0.02 (0.00 – 0.40)	0.14 (0.01 – 1.07)	0.18 (0.00 – 5.90)	0.33 (0.01 – 7.41)	0.39 (0.03 – 3.36)	0.47 (0.00 – 10.31)	0.54 (0.08 – 2.78)	0.61 (0.03 – 12.85)	**Placebo / Control**					
0.02 (0.00 – 0.55)	0.13 (0.00 – 1.93)	0.16 (0.00 – 7.62)	0.30 (0.01 – 9.64)	0.36 (0.01 – 7.77)	0.40 (0.00 – 20.18)	0.49 (0.05 – 4.49)	0.55 (0.02 – 16.42)	0.91 (0.06 – 15.38)	**Ergometrine 2 mg**				
0.01 (0.00 – 0.62)	0.10 (0.00 – 2.05)	0.12 (0.00 – 8.35)	0.22 (0.00 – 11.47)	0.26 (0.01 – 6.35)	0.29 (0.00 – 17.94)	0.36 (0.02 – 6.49)	0.40 (0.01 – 20.84)	0.66 (0.04 – 13.06)	0.74 (0.02 – 29.99)	**ZB11**			
0.01 (0.00 – 0.40)	0.08 (0.00 – 1.44)	0.10 (0.00 – 5.43)	0.19 (0.00 – 6.86)	0.22 (0.01 – 5.88)	0.25 (0.00 – 14.20)	0.31 (0.02 – 3.97)	0.34 (0.01 – 11.58)	0.56 (0.03 – 12.37)	0.62 (0.02 – 17.48)	0.85 (0.02 – 41.53)	**Oxytocin/Syntometrine**		
0.01 (0.00 – 0.08)	0.05 (0.00 – 0.27)	0.06 (0.00 – 1.28)	0.11 (0.01 – 1.47)	0.13 (0.01 – 1.11)	0.15 (0.00 – 3.52)	0.18 (0.07 – 0.42)	0.20 (0.02 – 2.55)	0.33 (0.06 – 2.01)	0.37 (0.04 – 3.47)	0.50 (0.02 – 10.00)	0.58 (0.05 – 6.60)	**Misoprostol 400 µg**	
0.00 (0.00 – 0.06)	0.03 (0.00 – 0.15)	0.03 (0.00 – 0.90)	0.06 (0.00 – 1.12)	0.08 (0.01 – 0.46)	0.09 (0.00 – 1.74)	0.10 (0.03 – 0.34)	0.12 (0.01 – 1.96)	0.19 (0.06 – 0.63)	0.21 (0.02 – 2.58)	0.29 (0.02 – 4.06)	0.34 (0.02 – 5.24)	0.57 (0.15 – 2.18)	**Misoprostol 600 µg**

Figure 15: Network diagram for the outcome “shivering”

Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Syntometrine	D
Methylergometrine 0.2 mg	E
15-methyl PGF2α 125 µg	F
Ergometrine 2 mg	G
Ergometrine 0.5 mg	H
Oxytocin 3 / 2.5 IU	I
Placebo / Control	J
Oxytocin/Syntometrine	K
Oxytocin 5 IU	L
Oxytocin 20 IU	M
ZB 11	N
	O

Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

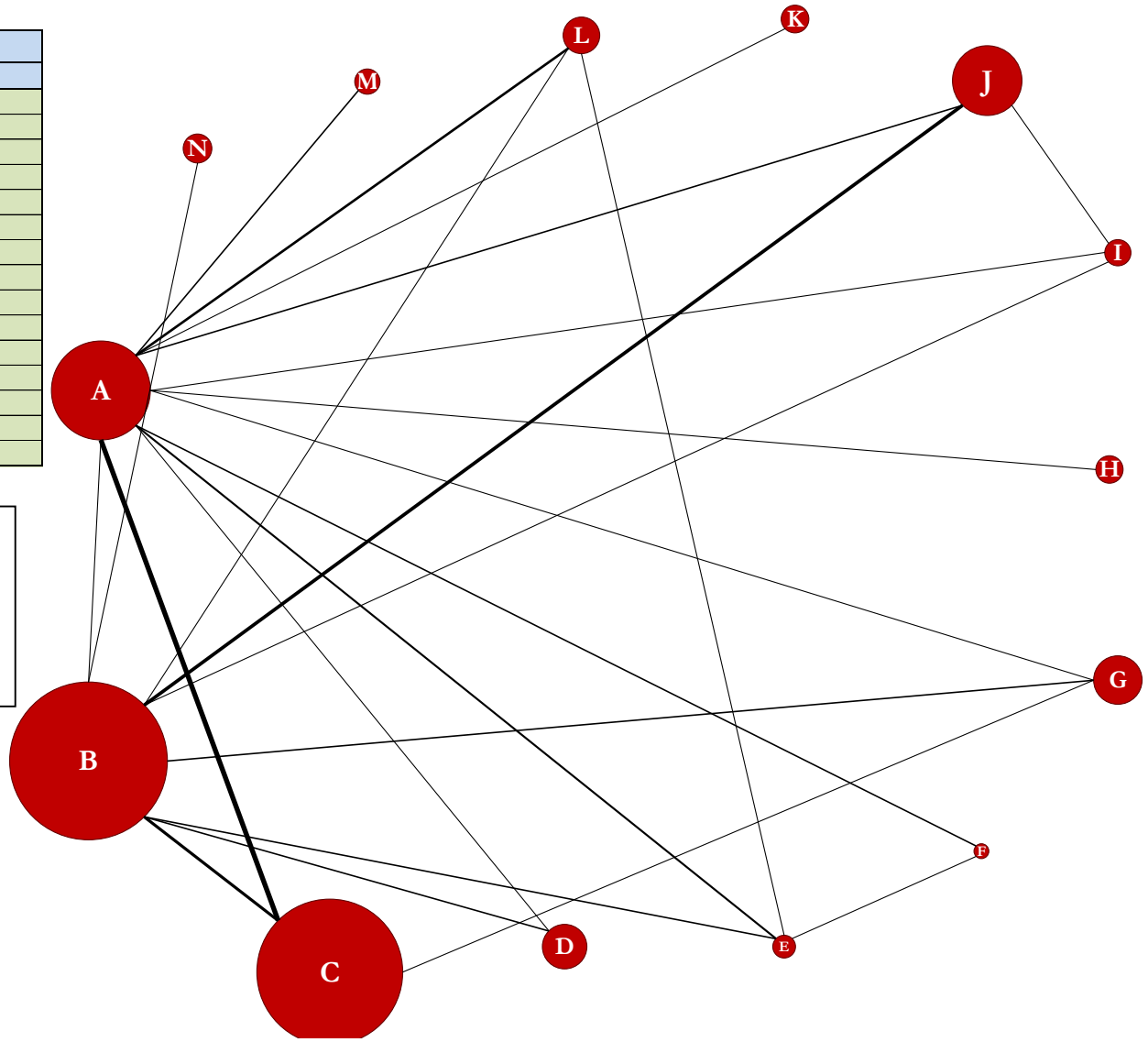


Figure 16: Inconsistency results for the outcome “shivering”

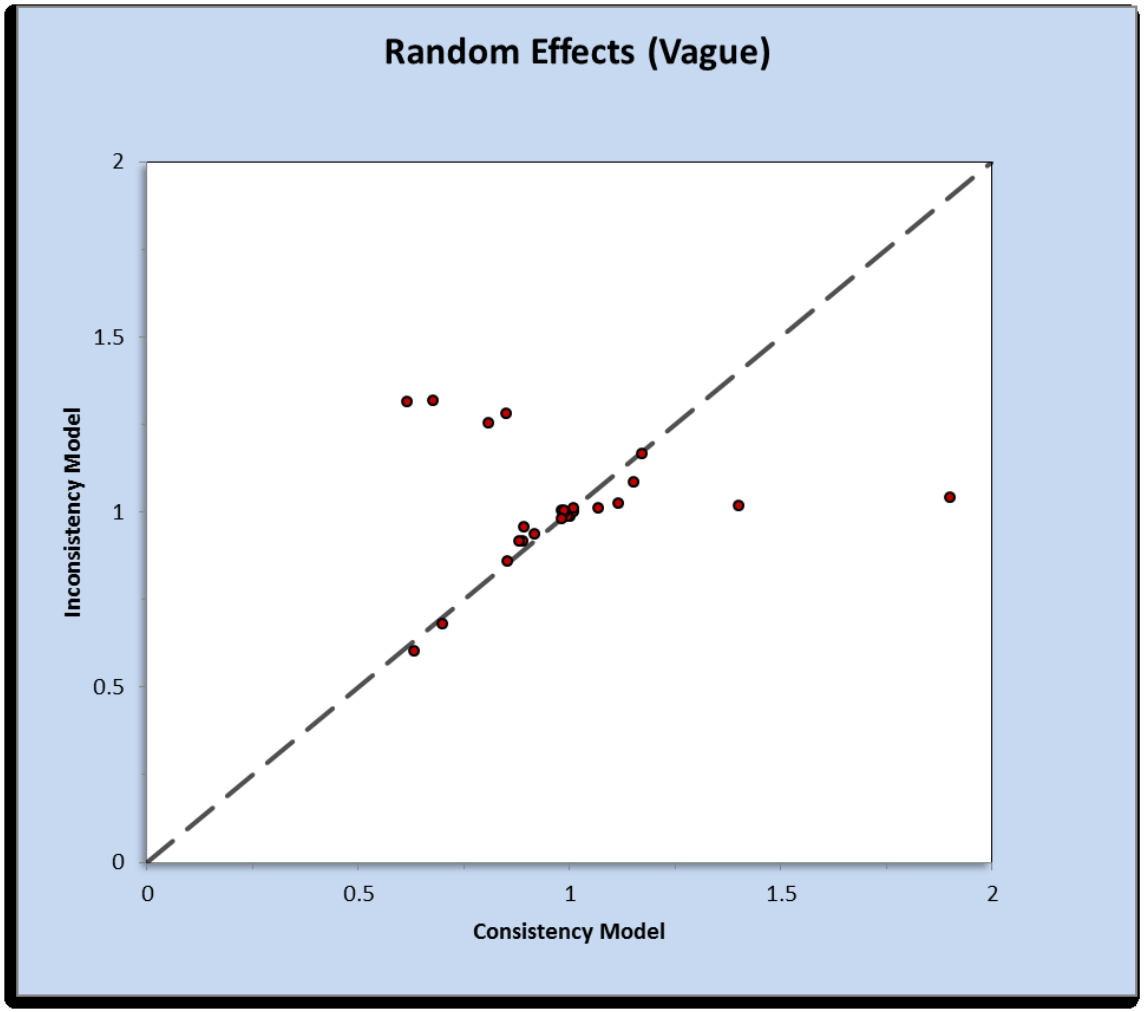
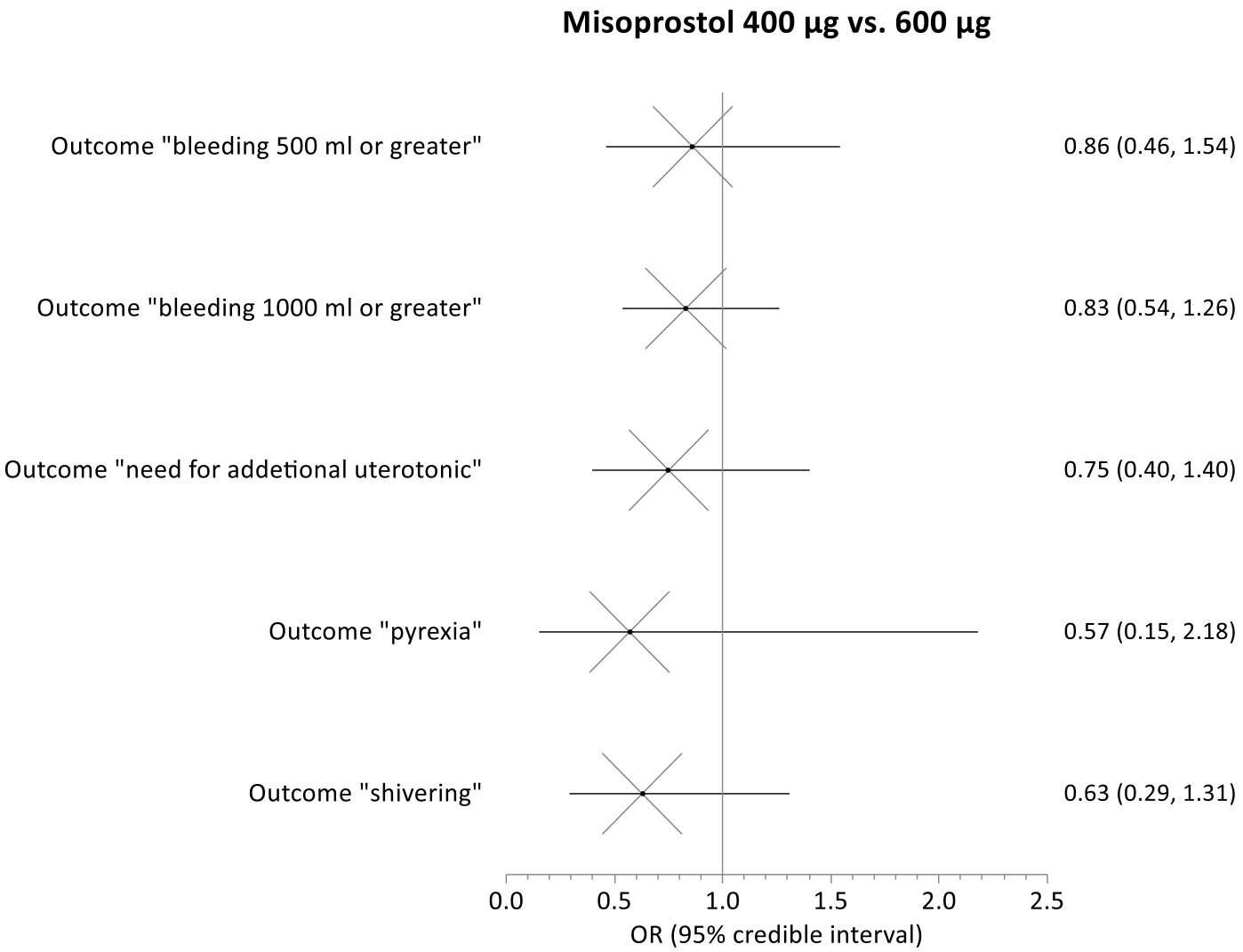


Figure 17: League table for the outcome “shivering”

15-methyl PGF2α 125 µg													
0.24 (0.00 – 4.55)	Oxytocin 5 IU												
0.10 (0.00 – 1.32)	0.42 (0.06 – 2.58)	Methylergometrine 0.2 mg											
0.09 (0.00 – 8.80)	0.35 (0.02 – 26.39)	0.85 (0.05 – 54.29)	Oxytocin 3 / 2.5 IU										
0.04 (0.00 – 0.51)	0.18 (0.03 – 0.75)	0.42 (0.11 – 1.41)	0.50 (0.01 – 6.70)	Oxytocin 10 IU									
0.03 (0.00 – 0.62)	0.12 (0.01 – 1.16)	0.29 (0.03 – 2.46)	0.33 (0.00 – 8.12)	0.70 (0.11 – 4.75)	Oxytocin/Syntometrine								
0.03 (0.00 – 0.41)	0.12 (0.02 – 0.65)	0.28 (0.05 – 1.23)	0.33 (0.01 – 5.15)	0.68 (0.22 – 2.01)	0.97 (0.12 – 7.79)	Ergometrine 2 mg							
0.03 (0.00 – 0.35)	0.11 (0.02 – 0.57)	0.28 (0.06 – 1.03)	0.32 (0.01 – 4.38)	0.66 (0.25 – 1.64)	0.95 (0.12 – 6.74)	0.98 (0.28 – 3.30)	Placebo / Control						
0.02 (0.00 – 0.36)	0.09 (0.01 – 0.62)	0.21 (0.03 – 1.17)	0.24 (0.00 – 4.33)	0.51 (0.11 – 2.09)	0.73 (0.07 – 6.99)	0.76 (0.14 – 3.85)	0.77 (0.18 – 3.34)	Syntometrine					
0.01 (0.00 – 0.22)	0.04 (0.00 – 0.42)	0.11 (0.01 – 0.91)	0.12 (0.00 – 2.97)	0.25 (0.04 – 1.74)	0.36 (0.03 – 4.58)	0.38 (0.04 – 3.22)	0.38 (0.05 – 2.97)	0.50 (0.05 – 5.35)	Ergometrine 0.5 mg				
0.01 (0.00 – 0.18)	0.04 (0.00 – 0.34)	0.10 (0.01 – 0.74)	0.11 (0.00 – 2.52)	0.23 (0.04 – 1.32)	0.33 (0.03 – 3.85)	0.35 (0.05 – 2.60)	0.35 (0.06 – 2.30)	0.46 (0.05 – 4.31)	0.92 (0.08 – 11.00)	Oxytocin 20 IU			
0.01 (0.00 – 0.11)	0.04 (0.01 – 0.16)	0.10 (0.03 – 0.30)	0.11 (0.00 – 1.49)	0.23 (0.13 – 0.41)	0.33 (0.05 – 1.92)	0.34 (0.11 – 1.06)	0.35 (0.14 – 0.90)	0.45 (0.11 – 2.05)	0.90 (0.14 – 5.75)	0.98 (0.19 – 4.92)	Misoprostol 400 µg		
0.01 (0.00 – 0.19)	0.03 (0.00 – 0.34)	0.08 (0.01 – 0.67)	0.09 (0.00 – 2.23)	0.20 (0.03 – 1.31)	0.28 (0.02 – 3.78)	0.30 (0.04 – 2.29)	0.30 (0.04 – 2.11)	0.39 (0.04 – 3.53)	0.79 (0.05 – 10.93)	0.86 (0.07 – 10.39)	0.88 (0.12 – 5.81)	ZB 11	
0.01 (0.00 – 0.07)	0.03 (0.00 – 0.11)	0.06 (0.02 – 0.19)	0.07 (0.00 – 0.92)	0.15 (0.07 – 0.29)	0.21 (0.03 – 1.41)	0.22 (0.07 – 0.60)	0.22 (0.11 – 0.46)	0.29 (0.08 – 1.05)	0.57 (0.08 – 4.07)	0.62 (0.10 – 3.56)	0.63 (0.29 – 1.31)	0.73 (0.12 – 4.31)	Misoprostol 600 µg

Figure 18: Forest plot of Misoprostol 400 µg vs. 600 µg



Appendix A:

Ovid search strategy

Search	Query
#1	Postpartum Hemorrhage/pc [Prevention & Control]
#2	Misoprostol/
#3	(prevent* adj2 postpartum adj2 hemorrhage).tw.
#4	(prevent* adj2 postpartum adj2 haemorrhage).tw.
#5	Misoprostol*.tw.
#6	1 or 3 or 4
#7	2 or 5
#8	6 and 7
#9	limit 8 to (english or french)

Appendix B:

Extraction sheets

Trials' characteristics:

Trial characteristics (reviewer 1)

Trial ID and Reference						**Trial design**								**Treament**				**Inclusion c**	**Exclusion criteria**	**Follow up**				**Mortality**
ID (included studies)	Trial Name or NCT Code or Author (Year)	Primary Author	Year	Title	Relationship with other primary publication	Observational vs experimental	Clinical vs Community settings	Randomisation (yes, no)	Double blind / open label	Year of Study Completion	Region	Multicentre (Y/N)	Method of blood estimation	Arm 1	Arm 2	Arm 3	Additional information about interventions			Estimate type	Dispersion type	Estimate duration (hours)	Dispersion duration (hours)	All Cause Mortality

Patients' characteristics:

Patient characteristics (reviewer 1)

Trial ID and References				**Treament**												**Populatio**	**Age**			
ID (included studies)	Primary Author	Year	Relationship with other primary publication	Intervention	Dosage	Route of administration	Self administration (yes/no)	Trained Birth Attendant (TBA) administration	Health-care facility settings (yes/no)	Community setting (yes/no)	Home birth (yes/no)	Cord traction (yes/no)	Uterine massage (yes/no)	Early cord clamping (yes/no)	Active management of labour (yes/no)	Total population at baseline (N)	Estimate type	Dispersion type	Estimat age (years)	Dispersion age (years)

Cont.

Labour																			
NO. of Caesarean Section (n)	Percentage of Caesarean Section (%)	NO. of emergency CS (n)	Percentage of emergency CS (%)	NO of elective CS (n)	Percentage of elective CS (%)	NO. of vaginal deliveries (n)	Percentage of vaginal delivered (%)	NO. of spontaneous vertex (n)	Percentage of spontaneous vertex (%)	NO. of spontaneous breech (n)	Percentage of spontaneous breech (%)	NO. of preterm deliveries (n)	Percentage of preterm deliveries (%)	NO. of induced labour (n)	Percentage of induced labour (%)	Type of induction	Dose of induction drug	No. of augmented labour	Percentage of augmented labour (%)

Cont.

Type of augmentation	Dose of augmentation drug	NO. of patients with episiotomy (n)	Percentage of patients with episiotomy (%)	NO. of patients with perineal/ vaginal/cervical	Percentage of patients with perineal/ vaginal/c	NO. of instrumental deliveries (n)	Percentage of instrumental deliveries (%)	NO. of forceps deliveries (n)	Percentage of forceps deliveries (%)	NO. of suction (vacuum) deliveries (n)	Percentage of suction (vacuum) deliveries (%)	NO. of intact membrane (n)	Percentage of intact membrane (%)	NO. of ruptured membrane (n)	Percentage of ruptured membrane (%)	NO. of patients receiving Oxytocin or prostagla	Percentage of patients receiving Oxytocin or

Cont.

Obstetrical characteristics																			
NO. of PrimiGravida (n)	Percentage of PrimiGravida (%)	NO. of MultiGravida (n)	Percentage of MultiGravida (%)	NO. of GrandMultiGravida (n)	Percentage of GrandMultiGravida (%)	Mean Parity	SD Parity	NO. of Nulliparous (n)	Percentage of Nulliparous (%)	NO. of MultiParous (n)	Percentage of MultiParous (%)	NO. of GrandMultiParous (n)	Percentage of GrandMultiParous (%)	Mean weight (Kg)	Median weight (Kg)	SD weight	95%CI weight	Mean BMI (kg/m^2)	Median BMI (kg/m^2)

Cont.

						Obstetrical history									
SD BMI	95%CI BMI	Mean period of gestation (weeks)	Median period of gestation (weeks)	SD period of gestation	95%CI period of gestation	No AnteNatal Visits (n)	No AnteNatal visits (%)	1 or more AnteNatal Visits (n)	1 or more Antenatal visits (%)	Mean number of antenatil visits	SD of antenatal visits	Previous PPH (n)	Previous PPH (%)	Patients with previous CS (n)	Patients with previous CS (%)	Median number of previous CS	Range of number of previous CS

Outcomes:

Outcomes (reviewer 1)

Trial ID and References				Treament				Efficacy									
ID (included studies)	Primary Author	Year	Relationship with other primary publication	Type of uterotonic	Reprted treated population	Route	Dosage	Mean blood loss (ml)	Avarage blood loss (ml)	Median blood loss (ml)	SD blood loss	95%CI blood loss	Blood loss ≥500 ml (n)	Blood loss ≥500 ml (%)	Blood loss ≥1000 ml (n)	Blood loss ≥1000 ml (%)

Cont.

Additional uterotonics needed (n)	Additional uterotonics needed (%)	Blood transfusion required (n)	Blood transfusion required (%)	Refferal (n)	Refferal (%)	**Safety** Safety population (n)	Death (n)	Death (%)	Pyrexia (38 > C < 40 OR not otherwise specified)	Pyrexia (38 > C < 40) (%)	Severe Pyrexia (≥ 40) (n)	Severe Pyrexia (≥ 40) (%)	Shivering (n)	Shivering (%)	Diarrhea (n)	Diarrhea (%)	Headache (n)	Headache (%)

Appendix C

Winbugs generated code for the random effect model

```
model     # this code for this model was adapted from WinBUGS code from the multi-parameter Evidence Synthesis Research Group at the University of Bristol:  Website: www.bris.ac.uk/cobm/research/mpes

{
 for(i in 1:NS)
 {
       w[i,1] <-0   # adjustment for multi-arm trials is zero for control arm
        delta[i,1]<-0   # treatment effect is zero for control arm
        mu[i] ~ dnorm(0,.0001)                                          # vague priors for all trial baselines
        for (k in 1:na[i])          # LOOP THROUGH ARMS
   {
         r[i,k] ~ dbin(p[i,k],n[i,k])       # binomial likelihood
            logit(p[i,k]) <- mu[i] + delta[i,k]        # model for linear predictor
           rhat[i,k] <- p[i,k] * n[i,k]        # expected value of the numerators
         #Deviance contribution
   dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))   +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
   resdev[i] <- sum(dev[i,1:na[i]])      #  summed residual deviance contribution for this trial
   for (k in 2:na[i])        # LOOP THROUGH ARMS
   {
```

```
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])       # trial-specific LOR distributions
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]       # mean of LOR distributions (with multi-arm trial correction)
         taud[i,k] <- tau *2*(k-1)/k       # precision of LOR distributions (with multi-arm trial correction)
          w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])       # adjustment for multi-arm RCTs
           sw[i,k] <- sum(w[i,1:k-1])/(k-1)       # cumulative adjustment for multi-arm trials
  }
}
totresdev <- sum(resdev[])     # Total Residual Deviance

d[1]<-0
for (k in 2:NT)
{
  d[k] ~ dnorm(0,.0001) #  vague priors for basic parameters
}
sd~dunif(0,2)               #  vague prior for random effects standard deviation
tau<-1/pow(sd,2)            #  vague prior for random effects standard deviation
          # Informative log-normal prior  for heterogeneity variance parameter tau - Turner 2012
          # Informative log-normal prior  for heterogeneity variance parameter tau - Turner 2012
          # Informative log-normal prior  for heterogeneity variance parameter tau - Turner 2012
```

```
# Treatment 1 baseline, based on average of NP trials including it.


# ranking
for (k in 1:NT)
{
      # events good
  rk[k]<- rank(d[],k)     # events bad
  best[k]<-equals(rk[k],1)
  for (h in 1:NT)
  {
    prob[k,h]<-equals(rk[k],h)
  }
}
for (k in 1:NT)
{
  for (h in 1:NT)
  {
    cumeffectiveness[k,h]<-sum(prob[k,1:h])   # The cumulative ranking probability of treatment i to be among the j best treatments.
  }
}
for(i in 1:NT)
```

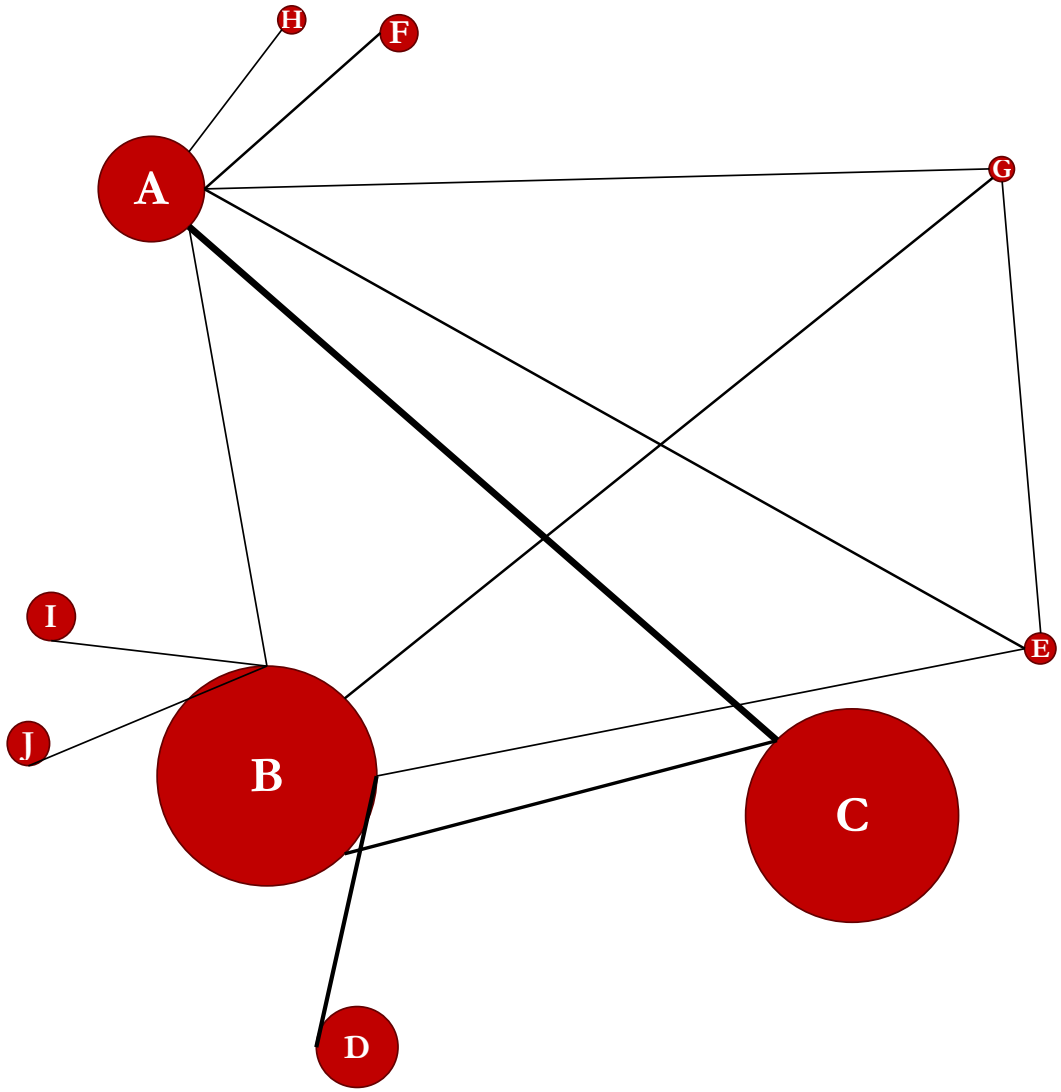
```
 {
        SUCRA[i]<-sum(cumeffectiveness[i,1:(NT-1)])/(NT-1) # The surface under the cumulative rankings for treatment i.
 }
 # pairwise ORs
 for (c in 1:(NT-1))
 {
  for (k in (c+1):NT)
  {
    OR[c,k] <- exp(d[k] - d[c] )
    lOR[c,k]<-d[k]-d[c]
  }
 }

} #END Program
```

Appendix D: **Network diagrams, inconsistency, and league tables for subgroup analysis for the outcome of bleeding 500 ml or greater.**

1.0 Blinded trials:

1.1 Network diagram:

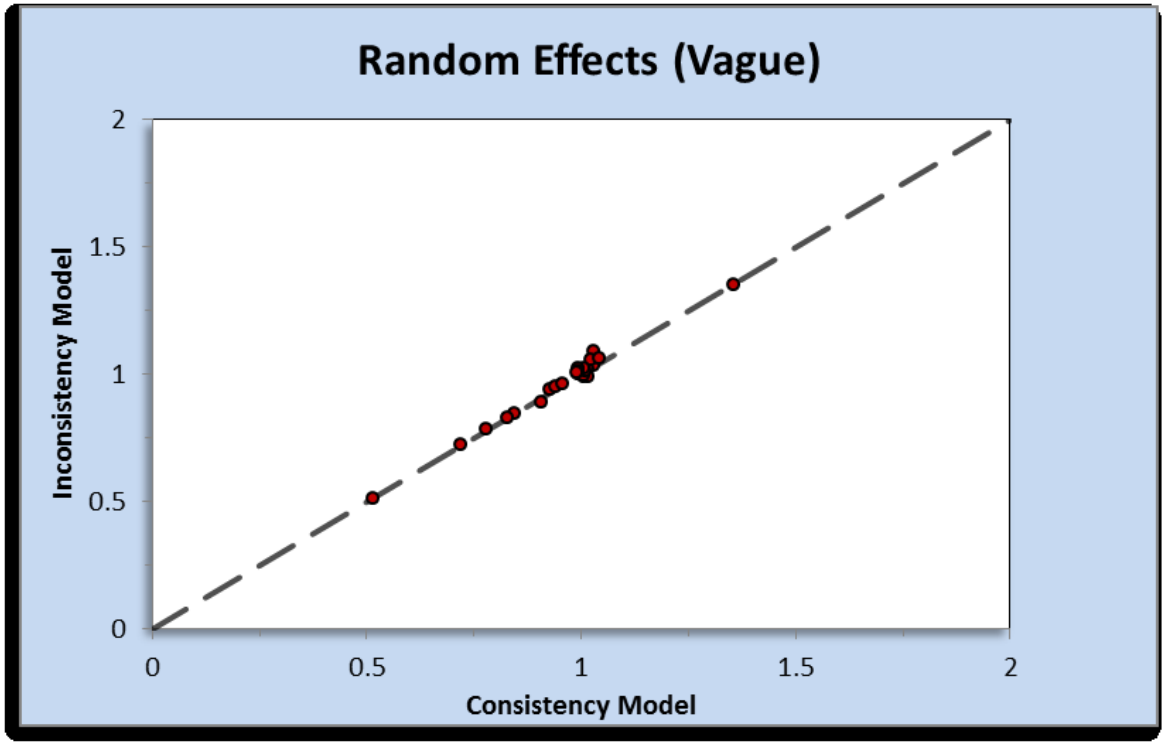
Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Placebo	D
Oxytocin 5 IU	E
Oxytocin 20 IU	F
Methylergometrin 0.2 mg	G
Oxytocin 3 IU	H
Ergometrin 2.0 mg	I
ZB11	J
	K
	L
	M
	N
	O



Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

1.2 Inconsistency results:



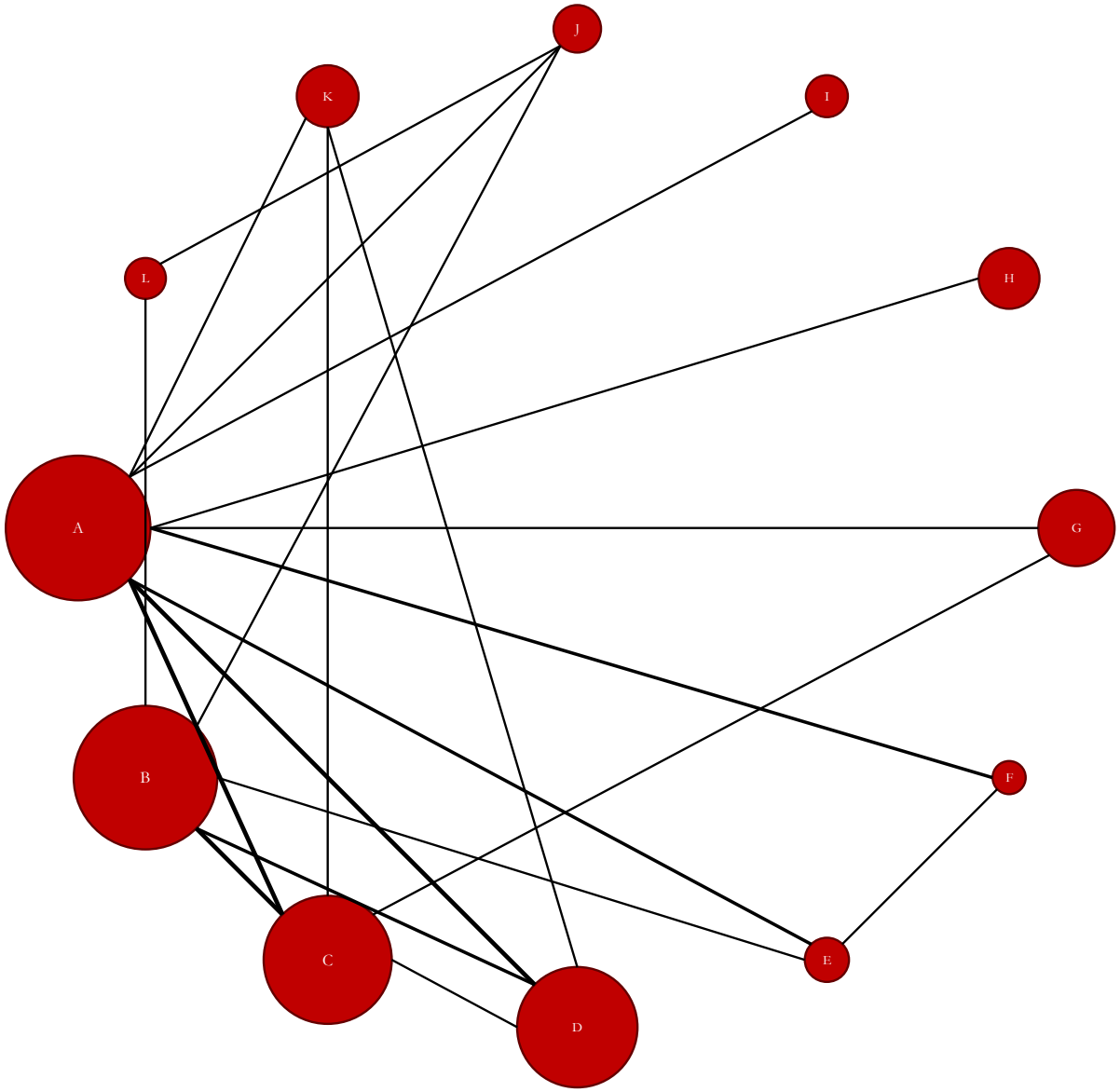
1.3 League table:

Oxytocin 5 IU									
0.46 (0.13 – 1.60)	**Misoprostol 400 µg**								
0.48 (0.10 – 2.35)	1.04 (0.36 – 2.89)	**Oxytocin 20 IU**							
0.42 (0.11 – 1.53)	0.91 (0.53 – 1.40)	0.89 (0.26 – 2.63)	**Oxytocin 10 IU**						
0.46 (0.04 – 3.84)	0.97 (0.14 – 5.68)	0.94 (0.10 – 7.21)	1.06 (0.17 – 6.11)	**Methylergometrin 0.2 mg**					
0.24 (0.04 – 1.04)	0.54 (0.15 – 1.20)	0.52 (0.10 – 1.77)	0.59 (0.21 – 1.20)	0.54 (0.10 – 2.63)	**Misoprostol 600 µg**				
0.23 (0.05 – 1.21)	0.51 (0.18 – 1.49)	0.49 (0.11 – 2.22)	0.55 (0.19 – 1.92)	0.52 (0.07 – 5.21)	0.93 (0.27 – 5.34)	**Oxytocin 3 IU**			
0.22 (0.03 – 1.20)	0.49 (0.09 – 1.63)	0.47 (0.07 – 2.19)	0.53 (0.12 – 1.72)	0.49 (0.07 – 3.15)	0.90 (0.33 – 2.50)	0.97 (0.12 – 4.55)	**Ergometrin 2.0 mg**		
0.16 (0.02 – 0.89)	0.36 (0.07 – 1.21)	0.35 (0.05 – 1.62)	0.40 (0.09 – 1.27)	0.36 (0.05 – 2.33)	0.67 (0.24 – 1.81)	0.73 (0.09 – 3.36)	0.74 (0.18 – 3.08)	**ZB11**	
0.16 (0.02 – 0.72)	0.35 (0.08 – 0.87)	0.33 (0.05 – 1.23)	0.38 (0.11 – 0.89)	0.35 (0.06 – 1.81)	0.64 (0.36 – 1.07)	0.69 (0.10 – 2.56)	0.71 (0.22 – 2.18)	0.96 (0.29 – 3.01)	**Placebo**

2.0 Open label trials:

2.1 Network diagram:

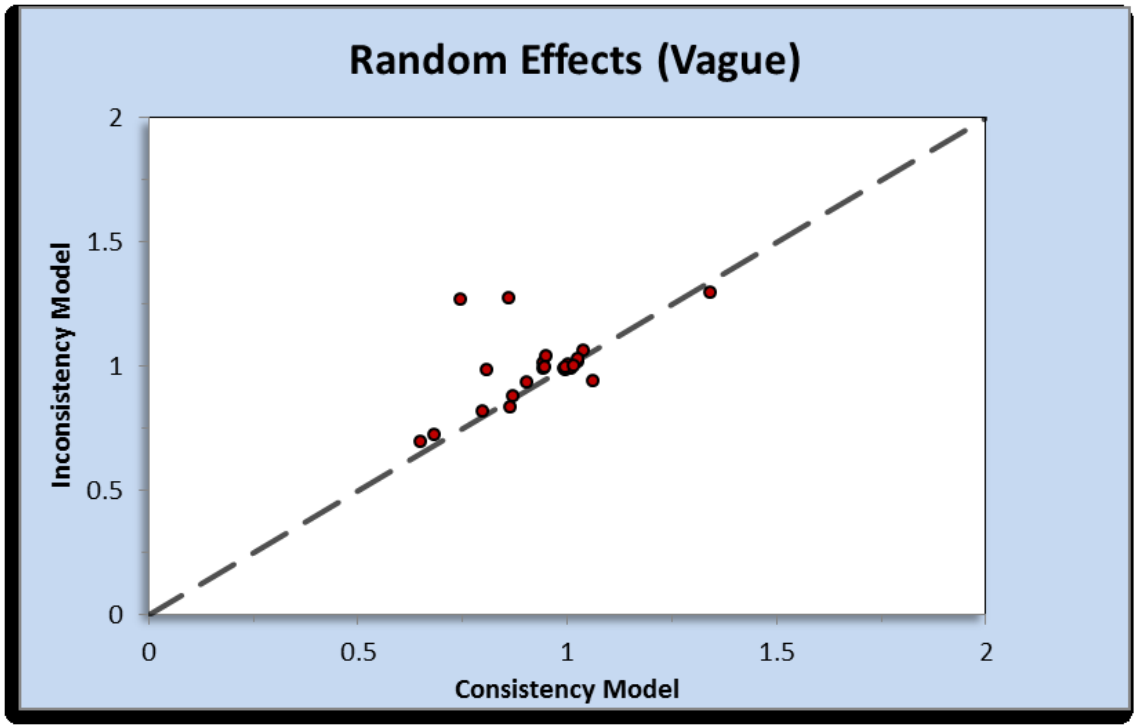
Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Syntometrine	D
Methylergometrine 0.2 mg	E
15-methyl PGF2α 125 µg	F
Ergometrine 2 mg	G
Ergometrine 0.5 mg	H
Oxytocin 5 IU	I
Control	J
Oxytocin/Syntometrine	K
Oxytocin 2.5 IU	L
	M
	N
	O



Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

2.2 Inconsistency results

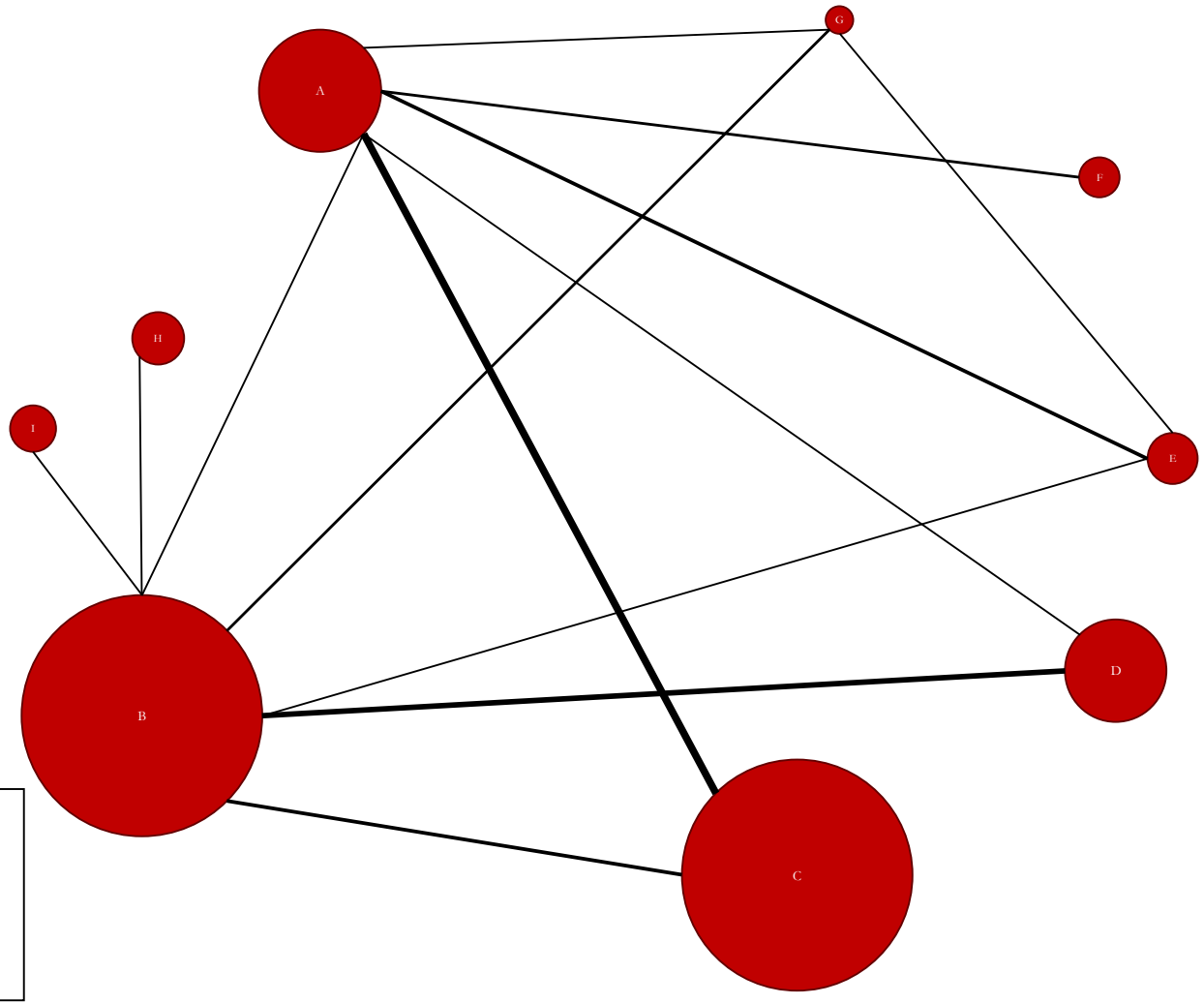


2.3 League table:

Oxytocin 10 IU											
1.04 (0.08 – 10.70)	**Control**										
1.05 (0.07 – 13.33)	1.01 (0.10 – 10.99)	**Oxytocin 2.5 IU**									
0.85 (0.13 – 6.25)	0.82 (0.06 – 14.65)	0.80 (0.05 – 17.30)	**Methylergometrine 0.2 mg**								
0.81 (0.08 – 5.87)	0.78 (0.04 – 14.14)	0.76 (0.03 – 16.91)	0.95 (0.06 – 9.96)	**Oxytocin/Syntometrine**							
0.76 (0.19 – 2.61)	0.73 (0.09 – 6.58)	0.73 (0.07 – 7.33)	0.89 (0.13 – 4.88)	0.95 (0.11 – 9.91)	**Misoprostol 600 µg**						
0.72 (0.14 – 2.95)	0.68 (0.06 – 8.23)	0.68 (0.05 – 9.20)	0.83 (0.10 – 5.20)	0.88 (0.12 – 7.63)	0.94 (0.22 – 3.62)	**Syntometrine**					
0.63 (0.04 – 9.89)	0.61 (0.02 – 19.83)	0.60 (0.02 – 23.00)	0.74 (0.03 – 13.28)	0.79 (0.04 – 21.46)	0.82 (0.05 – 14.68)	0.89 (0.06 – 15.84)	**Oxytocin 5 IU**				
0.54 (0.06 – 4.48)	0.52 (0.03 – 12.20)	0.51 (0.02 – 13.40)	0.64 (0.04 – 7.83)	0.66 (0.05 – 13.56)	0.71 (0.07 – 7.88)	0.75 (0.07 – 9.06)	0.85 (0.03 – 22.17)	**Ergometrine 2 mg**			
0.53 (0.06 – 4.71)	0.51 (0.03 – 10.83)	0.51 (0.03 – 12.24)	0.63 (0.08 – 4.42)	0.66 (0.06 – 11.70)	0.70 (0.09 – 6.66)	0.75 (0.10 – 7.40)	0.85 (0.04 – 18.46)	1.00 (0.07 – 15.65)	**15-methyl PGF2α 125 µg**		
0.50 (0.12 – 1.88)	0.48 (0.04 – 5.74)	0.48 (0.03 – 7.04)	0.59 (0.10 – 2.81)	0.62 (0.09 – 5.51)	0.66 (0.15 – 2.89)	0.70 (0.19 – 3.00)	0.80 (0.07 – 9.13)	0.93 (0.11 – 7.76)	0.94 (0.16 – 5.05)	**Misoprostol 400 µg**	
0.06 (0.00 – 0.95)	0.06 (0.00 – 1.99)	0.06 (0.00 – 2.18)	0.07 (0.00 – 1.19)	0.08 (0.00 – 2.12)	0.08 (0.00 – 1.39)	0.08 (0.01 – 1.47)	0.10 (0.00 – 3.12)	0.11 (0.00 – 2.91)	0.11 (0.01 – 2.11)	0.12 (0.01 – 1.36)	**Ergometrine 0.5 mg**

Appendix E: **Network diagrams, inconsistency, and league tables for subgroup analysis for the outcome "bleeding 1000 ml or greater"**.1.0

Blinded trials:1.1 Network diagram:

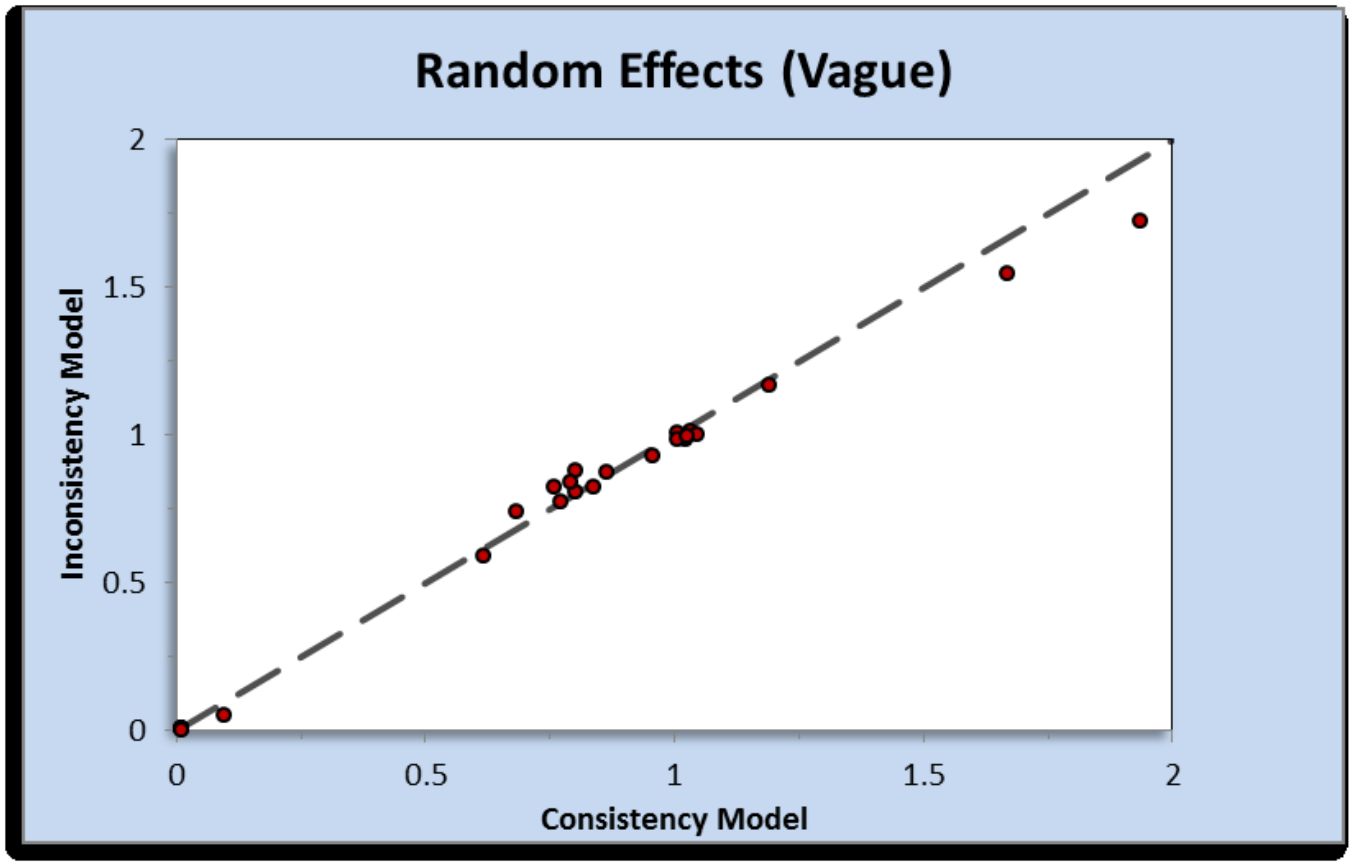


Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Placebo	D
Oxytocin 5 IU	E
Oxytocin 20 IU	F
Methylergometrin 0.2 mg	G
Ergometrin 2.0 mg	H
ZB11	I
	J
	K

Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

1.2 Inconsistency results:



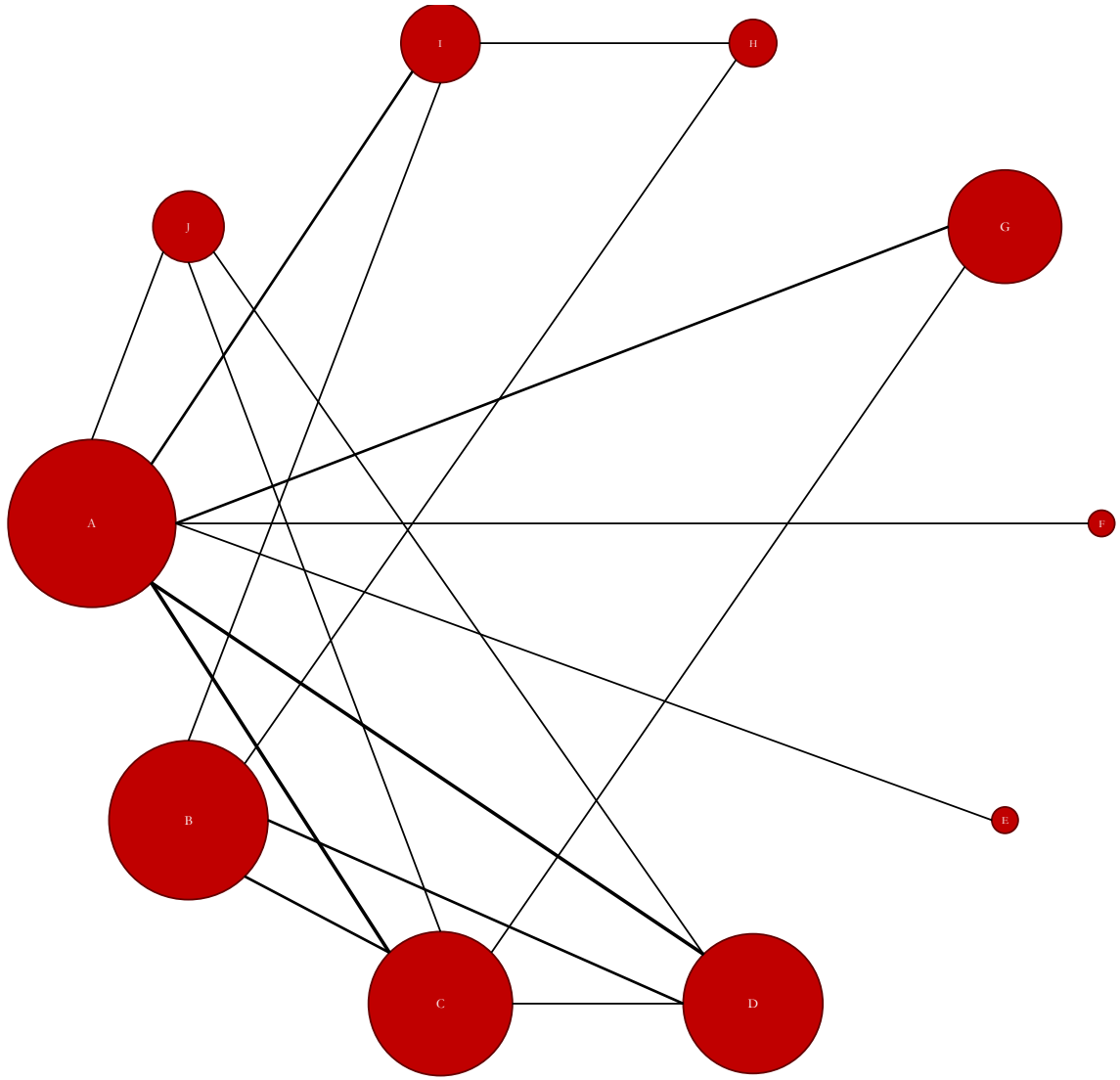
1.3 League table:

Methylergometrin 0.2 mg								
0.00 (0.00 – 3.51)	**Oxytocin 5 IU**							
0.00 (0.00 – 1.70)	0.53 (0.17 – 1.54)	**Oxytocin 10 IU**						
0.00 (0.00 – 1.44)	0.51 (0.13 – 2.05)	0.98 (0.35 – 2.75)	**Oxytocin 20 IU**					
0.00 (0.00 – 1.42)	0.46 (0.16 – 1.25)	0.88 (0.59 – 1.38)	0.89 (0.36 – 2.31)	**Misoprostol 400 µg**				
0.00 (0.00 – 1.24)	0.38 (0.12 – 1.27)	0.72 (0.46 – 1.30)	0.74 (0.26 – 2.34)	0.83 (0.48 – 1.55)	**Misoprostol 600 µg**			
0.00 (0.00 – 0.89)	0.25 (0.05 – 1.17)	0.47 (0.16 – 1.41)	0.48 (0.11 – 2.27)	0.54 (0.17 – 1.71)	0.64 (0.23 – 1.70)	**ZB11**		
0.00 (0.00 – 0.80)	0.25 (0.07 – 0.78)	0.48 (0.26 – 0.84)	0.48 (0.16 – 1.49)	0.54 (0.28 – 0.98)	0.65 (0.42 – 0.95)	1.02 (0.35 – 2.85)	**Placebo**	
0.00 (0.00 – 0.82)	0.15 (0.01 – 1.38)	0.30 (0.04 – 2.07)	0.29 (0.03 – 2.62)	0.33 (0.04 – 2.43)	0.41 (0.05 – 2.57)	0.63 (0.07 – 5.09)	0.63 (0.07 – 4.19)	**Ergometrin 2.0 mg**

2.0 Open label trials:

2.1 Network diagram:

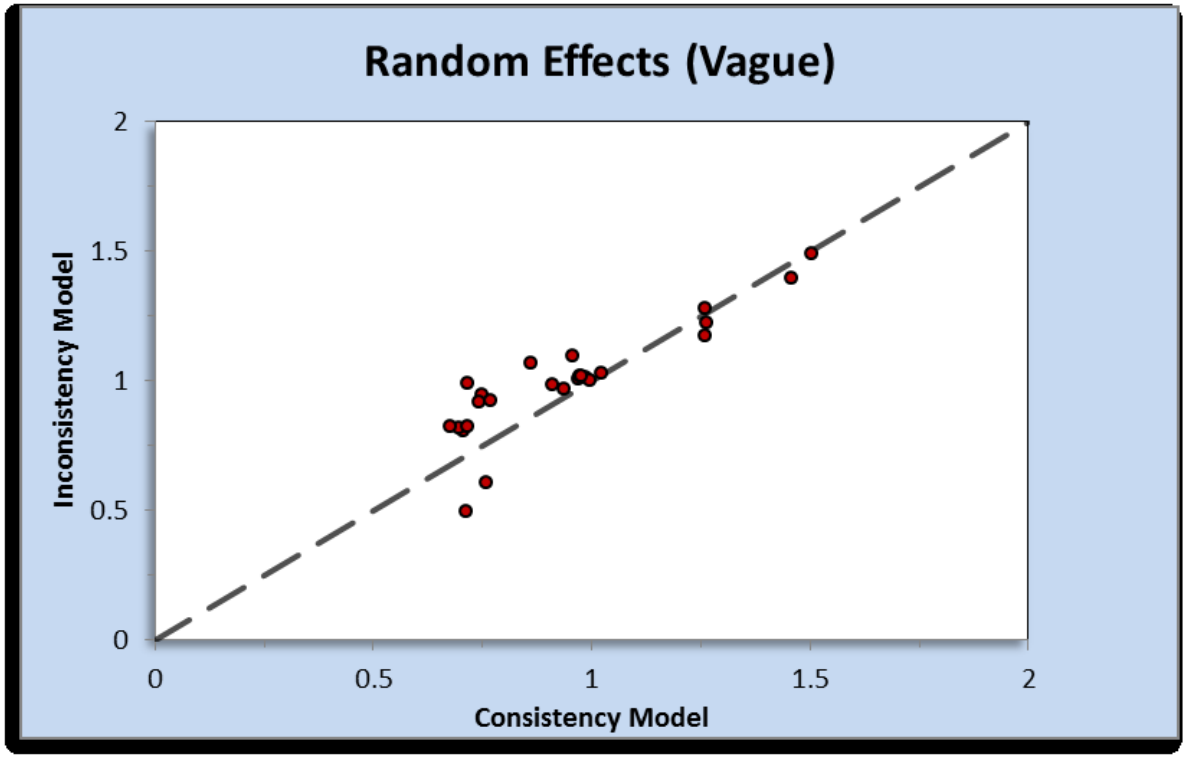
Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Syntometrine	D
Methylergometrine 0.2 mg	E
15-methyl PGF2α 125 µg	F
Ergometrine 2 mg	G
Oxytocin 2.5 IU	H
Control	I
Oxytocin/Syntometrine	J
	K
	L
	M
	N
	O



Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

2.2 Inconsistency results



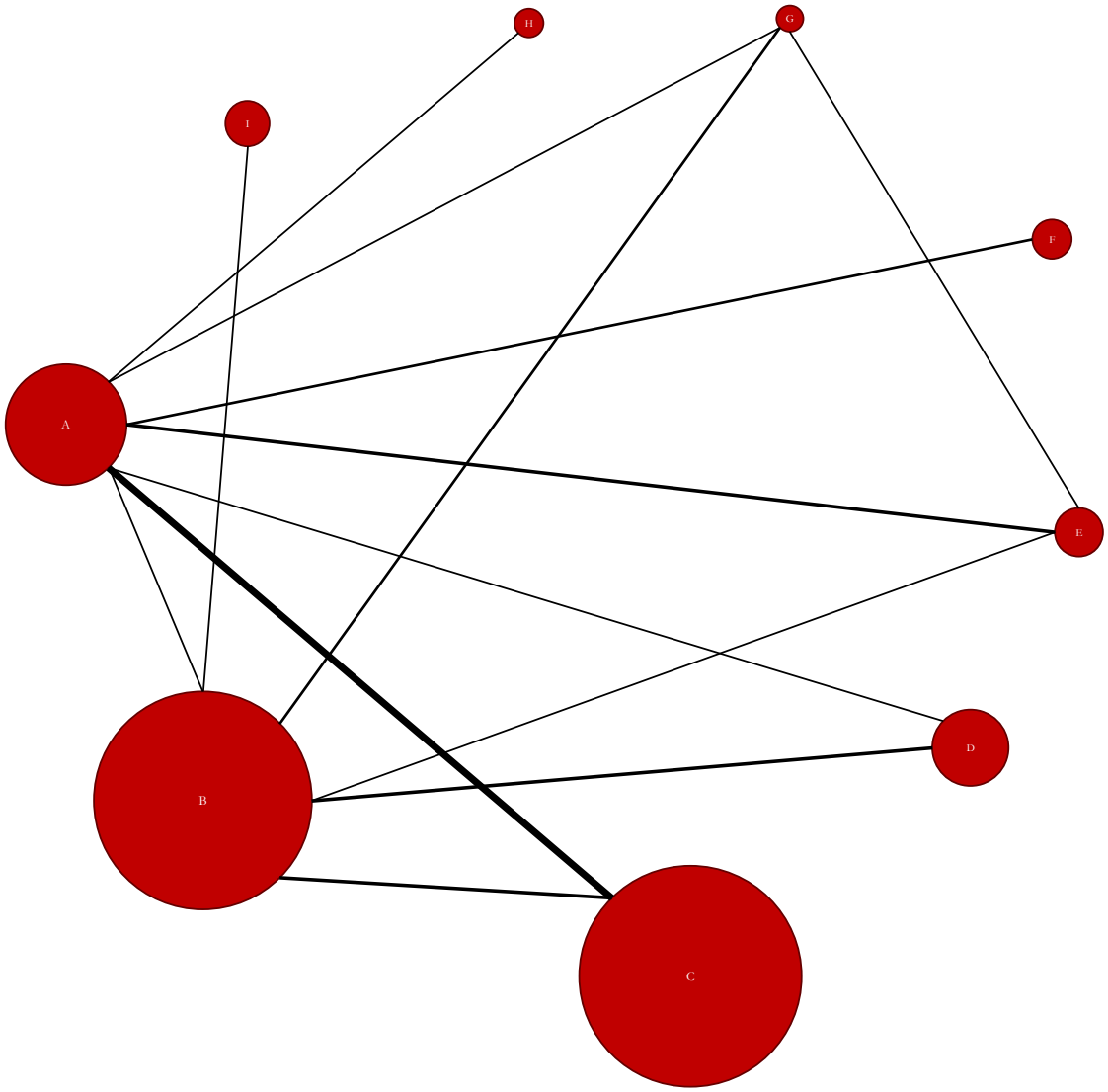
2.3 League table:

Oxytocin 10 IU									
0.89 (0.05 – 8.62)	**Oxytocin/Syntometrine**								
0.79 (0.13 – 4.46)	0.88 (0.12 – 11.03)	**Misoprostol 400 µg**							
0.92 (0.00 – 655.74)	1.09 (0.00 – 954.20)	1.18 (0.00 – 695.41)	**Methylergometrine 0.2 mg**						
0.78 (0.00 – 751.31)	0.93 (0.00 – 1144.00)	0.99 (0.00 – 793.65)	0.84 (0.00 – 8250.83)	**15-methyl PGF2α 125 µg**					
0.60 (0.06 – 4.21)	0.68 (0.07 – 7.46)	0.76 (0.11 – 3.62)	0.63 (0.00 – 459.50)	0.74 (0.00 – 641.00)	**Syntometrine**				
0.58 (0.03 – 9.23)	0.63 (0.03 – 19.35)	0.73 (0.04 – 8.93)	0.61 (0.00 – 633.31)	0.69 (0.00 – 749.63)	0.92 (0.06 – 15.58)	**Oxytocin 2.5 IU**			
0.59 (0.05 – 5.54)	0.64 (0.05 – 12.75)	0.74 (0.11 – 4.35)	0.63 (0.00 – 487.57)	0.74 (0.00 – 656.60)	0.95 (0.12 – 9.78)	1.01 (0.11 – 11.15)	**Control**		
0.37 (0.04 – 3.64)	0.42 (0.03 – 11.78)	0.48 (0.05 – 4.37)	0.42 (0.00 – 380.52)	0.48 (0.00 – 518.40)	0.63 (0.05 – 11.15)	0.66 (0.02 – 22.83)	0.65 (0.04 – 11.69)	**Ergometrine 2 mg**	
0.39 (0.04 – 2.94)	0.45 (0.03 – 7.56)	0.50 (0.06 – 3.11)	0.42 (0.00 – 316.60)	0.48 (0.00 – 459.20)	0.65 (0.11 – 4.39)	0.69 (0.07 – 6.82)	0.68 (0.09 – 4.20)	1.03 (0.05 – 16.04)	**Misoprostol 600 µg**

Appendix F: **Subgroup analysis for the outcome "Need for additional uterotonics"**1.0 Blinded trials

1.1. Network diagram

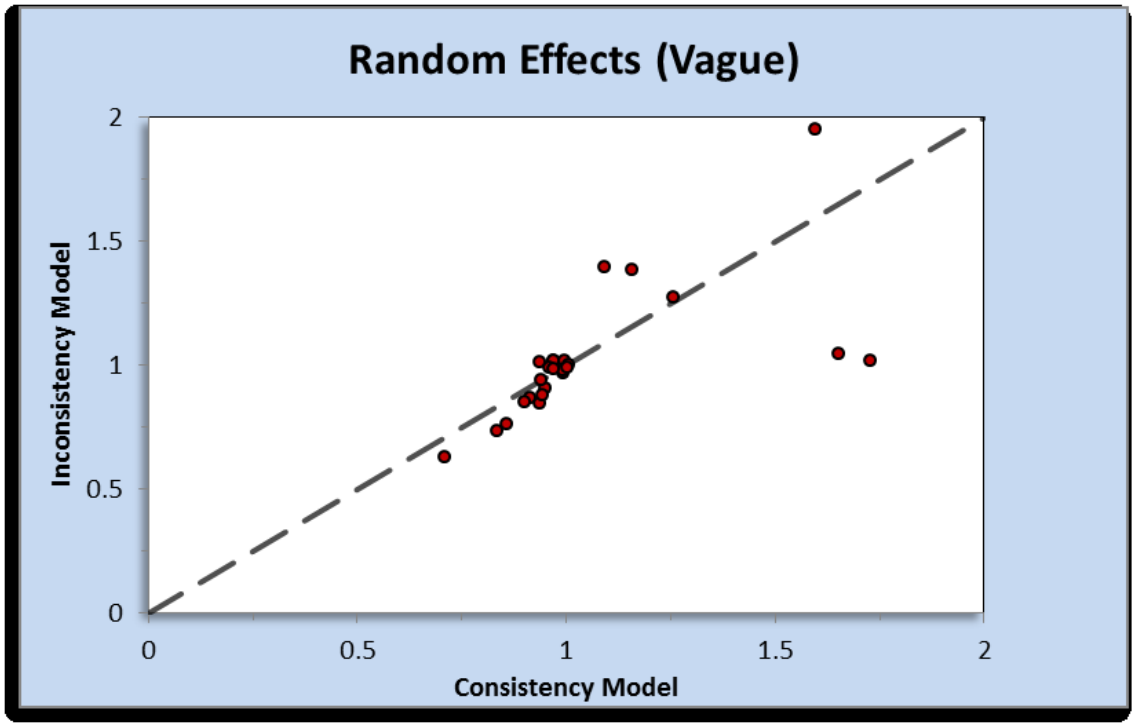
Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Placebo	D
Oxytocin 5 IU	E
Oxytocin 20 IU	F
Methylergometrin 0.2 mg	G
Oxytocin 3 IU	H
ZB11	I
	J
	K
	L
	M
	N
	O



1.2 Inconsistency results

Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons



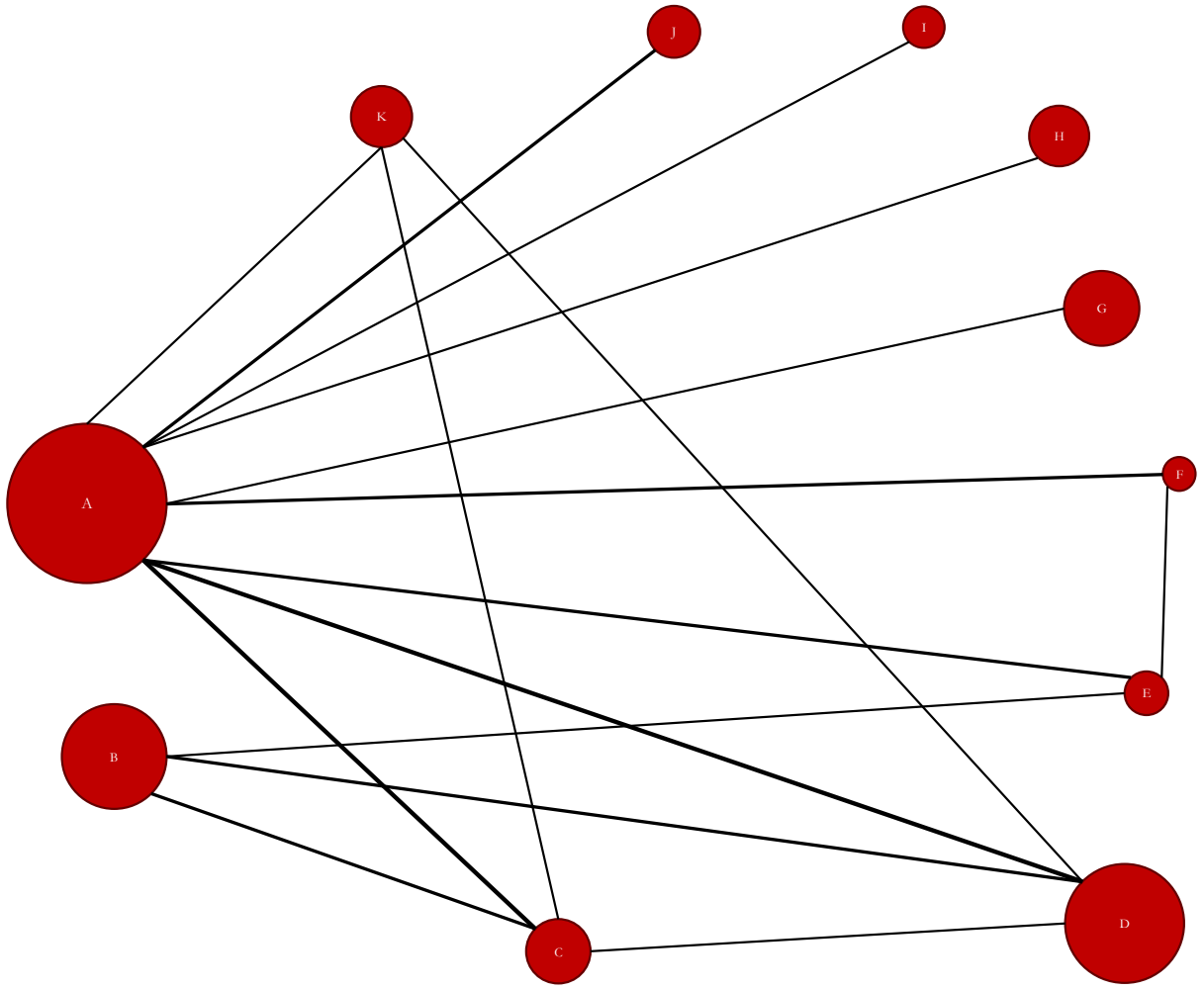
1.3 League table

Oxytocin 5 IU								
0.63 (0.23 – 1.84)	**Misoprostol 400 µg**							
0.65 (0.13 – 3.26)	1.03 (0.29 – 3.42)	**Oxytocin 20 IU**						
0.61 (0.19 – 2.06)	0.97 (0.50 – 1.83)	0.93 (0.23 – 3.87)	**Oxytocin 10 IU**					
0.43 (0.12 – 1.66)	0.68 (0.26 – 1.74)	0.66 (0.14 – 3.16)	0.71 (0.30 – 1.71)	**Misoprostol 600 µg**				
0.33 (0.04 – 3.03)	0.53 (0.08 – 3.66)	0.51 (0.05 – 5.34)	0.55 (0.08 – 3.66)	0.78 (0.15 – 4.13)	**ZB11**			
0.30 (0.04 – 2.23)	0.48 (0.09 – 2.54)	0.46 (0.06 – 3.89)	0.50 (0.08 – 2.95)	0.71 (0.10 – 4.72)	0.91 (0.07 – 11.35)	**Oxytocin 3 IU**		
0.25 (0.05 – 1.20)	0.40 (0.09 – 1.56)	0.39 (0.06 – 2.50)	0.41 (0.09 – 1.67)	0.58 (0.14 – 2.11)	0.75 (0.08 – 5.81)	0.82 (0.09 – 7.04)	**Methylergometrin 0.2 mg**	
0.26 (0.06 – 1.13)	0.41 (0.13 – 1.22)	0.40 (0.07 – 2.11)	0.43 (0.13 – 1.29)	0.60 (0.22 – 1.52)	0.77 (0.11 – 5.10)	0.85 (0.11 – 6.21)	1.04 (0.22 – 5.12)	**Placebo**

2.0 Open-label trials

2.1 Network diagram

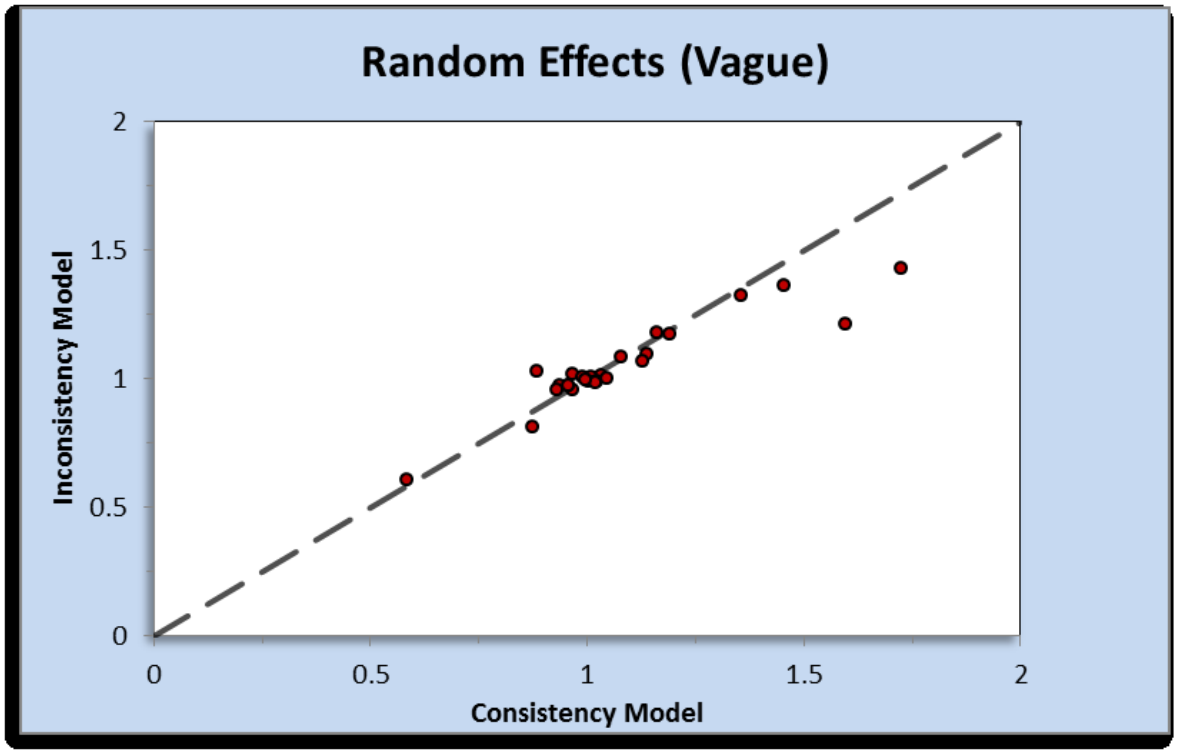
Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Syntometrine	D
Methylergometrine 0.2 mg	E
15-methyl PGF2α 125 µg	F
Ergometrine 2 mg	G
Ergometrine 0.5 mg	H
Oxytocin 5 IU	I
Control	J
Oxytocin/Syntometrine	K
	L
	M
	N
	O



Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

2.2 Inconsistency results



2.3 League table

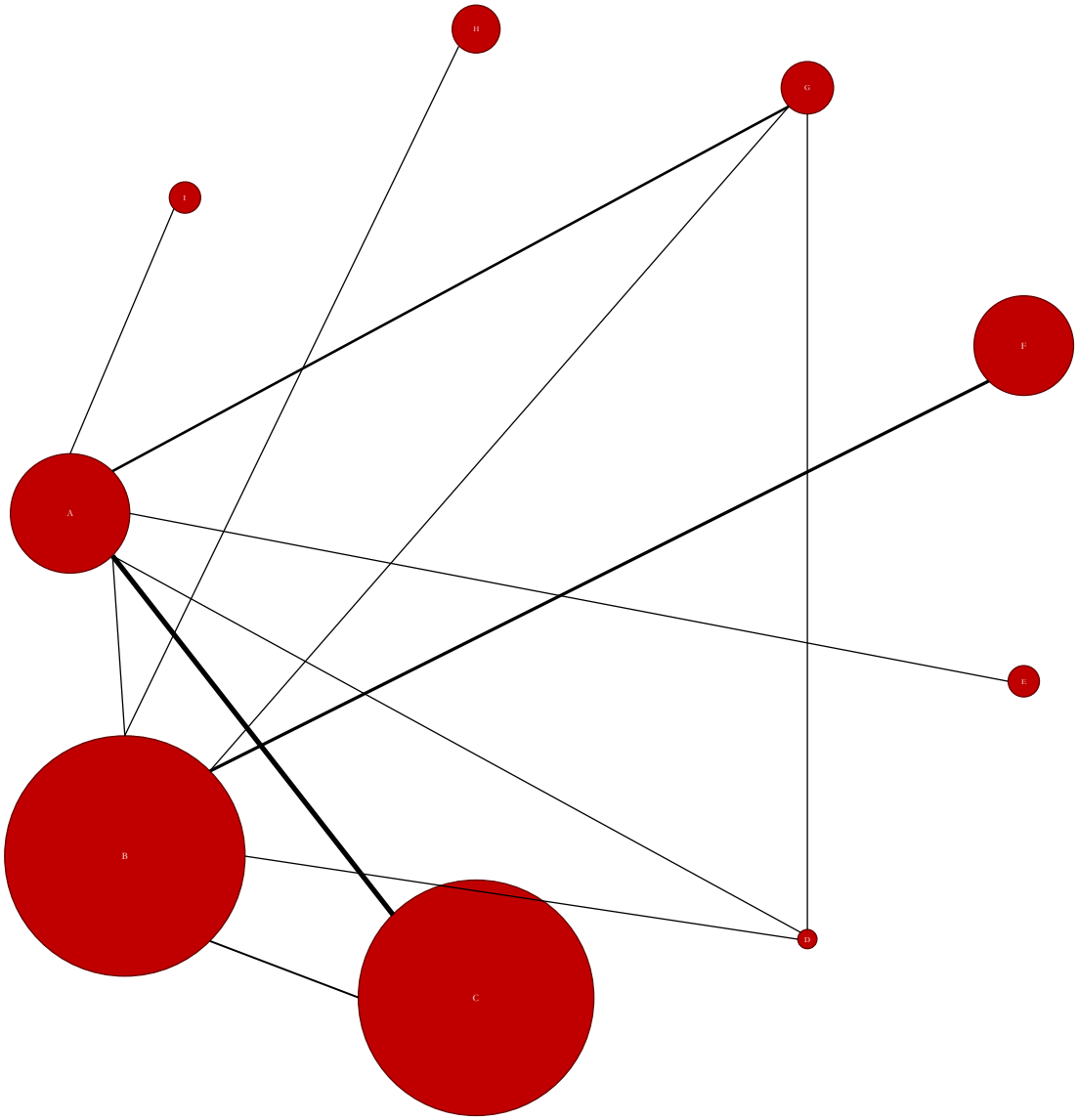
Oxytocin/Syntometrine										
0.97 (0.19 – 6.54)	**15-methyl PGF2α 125 µg**									
0.85 (0.23 – 3.46)	0.88 (0.19 – 3.48)	**Oxytocin 10 IU**								
0.83 (0.24 – 3.58)	0.86 (0.19 – 3.60)	0.97 (0.38 – 2.83)	**Syntometrine**							
0.47 (0.08 – 3.75)	0.49 (0.07 – 3.09)	0.55 (0.11 – 3.28)	0.57 (0.11 – 3.15)	**Ergometrine 2 mg**						
0.49 (0.10 – 2.71)	0.50 (0.12 – 1.90)	0.56 (0.17 – 2.07)	0.58 (0.16 – 2.11)	1.01 (0.17 – 6.13)	**Methylergometrine 0.2 mg**					
0.41 (0.12 – 1.68)	0.42 (0.12 – 1.38)	0.48 (0.21 – 1.20)	0.49 (0.20 – 1.20)	0.86 (0.20 – 3.68)	0.84 (0.29 – 2.44)	**Misoprostol 400 µg**				
0.39 (0.09 – 1.68)	0.40 (0.08 – 1.59)	0.46 (0.17 – 1.13)	0.48 (0.16 – 1.12)	0.83 (0.12 – 4.24)	0.81 (0.21 – 2.44)	0.96 (0.31 – 2.37)	**Misoprostol 600 µg**			
0.18 (0.03 – 1.17)	0.19 (0.03 – 1.03)	0.22 (0.05 – 1.01)	0.22 (0.04 – 1.01)	0.39 (0.05 – 2.43)	0.38 (0.07 – 1.87)	0.46 (0.12 – 1.52)	0.47 (0.10 – 2.55)	**Control**		
0.15 (0.02 – 1.17)	0.15 (0.02 – 1.00)	0.17 (0.03 – 1.02)	0.17 (0.03 – 0.96)	0.31 (0.04 – 2.42)	0.30 (0.05 – 1.86)	0.36 (0.08 – 1.59)	0.37 (0.07 – 2.57)	0.79 (0.12 – 6.08)	**Ergometrine 0.5 mg**	
0.12 (0.02 – 1.04)	0.12 (0.02 – 0.86)	0.14 (0.02 – 0.89)	0.14 (0.02 – 0.89)	0.25 (0.03 – 2.12)	0.24 (0.03 – 1.66)	0.29 (0.06 – 1.45)	0.30 (0.05 – 2.30)	0.64 (0.08 – 5.30)	0.80 (0.09 – 7.05)	**Oxytocin 5 IU**

Appendix G: **Subgroup analysis for the outcome "pyrexia"**

1.0 Blinded trials

1.1 Network diagram

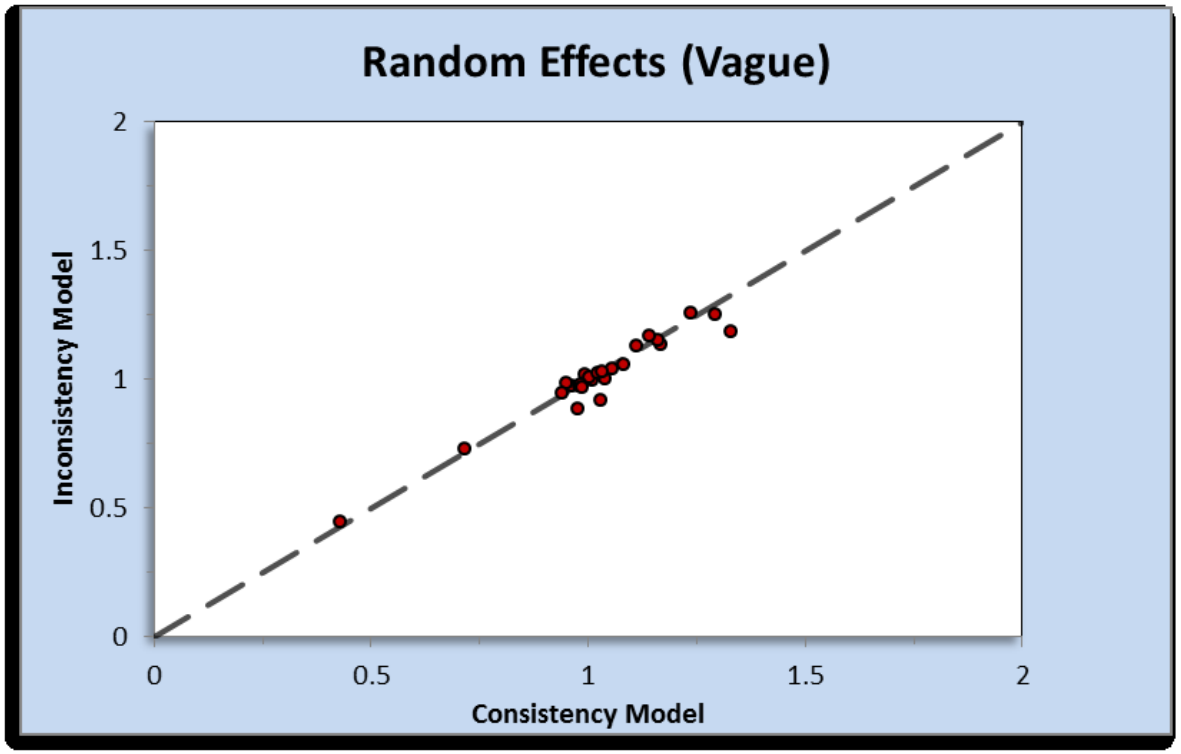
Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Methylergometrine 0.2 mg	D
Oxytocin 3 / 2.5 IU	E
Placebo / Control	F
Oxytocin 5 IU	G
ZB11	H
Oxytocin 20 IU	I
	J
	K
	L
	M
	N
	O



Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

1.2 Inconsistency results



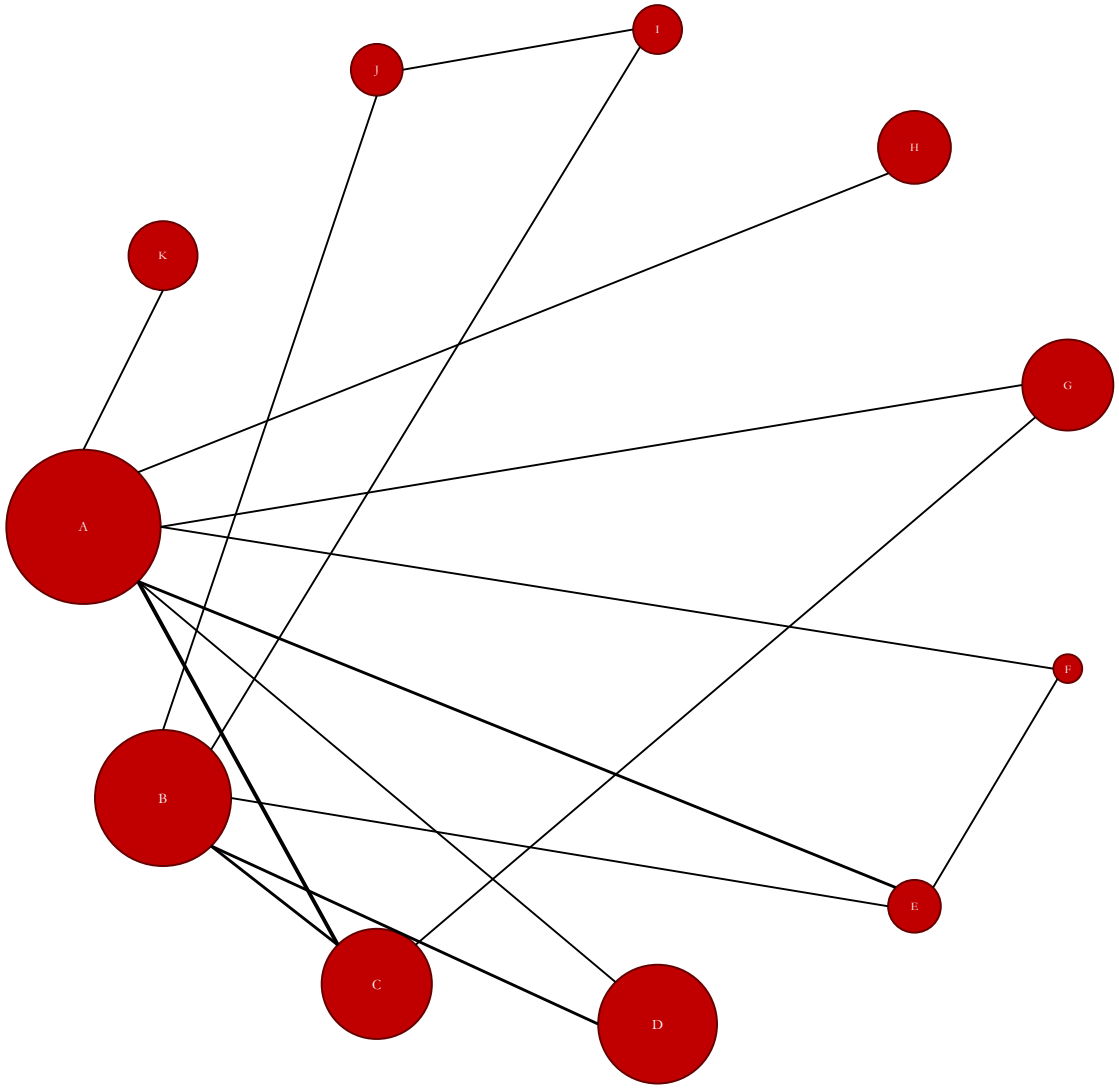
1.3 League table

Methylergometrine 0.2 mg								
0.27 (0.00 – 62.81)	**Oxytocin 5 IU**							
0.03 (0.00 – 5.13)	0.10 (0.00 – 2.55)	**Oxytocin 20 IU**						
0.02 (0.00 – 1.76)	0.06 (0.00 – 0.71)	0.63 (0.05 – 9.90)	**Oxytocin 10 IU**					
0.01 (0.00 – 0.83)	0.03 (0.00 – 0.44)	0.29 (0.01 – 5.82)	0.47 (0.05 – 2.69)	**Placebo / Control**				
0.01 (0.00 – 1.14)	0.02 (0.00 – 0.75)	0.21 (0.00 – 10.08)	0.35 (0.02 – 5.89)	0.75 (0.05 – 12.99)	**ZB11**			
0.00 (0.00 – 8.66)	0.01 (0.00 – 10.02)	0.10 (0.00 – 108.80)	0.16 (0.00 – 119.50)	0.36 (0.00 – 367.00)	0.45 (0.00 – 648.80)	**Oxytocin 3 / 2.5 IU**		
0.00 (0.00 – 0.27)	0.01 (0.00 – 0.10)	0.11 (0.01 – 1.23)	0.18 (0.05 – 0.47)	0.38 (0.06 – 3.27)	0.51 (0.03 – 10.26)	1.10 (0.00 – 842.20)	**Misoprostol 400 µg**	
0.00 (0.00 – 0.16)	0.01 (0.00 – 0.08)	0.06 (0.00 – 1.07)	0.10 (0.02 – 0.42)	0.21 (0.07 – 0.77)	0.29 (0.02 – 3.22)	0.62 (0.00 – 530.70)	0.56 (0.11 – 2.87)	**Misoprostol 600 µg**

2.0 Open-label trials

2.1 Network diagram

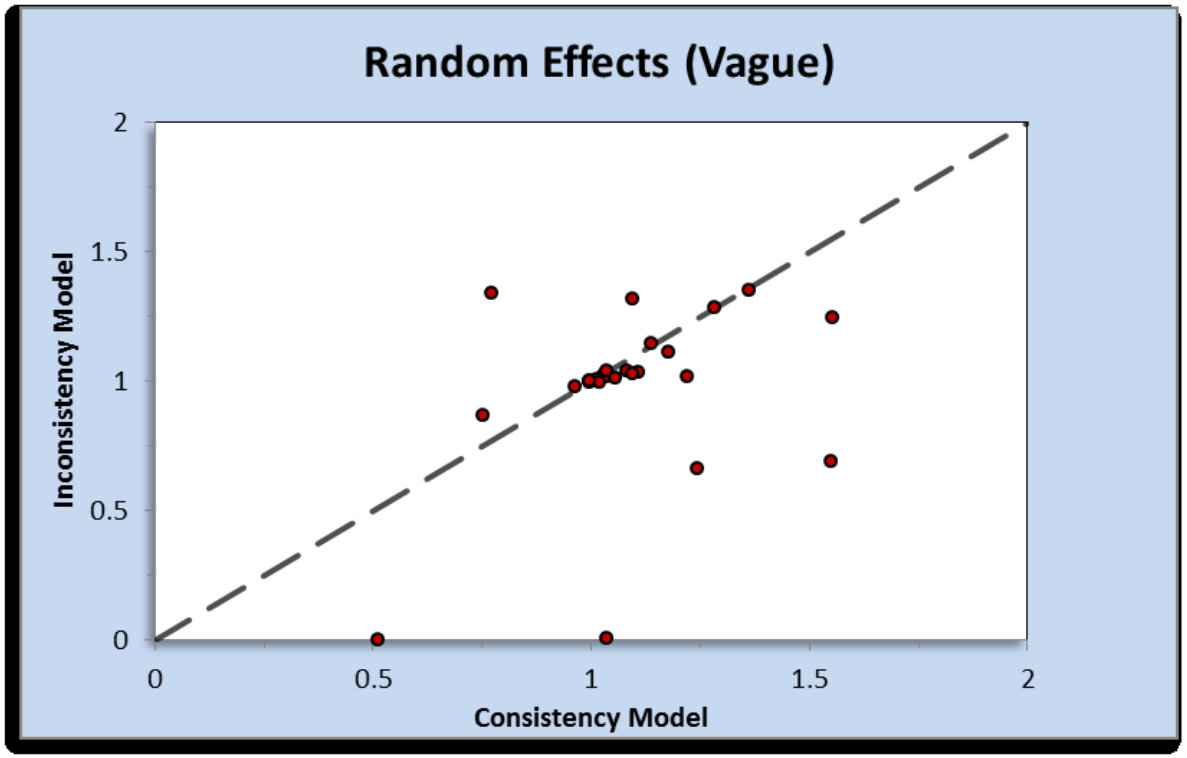
Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Syntometrine	D
Methylergometrine 0.2 mg	E
15-methyl PGF2α 125 µg	F
Ergometrine 2 mg	G
Ergometrine 0.5 mg	H
Oxytocin 2.5 IU	I
Control	J
Oxytocin/Syntometrine	K
	L
	M
	N
	O



Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

2.2 Inconsistency results



2.3 League table

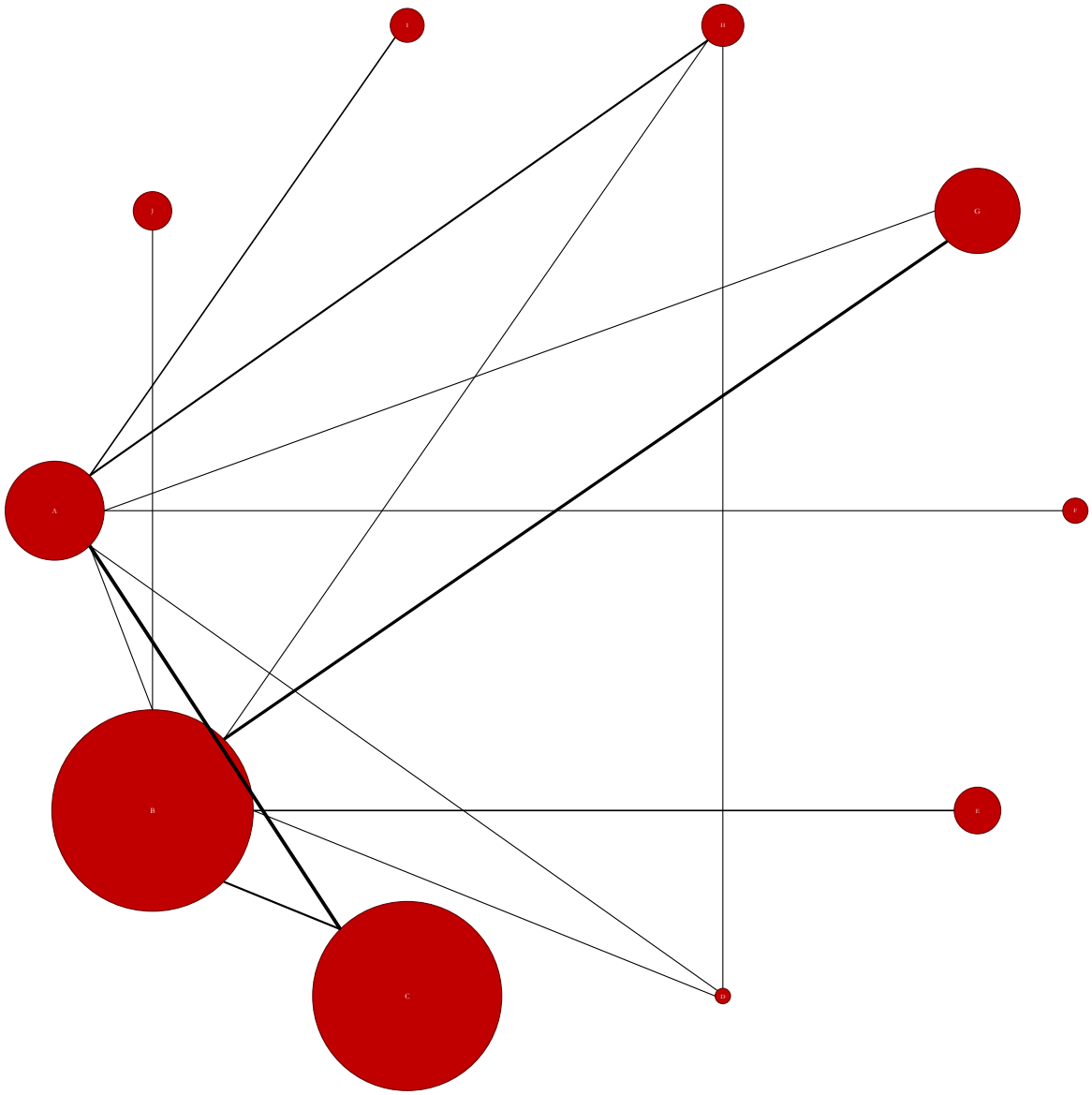
Oxytocin 2.5 IU										
0.89 (0.00 – 13804.53)	**Control**									
0.34 (0.00 – 106.30)	0.39 (0.00 – 99.58)	**Methylergometrine 0.2 mg**								
0.21 (0.00 – 205.80)	0.24 (0.00 – 184.10)	0.67 (0.01 – 56.75)	**15-methyl PGF2α 125 µg**							
0.17 (0.00 – 40.40)	0.19 (0.00 – 37.82)	0.52 (0.01 – 13.85)	0.75 (0.01 – 93.30)	**Syntometrine**						
0.09 (0.00 – 20.17)	0.10 (0.00 – 18.98)	0.28 (0.01 – 4.05)	0.40 (0.00 – 23.10)	0.54 (0.02 – 12.25)	**Oxytocin 10 IU**					
0.07 (0.00 – 41.94)	0.08 (0.00 – 44.09)	0.22 (0.00 – 12.71)	0.33 (0.00 – 39.82)	0.45 (0.00 – 38.87)	0.81 (0.02 – 33.48)	**Ergometrine 0.5 mg**				
0.04 (0.00 – 17.09)	0.04 (0.00 – 15.59)	0.13 (0.00 – 4.34)	0.19 (0.00 – 18.40)	0.24 (0.00 – 14.37)	0.46 (0.02 – 8.40)	0.56 (0.01 – 38.69)	**Ergometrine 2 mg**			
0.02 (0.00 – 14.20)	0.03 (0.00 – 14.45)	0.08 (0.00 – 3.74)	0.11 (0.00 – 13.36)	0.15 (0.00 – 11.99)	0.28 (0.01 – 10.13)	0.34 (0.00 – 29.19)	0.61 (0.01 – 41.79)	**Oxytocin/Syntometrine**		
0.02 (0.00 – 3.62)	0.02 (0.00 – 3.43)	0.05 (0.00 – 0.55)	0.07 (0.00 – 2.46)	0.09 (0.00 – 2.08)	0.16 (0.02 – 1.09)	0.20 (0.01 – 4.83)	0.36 (0.02 – 6.40)	0.59 (0.03 – 12.51)	**Misoprostol 400 µg**	
0.01 (0.00 – 1.34)	0.01 (0.00 – 1.24)	0.04 (0.00 – 0.40)	0.05 (0.00 – 3.71)	0.07 (0.01 – 0.66)	0.13 (0.01 – 1.15)	0.16 (0.00 – 8.69)	0.28 (0.01 – 9.36)	0.46 (0.01 – 23.57)	0.78 (0.06 – 9.63)	**Misoprostol 600 µg**

Appendix H: **Subgroup analysis for the outcome "shivering"**

1.0 Blinded trials

1.1 Network diagram

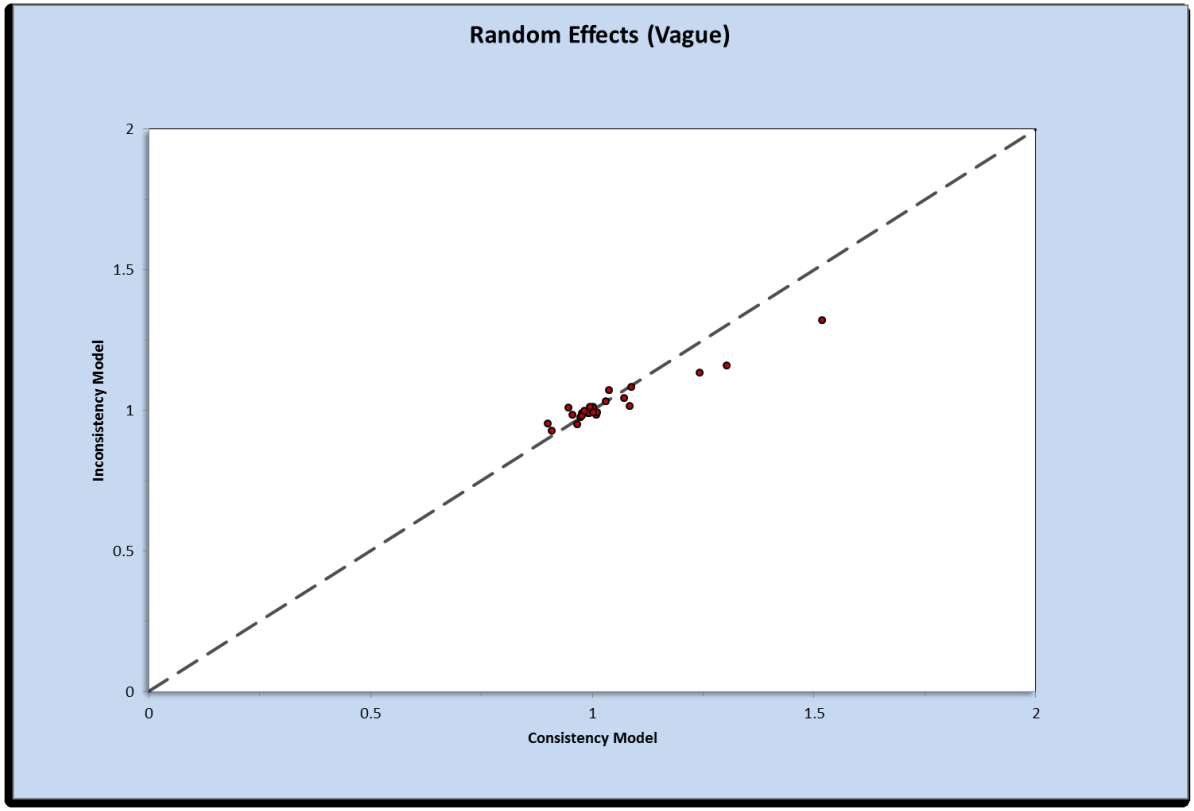
Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Methylergometrine 0.2 mg	D
Ergometrine 2 mg	E
Oxytocin 3 / 2.5 IU	F
Placebo / Control	G
Oxytocin 5 IU	H
Oxytocin 20 IU	I
ZB 11	J
	K
	L
	M
	N
	O



Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons

1.2 Inconsistency results



1.3 League table

Methylergometrine 0.2 mg									
0.19 (0.00 – 24.54)	**Oxytocin 5 IU**								
0.02 (0.00 – 1.68)	0.10 (0.01 – 1.00)	**Ergometrine 2 mg**							
0.02 (0.00 – 1.34)	0.09 (0.01 – 0.55)	0.95 (0.19 – 4.80)	**Oxytocin 10 IU**						
0.02 (0.00 – 1.33)	0.09 (0.01 – 0.65)	0.92 (0.19 – 4.34)	0.97 (0.32 – 2.97)	**Placebo / Control**					
0.02 (0.00 – 36.08)	0.10 (0.00 – 86.34)	1.06 (0.01 – 840.34)	1.08 (0.02 – 787.40)	1.11 (0.02 – 866.30)	**Oxytocin 3 / 2.5 IU**				
0.00 (0.00 – 0.57)	0.03 (0.00 – 0.35)	0.27 (0.03 – 2.59)	0.28 (0.04 – 2.21)	0.29 (0.04 – 2.11)	0.26 (0.00 – 23.39)	**ZB 11**			
0.00 (0.00 – 0.37)	0.02 (0.00 – 0.21)	0.20 (0.02 – 1.97)	0.21 (0.03 – 1.27)	0.21 (0.03 – 1.54)	0.18 (0.00 – 14.08)	0.73 (0.05 – 10.54)	**Oxytocin 20 IU**		
0.00 (0.00 – 0.27)	0.02 (0.00 – 0.12)	0.20 (0.05 – 0.74)	0.21 (0.08 – 0.50)	0.21 (0.09 – 0.46)	0.19 (0.00 – 11.38)	0.72 (0.12 – 4.51)	1.00 (0.14 – 6.95)	**Misoprostol 600 µg**	
0.00 (0.00 – 0.26)	0.02 (0.00 – 0.10)	0.19 (0.04 – 1.00)	0.20 (0.10 – 0.41)	0.21 (0.07 – 0.63)	0.19 (0.00 – 9.83)	0.71 (0.09 – 5.65)	0.97 (0.18 – 5.12)	0.98 (0.36 – 2.55)	**Misoprostol 400 µg**

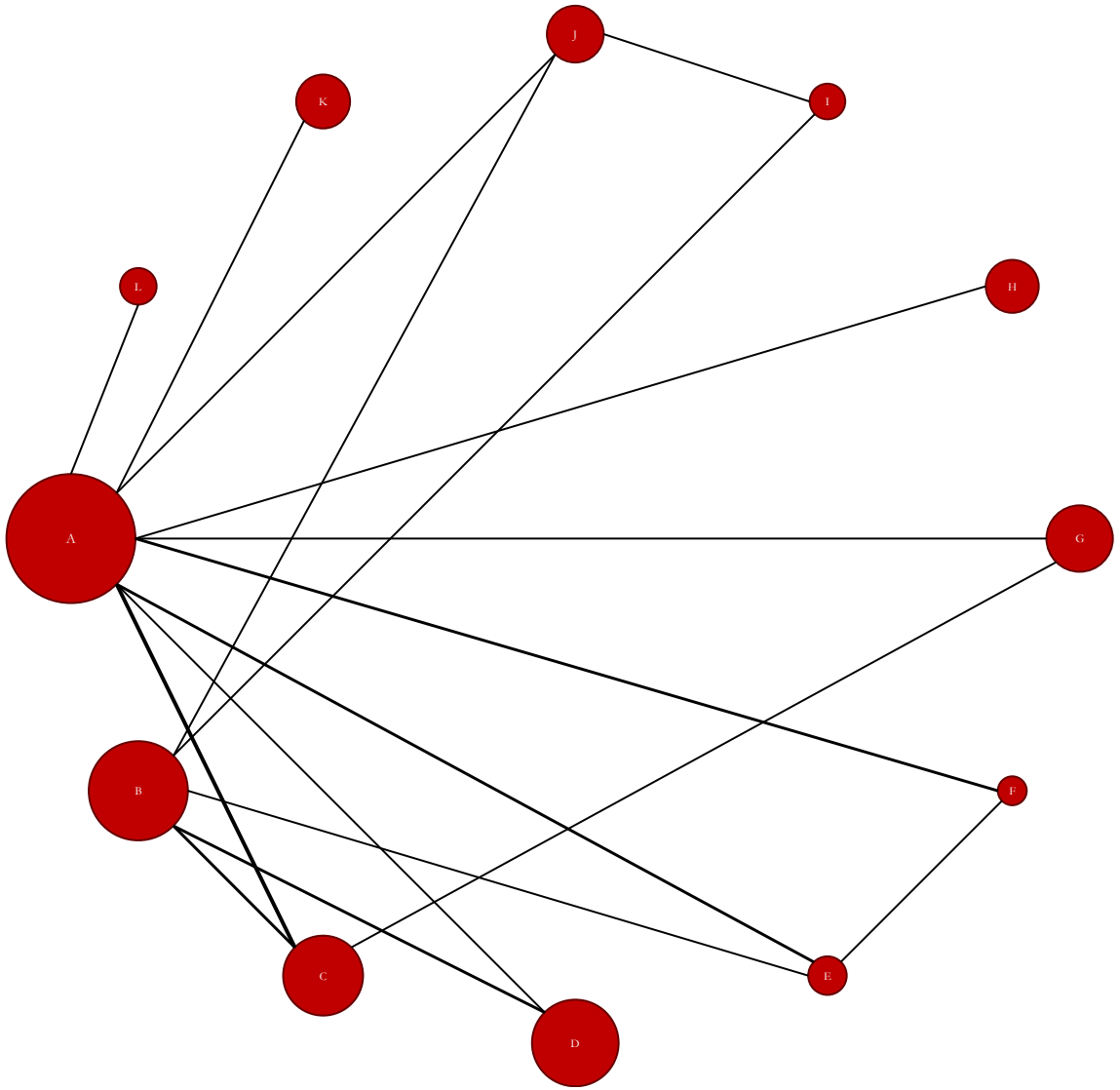
2.0 Open-label trials

2.1 Network diagram

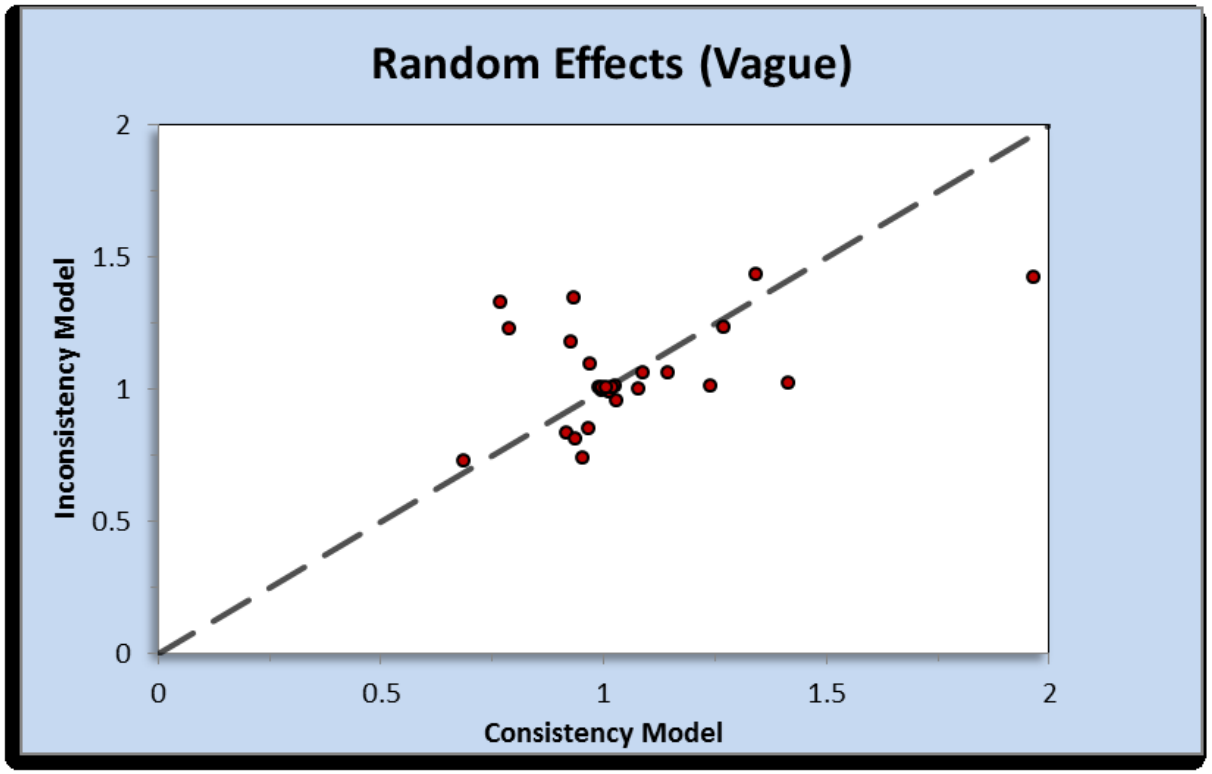
Legend	
Drug	**Abbreviation**
Misoprostol 400 µg	A
Misoprostol 600 µg	B
Oxytocin 10 IU	C
Syntometrine	D
Methylergometrine 0.2 mg	E
15-methyl PGF2α 125 µg	F
Ergometrine 2 mg	G
Ergometrine 0.5 mg	H
Oxytocin 2.5 IU	I
Control	J
Oxytocin/Syntometrine	K
Misoprostol 5 IU	L
	M
	N
	O

Size of a node is proportional to the size of included trials.

Thickness of an arm is proportional to the number of comparisons



2.2 Inconsistency results



2.3 League table

15-methyl PGF2α 125 µg											
0.07 (0.00 – 1.54)	**Methylergometrine 0.2 mg**										
0.12 (0.00 – 1903.67)	1.61 (0.01 – 25220.68)	**Oxytocin 2.5 IU**									
0.04 (0.00 – 0.92)	0.58 (0.06 – 4.61)	0.36 (0.00 – 43.02)	**Oxytocin 10 IU**								
0.04 (0.00 – 3.21)	0.61 (0.02 – 24.89)	0.35 (0.00 – 120.79)	1.06 (0.04 – 36.05)	**Misoprostol 5 IU**							
0.03 (0.00 – 1.47)	0.46 (0.02 – 10.89)	0.26 (0.00 – 71.89)	0.80 (0.04 – 16.89)	0.75 (0.01 – 41.71)	**Oxytocin/Syntometrine**						
0.03 (0.00 – 0.98)	0.37 (0.02 – 6.56)	0.21 (0.00 – 45.08)	0.63 (0.05 – 7.15)	0.59 (0.01 – 28.03)	0.79 (0.02 – 29.10)	**Ergometrine 2 mg**					
0.01 (0.00 – 0.59)	0.17 (0.01 – 4.08)	0.10 (0.00 – 27.15)	0.29 (0.01 – 6.13)	0.27 (0.00 – 16.24)	0.36 (0.01 – 16.02)	0.46 (0.01 – 17.00)	**Ergometrine 0.5 mg**				
0.01 (0.00 – 0.38)	0.17 (0.01 – 1.88)	0.10 (0.00 – 11.30)	0.29 (0.02 – 2.85)	0.27 (0.00 – 11.91)	0.37 (0.01 – 11.27)	0.47 (0.02 – 10.40)	1.01 (0.02 – 33.23)	**Syntometrine**			
0.01 (0.00 – 0.45)	0.15 (0.01 – 2.65)	0.09 (0.00 – 10.27)	0.25 (0.01 – 4.00)	0.24 (0.00 – 12.86)	0.32 (0.01 – 12.55)	0.40 (0.01 – 12.09)	0.89 (0.02 – 34.72)	0.87 (0.04 – 23.09)	**Control**		
0.01 (0.00 – 0.17)	0.15 (0.02 – 0.88)	0.09 (0.00 – 10.90)	0.26 (0.06 – 1.11)	0.24 (0.01 – 5.31)	0.33 (0.02 – 4.84)	0.41 (0.04 – 4.78)	0.90 (0.06 – 12.78)	0.90 (0.09 – 12.24)	1.03 (0.08 – 14.23)	**Misoprostol 400 µg**	
0.00 (0.00 – 0.07)	0.05 (0.00 – 0.28)	0.03 (0.00 – 2.06)	0.08 (0.01 – 0.39)	0.07 (0.00 – 2.31)	0.10 (0.00 – 2.08)	0.13 (0.01 – 1.85)	0.27 (0.01 – 6.04)	0.27 (0.04 – 1.59)	0.31 (0.02 – 3.75)	0.30 (0.04 – 1.65)	**Misoprostol 600 µg**

Article 2: The Incidence of Postpartum Hemorrhage in Patients Receiving Misoprostol for Prevention Purposes: A Meta-analysis and a Mixed-effects Model of Misoprostol Trials.

Authors: Ghayath Janoudi, Laura Mesana, Edward Mills, Mark Walker

Abstract

Objectives:

To estimate the incidence of postpartum hemorrhage (PPH) in mothers taking misoprostol for the prevention of PPH. In addition, we aimed to identify factors that may influence the incidence of PPH.

Methods:

A systematic review of all randomised clinical trials (RCT), single-arm trials, and quasi experimental trials, assessing misoprostol for the prevention of PPH in mothers giving birth vaginally. A random effects model was subsequently conducted, pooling the incidence of PPH from each misoprostol arm. Subsequently, a meta-regression model was performed on identified potential effect-modifiers.

Results:

Fifty-six trials met our inclusion/ exclusion criteria, representing 27,254 mothers that took misoprostol for the purposes of PPH prevention. The overall incidence of PPH was 6.62 per 100 pregnancies (95%CI 4.71 per 100 – 8.53 per 100). Blinding of the trial, induction of labour, and previous PPH were three effect-modifiers that significantly accounted for the majority of the heterogeneity, and led to increase in the incidence of PPH.

Conclusion:

An incidence of PPH of 6.62 per 100 pregnancies can be estimated form a population of delivering mothers taking misoprostol for the prevention of PPH.

Introduction

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality (1). Defined as vaginal bleeding of 500 ml or more within 24 hours of delivery(2), the condition is an emergency situation that can strike fast and worsen faster (1). The incidence of PPH varies from one place to another; in the

US the incidence was found to differ between hospitals, ranging from 1.6% to 4.9% (3), in Canada the rate of PPH has increased from 5.1% in 2003 to 6.2% in 2010 (4), while in the developing countries we can see rates ranging from 7.2% in Oceania to 25.7% in Africa (5). The large difference between developed and developing countries points to the preventable nature of this disease.

Misoprostol has been advocated as an effective, cheap, and feasible intervention to prevent postpartum hemorrhage (6, 7). Although considered inferior than the conventional first-line therapy oxytocin (7), the facts that it is thermally stable and requires no special training to administer as a pill, orally, make it a suitable alternative for resource poor countries (6).

In this study, we will systematically review the literature for experimental studies that assessed misoprostol for the prevention of PPH. Our aim is to be able to estimate the overall incidence rate of PPH in mothers taking misoprostol for prevention purposes, and to assess the effect of study, population, and intervention characteristics on this outcome.

Methods

Eligibility criteria

We included randomised clinical trials (RCT), single arm trials, and quasi-experimental trials. The included trial had to report on a population of women giving birth vaginally, included misoprostol as an intervention given for the purposes of preventing PPH, and reported the outcome of PPH as a bleeding 500 ml or greater. Trials had to be written in either English or French. A study would be excluded if it employed an observational design, if it did not report any one of the previously mentioned eligibility criteria, if full-text could not be retrieved, if it is a conference abstract, or if misoprostol was given vaginally. Studies that do not report on the number of mothers with a bleeding of 500 ml or greater, but report on the overall mean blood loss with a standard deviation, standard error, or confidence interval, where included. In such trials, an estimate of the number of mothers with a bleeding of 500 ml or greater was reached through calculating the cumulative distribution function of bleeding over 499 ml, under a normal distribution assumption.

Study endpoints

The main outcome of this study was to calculate the incidence of PPH, defined as bleeding of 500 ml or greater within 24 hours of delivery, across all patients who received misoprostol. In addition to running a subgroup analysis of trials conducted under clinical settings and trials conducted under community settings (community settings were defined as any trial that takes place in an area with no direct and quick access to surgical facilities or specialised medical services). Our secondary outcome was to analyse trial specific, population specific, and intervention specific characteristics for possible influence on the incidence of PPH as an effect modifier. Our third outcome was to predict the incidence of PPH under a varying measure of effect modifiers that have exerted significant effect on the outcome.

Trial specific characteristics to be studied were; year of publication, country where trial took place, trial settings as either community or clinical, management of labour (active or passive), randomization, blinding, method of blood loss estimation, and length of observation time for blood loss.

Population specific characteristics to be studied were; mean age of the trial's population, percentage of mothers underwent induction of labour, percentage of mothers underwent augmentation of labour,

percentage of mothers underwent instrumental delivery, percentage of mothers underwent episiotomy, percentage of mothers with previous history of PPH, and percentage of nulliparous mothers.

Intervention specific characteristics to be studied were; route of misoprostol administration, and dosage of administered misoprostol.

Search strategy

In consultation with a medical librarian at the University of Ottawa we developed a search strategy across 5 key databases. We used Ovid to search Medline, EMBASE, Cochrane CENTRAL, and CINAHL, in addition to searching CAB direct global health. The search was conducted on September 25th, 2014

The specific search strategy used in OVID is provided in appendix A.

Study selection

Two reviewers (G.J and L.M) independently and in duplicate carried out screening all retrieved articles for title and abstract. Subsequently, full text for all included articles was retrieved and both reviewers carried an independent and duplicate screening of the full text. Data extraction was conducted using a pre-established data extraction sheet (available in appendix B). Both reviewers extracted all relevant data from retrieved full text in full and in duplicate. After both reviewers had completed extraction of all data independently, their extracted data was compared for agreement. Any discrepancy would have been solved by direct discussion and reaching consensus. If no consensus can be reached, a third reviewer (E.M) would be involved to provide arbitration.

Data analysis

Data for population and number of events were derived from the number of intent to treat (ITT) population in the misoprostol arm. If ITT was not present then per protocol number was used. If neither ITT or per-protocol information were reported then the randomised population to the misoprostol arm was used as the number of the population, in cases of non-randomised trials, number of enrolled population into the misoprostol intervention was taken as the baseline population number. In cases with multiple arms of misoprostol, each arm was regarded as a separate trial. Adjustment of zero cells was achieved by adding a 0.5 adjusted continuity correction factor only to cells with zero value(8).

PPH incidence rate per pregnancy in the misoprostol population for each trial was calculated by dividing the number of events in the misoprostol arm by the number of population assigned to the misoprostol intervention. As we expected to find considerable heterogeneity between studies, we used a random effect model meta-analysis to synthesise the incidence rate of all included trials into one overall incidence rate and to estimate between study variance (9). A pooled effect was reported as an incidence rate per pregnancy with corresponding 95% confidence interval (95%CI). Statistical heterogeneity was tested using the I^2 measure and the Q test. Forest plots are provided for visual presentation of individual trials and the overall pooled effect. Radial plots are used to assess the consistency of observed outcomes (10). A sensitivity analysis was conducted by removing one study at a time from the model and assessing the study's influence over the model.

A meta-regression using mixed effects model was conducted on each of the previously specified trial, population, and intervention characteristics individually. Only trials that have reported on the examined characteristic were included in the model. The effect of each characteristic on the overall heterogeneity of the model was tested using the test for moderators (QM) with a corresponding p-value. A measure of

the percentage of heterogeneity accounted for in the tested characteristic was provided as R^2. Characteristics that have a significant effect on the heterogeneity of the model were further analysed using a predictive model to estimate possible PPH incidence rates under different values of the effect modifier.

Data gathering was conducted using Microsoft Excel. Data analysis and figures generating were conducted using the metafor package in R (11). The code used to analyse the results was provided in appendix C. The database used for the analysis is provided in appendix D.

This study is part of a systematic review and meta-analysis that has been registered with PROSPERO under PROSPERO 2014:CRD42014013802. Available from

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013802

Results

The Final search was conducted on September 24th, 2014. Our search retrieved 444 records. Of these records, 56 met our inclusion and exclusion criteria, with a total of 61 misoprostol arms (12-67). A flowchart of the identified, included, and excluded records is represented in figure 1. These 55 trials represent a total of 27,254 mothers who underwent delivery, with a total of 3,115 events. The mean age of the participants was 26.67, with a standard deviation of 2.29. Of the 56 included trials; twenty three employed a blinded RCT design (14, 17-20, 22, 25, 32-34, 37, 38, 41, 43, 44, 46, 48, 50, 53, 57, 58, 63, 64), twenty four employed an open-label RCT design (12, 13, 16, 23, 24, 27-30, 35, 39, 40, 45, 47, 49, 51, 54, 56, 59-62, 65, 67), and nine were of a quasi-experimental design (15, 21, 26, 31, 36, 42, 52, 55, 66)

We have identified seven different methods used in trials for the purpose of blood loss estimation; sixteen trial used a calibrated collection instrument (e.g. plastic bag, kidney dish) to collect blood after the delivery of the placenta (12, 16, 18, 21, 23, 25, 31, 32, 35, 41, 45, 54, 55, 59, 65, 66), six trials used the weight of soaked fabric (e.g. gauze, linen) minus the original weight (13, 22, 51, 53, 57, 64), eleven trials used both previous methods (17, 19, 20, 33, 34, 37, 38, 44, 56, 61, 62), fourteen trials used visual clinical judgement (15, 26, 27, 36, 40, 42, 43, 46-50, 52, 58), two trials used visual clinical judgement and calibrated blood collection (24, 39), one trial used visual clinical judgement and the weight of soaked fabric (28), one trial used a mathematical equation based on the 24 hours hematocrit difference (29), and five trials did not report on the method used for blood loss estimation (14, 30, 60, 63, 67).

In mothers taking misoprostol for PPH prevention, the overall incidence of PPH was 6.62 per 100 pregnancies (95%CI 4.71 per 100 – 8.53 per 100). The test for heterogeneity Q with a 60 degrees of freedom showed significant heterogeneity with a value of 3118.23. This is reflected on the I^2 value of 99.93% (95%CI 99.91% – 99.96%). Figure 2 shows a forest plot of all included misoprostol arms with the synthesised pooled result. A radial graph is presented in figure 3 and shows a good fit of the effect size as compared to the quality of the trial. A sensitivity analysis was conducted by leaving one trial out of the model, no one trial had a substantial weight on the heterogeneity or the final estimate.

Our subgroup analysis based on the settings the trial was conducted and showed no major differences than the overall analysis. Forty eight trials were conducted in a clinical environment (12-20, 22-24, 27-30, 32-35, 37-41, 43, 45-63, 65-67), the meta-analysis of these trials showed an overall incidence of PPH in the misoprostol arms of 6.73 per 100 (95%CI 4.55 per 100 – 8.90 per 100), with an I^2 of 99.94% (95%CI 99.92% – 99.97%). Eight trials were conducted under a community settings (21, 25, 26, 31, 36, 42, 44, 64),

meta-analysis of these trials showed an incidence of PPH in misoprostol arms of 6.17 per 100 (95%CI 2.48 per 100 – 9.86 per 100 pregnancies), with an I^2 of 98.28% (95%CI: 95.91 – 99.61).

In our meta-regression of the trial specific, population specific, and intervention specific characteristics, only three displayed a significant effect on the overall heterogeneity. Specifically; blinding, induction of labour, and previous PPH have significantly accounted for 9.81%, 37.93%, and 46.53% of the heterogeneity, respectively. Table 1 lists the results of the meta-regression for all of the analysed characteristics.

Based on the meta-regression results, a predictive model was constructed for each of study blinding, induction of labour, and previous PPH. The aim is to predict the possible incidence of PPH in different values of each of these characters. Incidence of PPH in misoprostol arms seems to increase by 5.02 per 100 pregnancy when a trial is blinded as compared to an unblended trial (figure 4). Induction of labour increases the incidence of PPH in misoprostol intervention by approximately 5.0 per 100 pregnancies for every 10% increase in the population undergoing induction of labour (figure 5). While for every 10% increase in the population with previous history of PPH, the incidence of PPH in misoprostol arms seems to increase approximately 50 per 100 pregnancies (figure 6).

Discussion

We conducted a meta-analysis of 56 identified trials through a systematic search. These trials represented over twenty five thousand mothers that took misoprostol for the purposes of PPH prevention. Our analysis showed that, in every one hundred delivering mothers taking misoprostol for the prevention of PPH, PPH would occur in almost seven of them. A subgroup analysis based on clinical settings and community settings failed to account for the observed significant heterogeneity in our results, and has showed similar results of the incidence of PPH in community and in clinical settings. A meta-regression model observed three effect modifiers that significantly accounted for the majority of the heterogeneity; blinding, induction of labour, and previous PPH. A predictive model for these three effect modifiers displayed an increased incidence of PPH in blinded studies, in a population with a high percentage of labour induction, and in a population with high percentage of previous history of PPH.

This study has several limitations. Firstly, the inclusion of only misoprostol arms in the analysis meant that randomisation has been broken and only descriptive statistics characterising a population taking misoprostol could be reported and no comparisons could be made. However, our aim was to report on the incidence of PPH in mothers taking misoprostol for prevention of PPH, therefore no comparison was necessary, and the inclusion of only misoprostol arms has allowed us to include all misoprostol trials regardless of the comparison. A second limitation was the inclusion of non-RCT experimental trials, this might have decreased the overall quality of the conducted analysis, but has also allowed us to capture several community trials and provide better generalisability and external validity. A third limitation was the high statistical heterogeneity found in our analysis, this was further analysed in our meta-regression model and has produced findings of specific factors that contributed to this heterogeneity. Lastly, meta-regression is considered an observational study (68). Therefore, we are unable to draw causality based on these observations. Time since the literature search is another limitation. However, and due to the large number of trials included, representing a large population, new studies are unlikely to exert any significant influence on the results obtained.

Our analysis has the capacity to inform policy makers, researchers, and practitioners. Policy makers who are contemplating a mass campaign of misoprostol distribution for the prevention of PPH can expect an incidence of PPH around 6.62 per 100. Our finding that blinding is associated with a higher incidence of PPH is in accordance with the general knowledge that an open-label trial would usually overestimate the protective effect of the intervention due to confirmatory bias(69). The observation that labour induction and history of previous PPH is associated with increased incidence of PPH is in line with the general knowledge regarding risk factors for PPH (70-75). It is therefore strange that out of the 56 included trials only twenty two reported on labour induction (14, 19, 20, 22, 23, 25-28, 31, 32, 39, 42, 44, 47, 49, 50, 58, 62-64, 67), and only eighteen reported on the number of mothers with previous history of PPH (22, 25, 27, 28, 32, 35, 37-39, 43, 48-50, 52, 58-60, 63). Thus, it is important for researchers to capture these risk factors of PPH in their study design and implementation.

Funding and conflict of interest

No funding has been received for this study. All authors declare no conflict of interest.

GJ Led the protocol development, co-ordinated the research efforts, developed the search strategy with a consultation of a medical librarian, performed the literature search, screened the articles as the first reviewer, extracted data as the first reviewer, assessed biases as the first reviewer, analysed data, wrote the manuscript, and performed necessary revisions. LM helped in developing the protocol, screened the articles as a second reviewer, extracted date as a second reviewer, and assessed biases as a second reviewer. MW provided clinical guidance and expertise, reviewed the protocol, reviewed the manuscript, and provided revisions. EM provided methodological guidance and expertise, acted as a third reviewer in cases of discrepancy among the first two reviewers, provided training in evidence synthesis practice, reviewed the protocol, reviewed the manuscript, and provided revisions.

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Figure 1: Flowchart of included trials

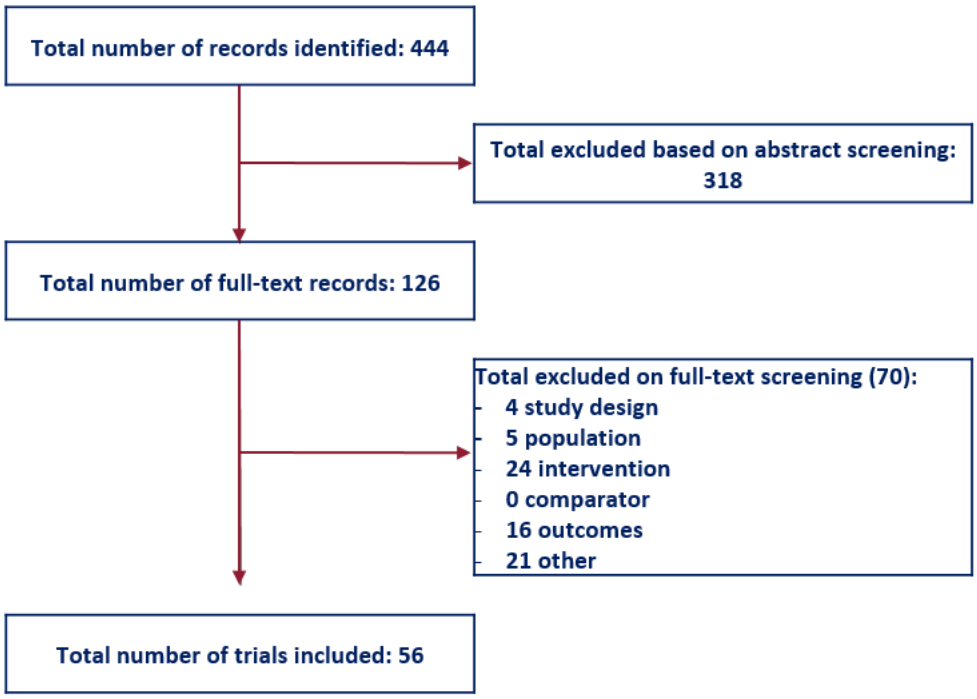


Figure 2: Forest plot of the incidence of PPH in mothers taking misoprostol for PPH prevention

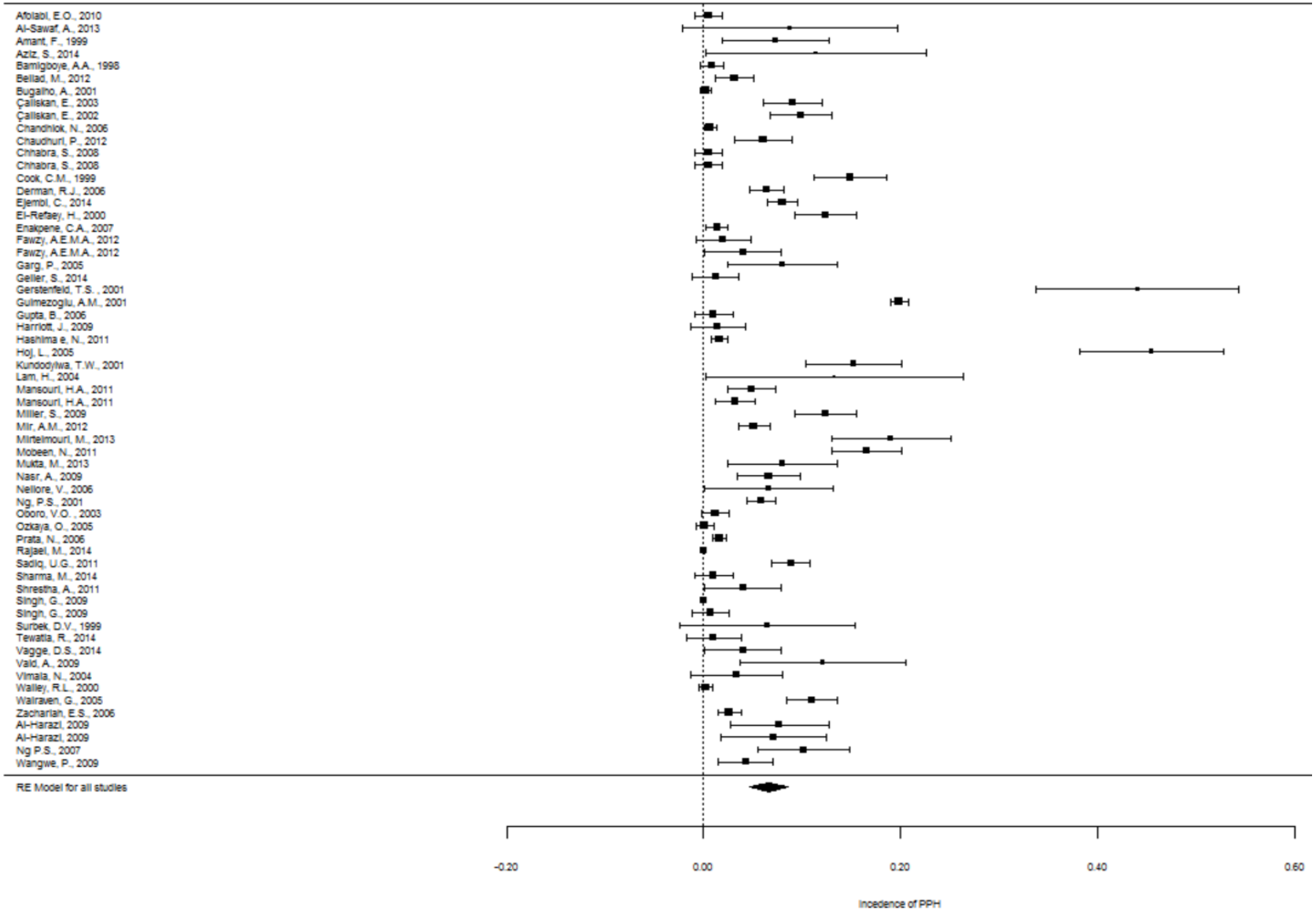


Figure 3: Radial graph representing the effect size as compared to the quality of the trial

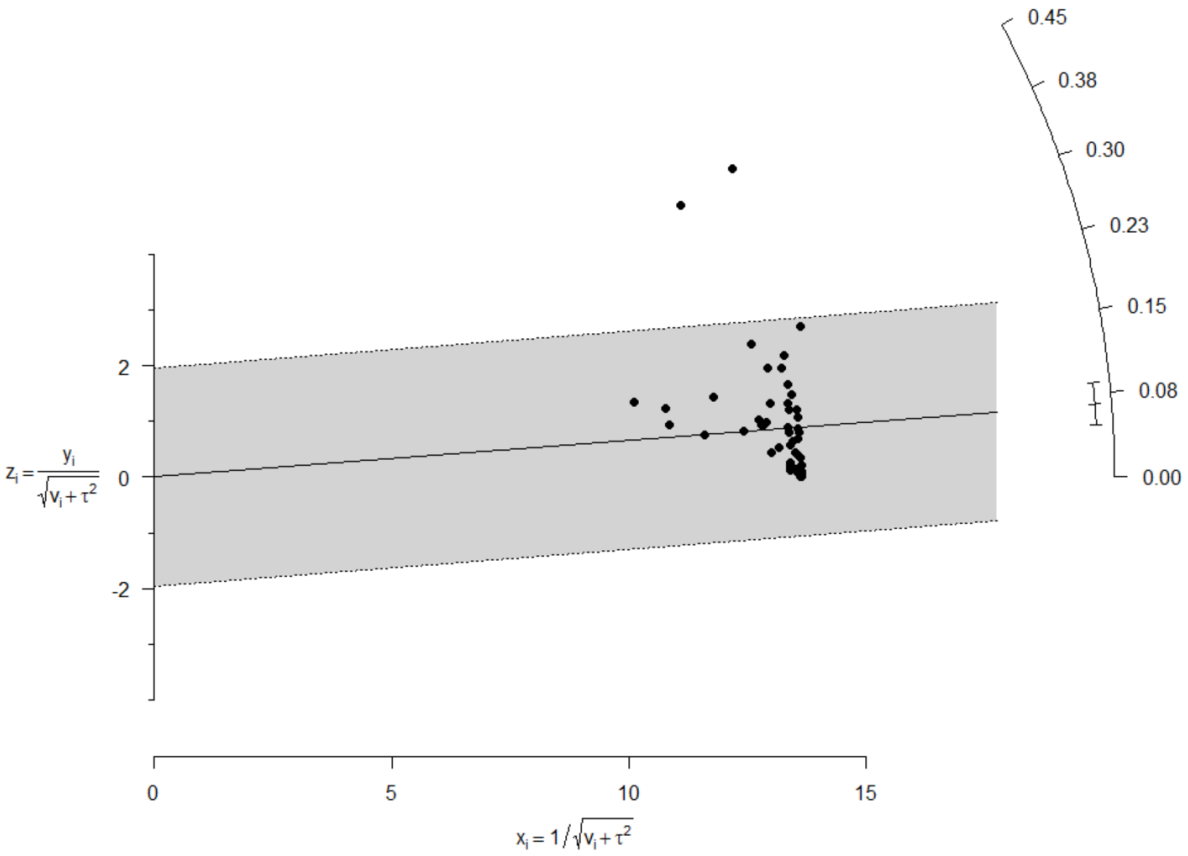


Table 3: Results of the mixed-effect model

Effect modifier	Number of trials reporting the effect modifier	Test of moderator QM	P-value of QM	Amount of heterogeneity accounted for "R^2"
Publication year	56	3.3471	0.0673	3.80%
Country	56	2.9089	0.0881	3.56%
Settings	56	0.0250	0.8745	0.00%
Management of labour	45	0.7360	0.3909	0.00%
Randomisation	56	1.2110	0.2711	0.14%
Blinding	56	6.9536	**0.0084**	9.81%
Blood loss estimation method	51	0.4011	0.5265	0.00%
Duration of blood loss observation	36	0.0518	0.8200	0.00%
Mean age	47	2.3155	0.1281	3.16%
Induction of labour	22	12.3771	**0.0004**	37.93%
Augmentation of labour	24	3.2297	0.0723	11.19%
Instrumental delivery	23	1.8243	0.1768	6.20%
Episiotomy	19	0.0010	0.9747	0.00%
Previous PPH	18	13.4134	**0.0002**	46.53%
Nulliparous	31	0.3138	0.5754	0.00%
Route of administration	56	0.0681	0.7941	0.00%
Dosage	56	0.7749	0.3787	0.00%

Figure 4:

Forest plot of the predictive incidence of PPH in misoprostol arms in blinded vs non-blinded trials

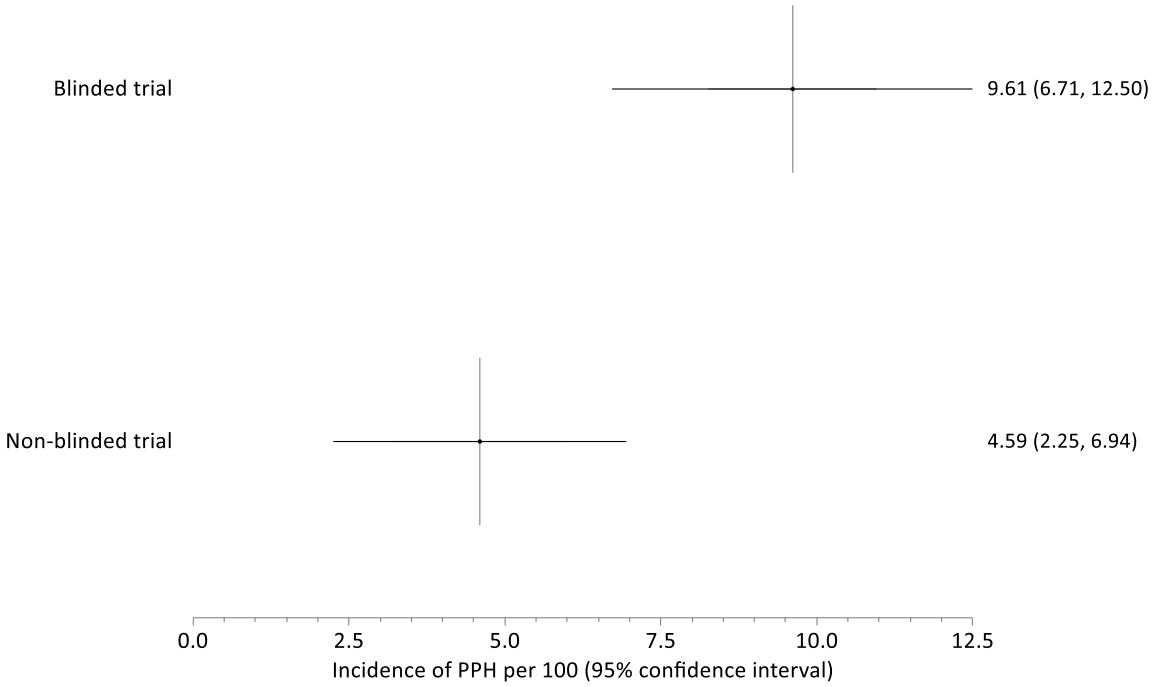


Figure 5:

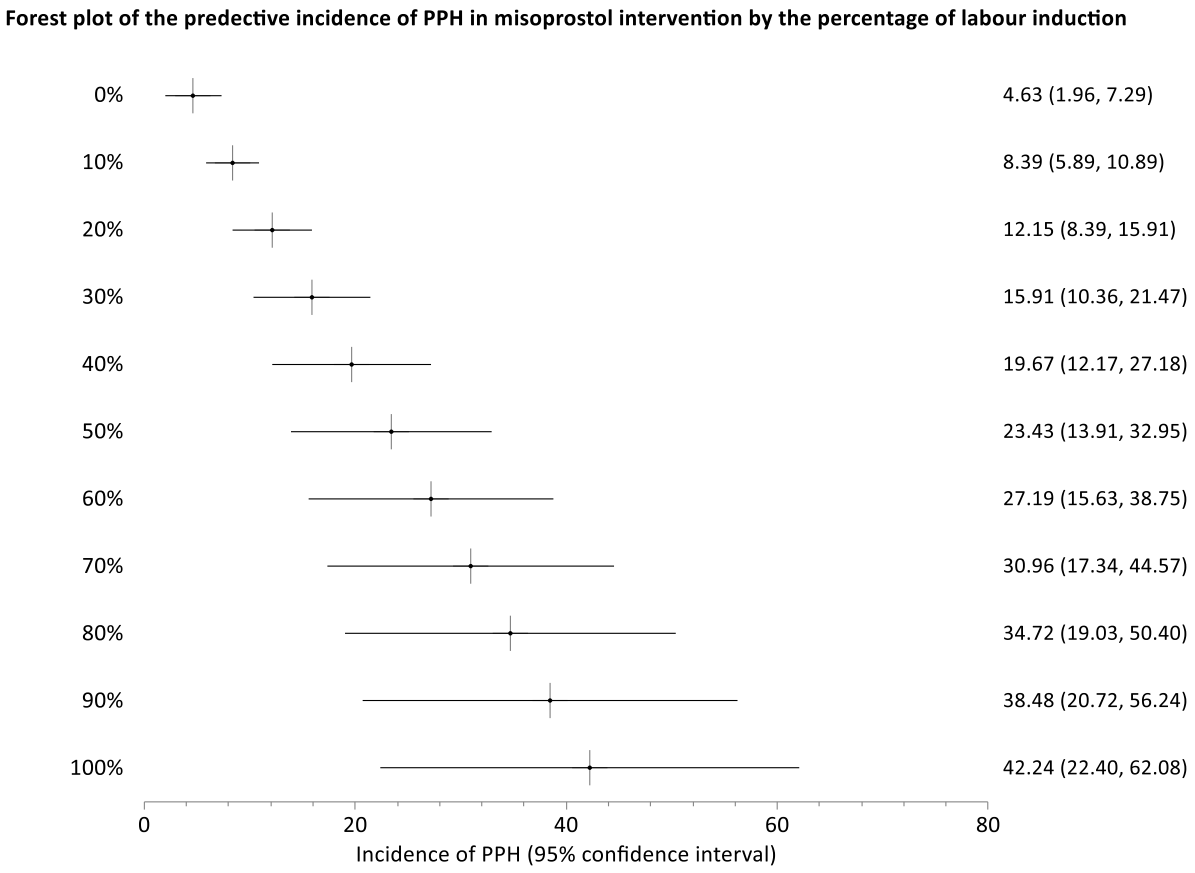
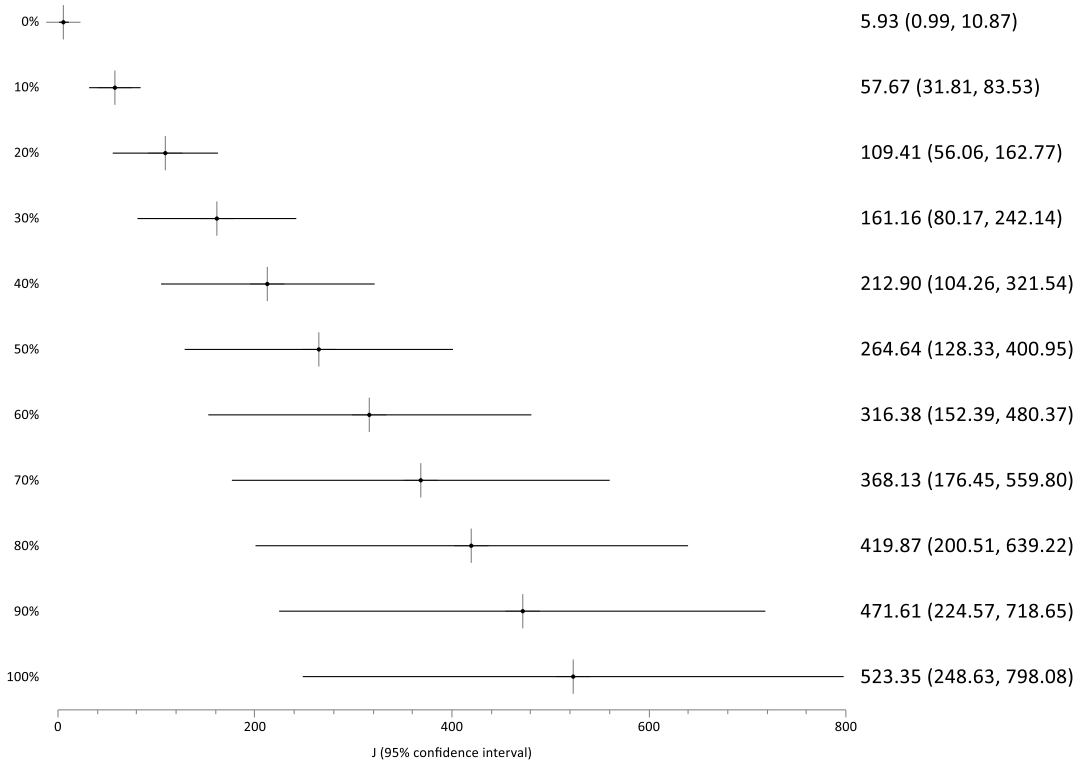

Forest plot of the predective incidence of PPH in misoprostol intervention by the percentage of labour induction
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
4.63 (1.96, 7.29)
8.39 (5.89, 10.89)
12.15 (8.39, 15.91)
15.91 (10.36, 21.47)
19.67 (12.17, 27.18)
23.43 (13.91, 32.95)
27.19 (15.63, 38.75)
30.96 (17.34, 44.57)
34.72 (19.03, 50.40)
38.48 (20.72, 56.24)
42.24 (22.40, 62.08)
0
20
40
60
80
Incidence of PPH (95% confidence interval)

Figure 6:

Forest plot of the predictive incidence of PPH in misoprostol intervention by the percentage of previous PPH mothers



Appendix A:

Ovid search strategy

Search	Query
#1	Postpartum Hemorrhage/pc [Prevention & Control]
#2	Misoprostol/
#3	(prevent* adj2 postpartum adj2 hemorrhage).tw.
#4	(prevent* adj2 postpartum adj2 haemorrhage).tw.
#5	Misoprostol*.tw.
#6	1 or 3 or 4
#7	2 or 5
#8	6 and 7
#9	limit 8 to (english or french)

Appendix B

Extraction sheets

Trials' characteristics:

Trial characteristics (reviewer 1)

Trial ID and Reference						**Trial design**								**Treament**				**Inclusion c**	**Exclusion criteria**	**Follow up**				**Mortality**
ID (included studies)	Trial Name or NCT Code or Author (Year)	Primary Author	Year	Title	Relationship with other primary publication	Observational vs experimental	Clinical vs Community settings	Randomisation (yes, no)	Double blind / open label	Year of Study Completion	Region	Multicentre (Y/N)	Method of blood estimation	Arm 1	Arm 2	Arm 3	Additional information about interventions			Estimate type	Dispersion type	Estimate duration (hours)	Dispersion duration (hours)	All Cause Mortality

Patients' characteristics:

Patient characteristics (reviewer 1)

Trial ID and References				**Treament**												**Populatio**	**Age**			
ID (included studies)	Primary Author	Year	Relationship with other primary publication	Intervention	Dosage	Route of administration	Self administration (yes/no)	Trained Birth Attendant (TBA) administration	Health-care facility settings (yes/no)	Community setting (yes/no)	Home birth (yes/no)	Cord traction (yes/no)	Uterine massage (yes/no)	Early cord clamping (yes/no)	Active management of labour (yes/no)	Total population at baseline (N)	Estimate type	Dispersion type	Estimat age (years)	Dispersion age (years)

Cont.

Labour																			
NO. of Caesarean Section (n)	Percentage of Caesarean Section (%)	NO. of emergency CS (n)	Percentage of emergency CS (%)	NO of elective CS (n)	Percentage of elective CS (%)	NO. of vaginal deliveries (n)	Percentage of vaginal delivered (%)	NO. of spontaneous vertex (n)	Percentage of spontaneous vertex (%)	NO. of spontaneous breech (n)	Percentage of spontaneous breech (%)	NO. of preterm deliveries (n)	Percentage of preterm deliveries (%)	NO. of induced labour (n)	Percentage of induced labour (%)	Type of induction	Dose of induction drug	No. of augmented labour	Percentage of augmented labour (%)

Cont.

Type of augmentation	Dose of augmentation drug	NO. of patients with episiotomy (n)	Percentage of patients with episiotomy (%)	NO. of patients with perineal/vaginal/cervical	Percentage of patients with perineal/vaginal/c	NO. of instrumental deliveries (n)	Percentage of instrumental deliveries (%)	NO. of forceps deliveries (n)	Percentage of forceps deliveries (%)	NO. of suction (vacuum) deliveries (n)	Percentage of suction (vacuum) deliveries (%)	NO. of intact membrane (n)	Percentage of intact membrane (%)	NO. of ruptured membrane (n)	Percentage of ruptured membrane (%)	NO. of patients receiving Oxytocin or prostagla	Percentage of patients receiving Oxytocin or

Cont.

Obstetrical characteristics																			
NO. of PrimiGravida (n)	Percentage of PrimiGravida (%)	NO. of MultiGravida (n)	Percentage of MultiGravida (%)	NO. of GrandMultiGravida (n)	Percentage of GrandMultiGravida (%)	Mean Parity	SD Parity	NO. of Nulliparous (n)	Percentage of Nulliparous (%)	NO. of MultiParous (n)	Percentage of MultiParous (%)	NO. of GrandMultiParous (n)	Percentage of GrandMultiParous (%)	Mean weight (Kg)	Median weight (Kg)	SD weight	95%CI weight	Mean BMI (kg/m^2)	Median BMI (kg/m^2)

Cont.

						Obstetrical history											
SD BMI	95%CI BMI	Mean period of gestation (weeks)	Median period of gestation (weeks)	SD period of gestation	95%CI period of gestation	No AnteNatal Visits (n)	No AnteNatal visits (%)	1 or more AnteNatal Visits (n)	1 or more Antenatal visits (%)	Mean number of antenatil visits	SD of antenatal visits	Previous PPH (n)	Previous PPH (%)	Patients with previous CS (n)	Patients with previous CS (%)	Median number of previous CS	Range of number of previous CS

Outcomes:

Outcomes (reviewer 1)

Trial ID and References				**Treament**				**Efficacy**									
ID (included studies)	Primary Author	Year	Relationship with other primary publication	Type of uterotonic	Reprted treated population	Route	Dosage	Mean blood loss (ml)	Avarage blood loss (ml)	Median blood loss (ml)	SD blood loss	95%CI blood loss	Blood loss ≥500 ml (n)	Blood loss ≥500 ml (%)	Blood loss ≥1000 ml (n)	Blood loss ≥1000 ml (%)	

Cont.

Additional uterotonics needed (n)	Additional uterotonics needed (%)	Blood transfusion required (n)	Blood transfusion required (%)	Refferal (n)	Refferal (%)	**Safety** Safety population (n)	Death (n)	Death (%)	Pyrexia (38 > C < 40 OR not otherwise specified)	Pyrexia (38 > C < 40) (%)	Severe Pyrexia (≥ 40) (n)	Severe Pyrexia (≥ 40) (%)	Shivering (n)	Shivering (%)	Diarrhea (n)	Diarrhea (%)	Headache (n)	Headache (%)

Appendix C

R code used for the analysis

```
library (metafor)



all <- read.csv("misoall.csv", header = TRUE)

print (all, row.names = FALSE)


pop <- sum (all$pop)

print (pop)

events <- sum (all$X500n)

print (events)

age.mean <- mean (all$age, na.rm = TRUE)

print (age.mean)

age.sd <- sd (all$age, na.rm = TRUE)

print (age.sd)

age.median <- median (all$age, na.rm = TRUE)

print (age.median)

age.range <- range (all$age, na.rm = TRUE)

print (age.range)



datall500 <- escalc (measure = "IR", xi = X500n, ti = pop, data = all,

        add = 1/2, to = "only0", append = TRUE,)

print (datall500, row.names = FALSE)

resall500 <- rma(yi, vi, data = datall500)

print (resall500)

confint (resall500)

forest (resall500, xlab = "Incedence of PPH", slab = paste(datall500$author,
```

```
      datall500$year, sep=(", ")), mlab = "RE Model for all studies")
radial (resall500)
leave1out (resall500)



regall500year <- rma (yi, vi, mods = cbind (year), data = datall500)
print (regall500year)
regall500setting <- rma (yi, vi, mods = cbind (setting), data = datall500)
print (regall500setting)
regall500manage <- rma (yi, vi, mods = cbind (manage), data = datall500)
print (regall500manage)
regall500rando <- rma (yi, vi, mods = cbind (rando), data = datall500)
print (regall500rando)
regall500blind <- rma (yi, vi, mods = cbind (blind), data = datall500)
print (regall500blind)
regall500htime <- rma (yi, vi, mods = cbind (htime), data = datall500)
print (regall500htime)
regall500bmethod <- rma (yi, vi, mods = cbind (bmethod), data = datall500)
print (regall500bmethod)
regall500route <- rma (yi, vi, mods = cbind (route), data = datall500)
print (regall500route)
regall500geo <- rma (yi, vi, mods = cbind (geo), data = datall500)
print (regall500geo)
regall500induce <- rma (yi, vi, mods = cbind (induce), data = datall500)
print (regall500induce)
regall500aug <- rma (yi, vi, mods = cbind (aug), data = datall500)
print (regall500aug)
regall500inst <- rma (yi, vi, mods = cbind (inst), data = datall500)
print (regall500inst)
```

```
regall500prevpph <- rma (yi, vi, mods = cbind (prevpph), data = datall500)
print (regall500prevpph)
regall500nulli <- rma (yi, vi, mods = cbind (nulli), data = datall500)
print (regall500nulli)
regall500epis <- rma (yi, vi, mods = cbind (epis), data = datall500)
print (regall500epis)
regall500dose <- rma (yi, vi, mods = cbind (dose), data = datall500)
print (regall500dose)
regall500age <- rma (yi, vi, mods = cbind (age), data = datall500)
print (regall500age)

predict(regall500blind, newmods = cbind(seq(from = 0, to = 1, by = 1)),
addx = TRUE)
induce <- predict(regall500induce, newmods = cbind(seq(from = 0, to = 100, by = 10)),
addx = TRUE)
predict(regall500prevpph, newmods = cbind(seq(from = 0, to = 100, by = 10)),
addx = TRUE)
predict(regall500setting, newmods = cbind(seq(from = 0, to = 1, by = 1)),
addx = TRUE)


comm <- read.csv("misocomm.csv", header = TRUE)
print (comm, row.names = FALSE)
datcomm <- escalc (measure = "IR", xi = X500n, ti = pop, data = comm,
        add = 1/2, to = "only0", append = TRUE,)
print (datcomm, row.names = FALSE)
rescomm <- rma(yi, vi, data = datcomm)
print (rescomm)
confint (rescomm)
```

```
forest (rescomm, xlab = "Incedence of PPH", slab = paste(datcomm$author,
    datcomm$year, sep=(", ")), mlab = "RE Model for all studies")
radial (rescomm)
leave1out (rescomm)


clin <- read.csv("misoclin.csv", header = TRUE)
print (clin, row.names = FALSE)
datclin <- escalc (measure = "IR", xi = X500n, ti = pop, data = clin,
        add = 1/2, to = "only0", append = TRUE,)
print (datclin, row.names = FALSE)
resclin <- rma(yi, vi, data = datclin)
print (resclin)
confint (resclin)
forest (resclin, xlab = "Incedence of PPH", slab = paste(datclin$author,
    datclin$year, sep=(", ")), mlab = "RE Model for all studies")
radial (resclin)
leave1out (resclin)
```

Appendix D

Data used for the analysis

trial	author	year	setting	manage	rando	blind	htime	bmethod	route	geo	age	induce	aug	inst	prevpph	nulli	epis	dose	pop	blm	blsd	500n	1000n	addutern	bloodn	safpop	dthn	fevn	shivn	dihrn	headn
1	Afolabi, E.	2010	0	1	1	0	1	1	1	19	27.1	NA	15	NA	NA	NA	NA	400	100	153.2	NA	0	0	3	NA	100	NA	0	4	NA	NA
2	Al-Sawaf,	2013	0	1	1	0	NA	2	2	5	NA	NA	0	NA	NA	NA	NA	200	28	348	112	2.446302	0	3	NA	NA	NA	NA	NA	NA	NA
3	Amant, F.	1999	0	1	1	1	NA	NA	1	2	29.8	37	NA	15	NA	51	79	600	96	NA	NA	7	1	12	1	86	NA	NA	36	0	NA
4	Aziz, S.	2014	0	1	0	0	1	4	1	20	25.26	NA	11.42	0	NA	NA	48.57	600	35	302.86	160.4	4	0	4	2	35	NA	6	11	NA	NA
5	Bamigboy	1998	0	NA	1	0	3	1	3	22	25	NA	NA	NA	NA	36	73	400	231	187	92	2	0	4	0	NA	NA	NA	NA	NA	NA
6	Bellad, M.	2012	0	1	1	1	NA	3	2	12	23	NA	NA	0	NA	12.5	53.3	400	321	192	124	10	0	1	1	321	0	4	173	NA	NA
7	Bugalho, A	2001	0	NA	1	1	1	1	3	16	25.4	NA	NA	NA	NA	NA	NA	400	323	155	122	0.756773	0	7	2	323	NA	0	123	0	NA
8	Çaliskan, E	2003	0	1	1	1	1	3	1	26	24.4	9.7	68.8	2	NA	46.6	74.4	400	388	328	152	35	14	23	14	388	NA	17	44	15	NA
9	Çaliskan, E	2002	0	1	1	1	2	3	3	26	25.3	10.1	68.6	3.5	NA	48.9	72.4	400	396	NA	NA	39	17	33	12	NA	NA	NA	NA	NA	NA
10	Chandhiol	2006	1	0	0	0	NA	1	1	12	24.3	NA	NA	NA	NA	NA	26.2	600	600	139.7	100.4	4	0	4	1	600	0	58	292	NA	NA
11	Chaudhur	2012	0	1	1	1	NA	2	2	12	22.07	0	0	0	0	67.9	72.5	400	265	153.21	143.51	16	1	20	5	265	0	6	51	2	NA
12	Chhabra, S	2008	0	NA	1	0	NA	1	2	12	22	0	0	NA	NA	60	NA	100	100	150	50	0	0	5	0	100	NA	4	6	NA	8
12	Chhabra, S	2008	0	NA	1	0	NA	1	2	12	22	0	0	NA	NA	62	NA	200	100	150	50	0	0	4	0	100	NA	6	8	NA	6
13	Cook, C.M	1999	0	NA	1	0	2	5	1	17	26	NA	NA	4	NA	NA	NA	400	424	279	14.6	63	13	95	5	424	NA	57/371	79	1	NA
14	Derman, R	2006	1	NA	1	1	24	1	1	12	23.3	0	0	0	0	30.5	NA	600	812	214.3	144.6	52	2	3	1	809	NA	34	419	NA	NA
15	Ejembi, C.	2014	1	0	0	0	1	4	1	19	NA	0	0	0	NA	NA	NA	600	1239	NA	NA	99	NA	5	NA	1239	NA	150	539	NA	NA
16	El-Refaey,	2000	0	1	1	0	NA	4	1	27	30	24	34	22.75	4	47	22	500	501	256	137.039	62	9	68	9	445	NA		319	17	46
17	Enakpene	2007	0	1	1	0	NA	6	1	19	26.8	0	0	NA	0	13.89	NA	400	432	191.6	134.5	6	4.00E-07	33	NA	432	NA	31	23	NA	1
18	Fawzy, A.E	2012	0	1	1	0	1	7	2	15	NA	NA	NA	NA	NA	100	NA	200	100	208.81	125.39	2	0	NA	NA	100	NA	4	31	NA	NA
18	Fawzy, A.E	2012	0	1	1	0	1	7	3	15	NA	NA	NA	NA	NA	100	NA	200	100	258.3	140.55	4	0	NA	NA	100	NA	5	21	NA	NA
19	Garg, P.	2005	0	NA	1	0	1	NA	1	12	22.86	NA	NA	NA	NA	NA	NA	600	100	124.1	NA	8	NA	10	NA	100	NA	29	31	3	4
20	Geller, S.	2014	1	NA	0	0	1	1	1	9	24.4	0	0	0	NA	34.4	NA	600	82	NA	NA	1	NA	NA	NA	93	0	4	27	NA	NA
21	Gerstenfe	2001	0	NA	1	1	1	1	3	28	27.8	41.79104	35.32338	NA	1.3	NA	NA	400	159	NA	NA	70	15	36	2	159	NA	NA	7	0	NA
22	Gulmezog	2001	0	1	1	1	1	3	1	17	26.5	NA	NA	9	NA	45	NA	600	9227	NA	NA	1830	366	1398	72	9227	2	559	1620	35	NA
23	Gupta, B.	2006	0	1	1	1	NA	3	3	12	NA	NA	NA	NA	NA	NA	NA	600	100	161.67	76.81	1	0	5	NA	100	NA	2	16		NA
24	Harriott, J	2009	0	1	1	0	NA	1	3	14	28	NA	NA	4.285714	0	NA	NA	400	70	180.1	120	1	0	6	0	70	0	0	11.48	0	NA
25	Hashima e	2011	1	0	0	0	1	4	1	1	23	NA	NA	NA	NA	NA	NA	400	884	NA	NA	14	NA	3	0	884	NA	11	11		NA
26	Hoj, L.	2005	0	1	1	1	1	3	2	10	23	NA	NA	NA	6.1	NA	NA	600	330	443	338.2936	150	37	NA	NA	330	1	78	189	10	NA
27	Kundodyiv	2001	0	1	1	1	0.1	3	1	30	24.4	NA	NA	0	0	51	37.4	400	243	NA	NA	37	9	13	NA	243	0	18	106	3	NA
28	Lam, H.	2004	0	1	1	0	NA	5	2	11	29.6	0	0	0	0	50	NA	600	30	NA	NA	4	1	3	NA	30	NA	10	10		NA
29	Mansouri,	2011	0	1	1	0	1	4	1	21	26.76	NA	NA	NA	NA	63.4	NA	600	309	232.8	151.2	15	2	94	1	309	NA	86	161	9	NA
29	Mansouri,	2011	0	1	1	0	NA	4	3	21	27.48	NA	NA	NA	NA	50.15	NA	600	309	207.2	93.4	10	1	92	0	309	NA	47	81	2	NA
30	Miller, S.	2009	0	1	1	1	NA	1	1	25	27	NA	NA	NA	NA	30.85375	50.4	600	484	304.3	218.1	60	10	64	NA	483	0	13	75	11	NA
31	Mir, A.M.	2012	1	NA	0	0	4	4	1	20	28	0	0	0	NA	23.78976	NA	600	784	NA	NA	40	NA	NA	NA	260	3	68	178	NA	NA
32	Mirteimou	2013	0	1	1	1	4	4	3	13	29.7	NA	NA	NA	0	NA	NA	400	200	NA	NA	38	NA	36	8	200	NA	0	1	0	31
33	Mobeen, I	2011	1	1	1	1	1	3	1	20	28	0	0	NA	NA	19.3	NA	600	514	337	226	85	10	NA	NA	533	0	4	50	1	6
34	Mukta, M.	2013	0	1	1	0	1	1	1	12	NA	NA	NA	NA	NA	NA	NA	600	100	145	NA	8	NA	22	NA	100	NA	6	50	10	NA
35	Nasr, A.	2009	0	1	1	1	24	4	3	5	27.4	NA	NA	NA	NA	0	NA	800	257	NA	NA	17	NA	6	8	257	NA	48	80	6	NA
36	Nellore, V.	2006	0	NA	1	0	1	4	3	12	NA	0	0	NA	NA	NA	NA	400	60	245	158	4	0	10	1	60	NA		5	3	NA
37	Ng, P.S.	2001	0	1	1	0	1	4	1	11	28.1	16.08187	15.8	NA	1.1	52.7	88.7	600	1026	296	160	60	5	232	15	1026	NA	87	310	NA	81
38	Oboro, V.(	2003	0	1	1	1	1	4	1	19	23.6	0	0	NA	0	49	28	600	247	341	19.3	3	0	31	0	247	NA	3	141	7	NA
39	Ozkaya, O	2005	0	1	1	0	1	2	3	26	26.2	NA	NA	NA	NA	14.58333	83	400	48	171.4	106.2	0.048894	0	2	NA		NA	NA	NA	NA	NA
40	Prata, N.	2006	0	1	0	0	1	4	1	5	25.2	NA	NA	NA	0.5	34.6	NA	600	1178	244.17	167.8451	19	1	2	NA	1178	NA	280	253	NA	NA
41	Rajaei, M.	2014	0	NA	1	1	1	2	1	13	NA	NA	NA	NA	NA	NA	NA	400	200	157	84.9	0.005619	0	9	1	200	NA	29	2	NA	NA
42	Sadiq, U.G	2011	0	1	1	0	1	1	1	19	NA	NA	NA	NA	NA	NA	NA	600	900	327.68	118.5	80	6.61E-06	NA	NA		NA	NA	NA	NA	NA
43	Sharma, N	2014	0	1	0	0	1	1	2	12	24.07	NA	NA	0	NA	51	NA	600	100	101.45	56.24	1	0	1	NA	100	NA	11	23	NA	0
44	Shrestha,	2011	0	1	1	0	NA	3	3	18	22.8	NA	NA	NA	NA	NA	NA	1000	100	156.7	124.2	4	5.93E-10	NA	NA	100	0	25	25	NA	NA
45	Singh, G.	2009	0	1	1	1	NA	2	2	12	24.17	NA	NA	NA	NA	34.7	NA	400	75	126.24	49.3	1.50E-12	0	2	0	75	NA	9	6	NA	NA
45	Singh, G.	2009	0	1	1	1	NA	2	2	12	23.83	NA	NA	NA	NA	44	NA	600	75	96.05	21.1	0	0	0	0	75	NA	16	13	NA	NA
46	Surbek, D.	1999	0	1	1	1	24	4	1	23	29.3	23	58	13	0	52	NA	600	31	345	108.5714	2	0	5		31	NA	NA	6.82	NA	NA
47	Tewatia, R	2014	0	1	1	0	NA	1	2	12	25.1	NA	NA	NA	0	46	NA	600	50	149.5	30.8	0	0	7	0	50	NA	13	10	0	NA
48	Vagge, D.S	2014	0	1	1	0	NA	NA	3	12	28.82	NA	NA	NA	0	NA	NA	800	100	321.72	87.78	4	6.00E-13	3	1	100	NA	12	15	5	NA
49	Vaid, A.	2009	0	1	1	0	1	3	2	12	26.04	NA	NA	10.61	NA	NA	66.67	400	66	NA	NA	8	NA	9	1	66	NA	13	29	1	NA
50	Vimala, N.	2004	0	1	1	0	1	3	2	12	25.6	0	0	3.3	NA	NA	60	400	60	185	56	2	0	5	0	60	NA	4	13	NA	3
51	Walley, R.	2000	0	1	1	1	NA	NA	1	9	25.7	0	0	NA	0	46	36.5	400	203	190	78	0	0	6	0	176	0	12	39	2	NA
52	Walraven,	2005	1	1	1	1	1	2	1	8	25.9	0	0	0	NA	9.4	NA	600	629	281	175	69	2	NA	NA	630	2	NA	202	6	NA
53	Zachariah,	2006	0	1	1	0	NA	1	1	12	24.4	NA	NA	7.7	NA	NA	NA	400	730	192.5	131	19	1	63	1	730	NA	48	68	1	2
54	Al-Harazi	2009	0	1	0	0	2	1	2	29	22.8	NA	NA	0	NA	NA	17.8	600	118	362.3	170	9.086	3	3	1	118	NA	NA	14	1	1
54	Al-Harazi	2009	0	1	0	0	2	1	3	29	22.7	NA	NA	0	NA	NA	16.5	600	97	342.3	154.7	6.887	4	2	1	97	NA	NA	5	0	0
55	Ng P.S.	2007	0	1	1	1	24	4	1	11	28.8	NA	19.7	NA	1.7	54.5	93.8	400	178	289	178	18	2	41	8	178	NA	7	35	0	8
56	Wangwe,	2009	0	1	1	0	NA	NA	3	24	NA	0	NA	NA	NA	NA	NA	400	210	NA	NA	9	NA	9	4	210	NA	NA	7	NA	1

Abbreviations and legend: 1000n = number of women bleeding 1000 ml or over; 500n = number of women bleeding 500 ml or over; addutern = additional uterotonics needed; aug = augmentation of labour; blind = blinding; blm = mean blood loss; bloodn = blood transfusion needed; blsd = blood loss standard deviation; dihrn = number

of women with diarrhea; dthn = number of death; epis = episiotomy; fevn = number of women with fever; geo = geographical location of the trial; headn = number of women with headache ; htime = time of observing hemorrhage; induce = induction of labour; inst = instrumental delivery; NA = not available; nulli = nulliparous; pop = population; prevpph = previous PPH; rando = randomisation; safpop = safety population; shivn = number of women with shivering;.

Value	setting	manage	rando	blind	bmethod	route	geo		
0	Clinical	Passive management of labour	Non-randomised	Open label					
1	Community	Active management of labour	Randomised	Blinded trial	calibrated measuement	Oral	Bangladesh		
2					weighted pads	Sublingual	Belgium		
3					1 & 2	Rectal	Canada		
4					visual or clinical estimation		Canada		
5					4 & 1		Egypt		
6					4 & 2		Ethiopia		
7					Hematocrit difference		France		
8							Gambia		
9							Ghana		
10							Guinea-Bissau		
11							Hong Kong SAR, China		
12							India		
13							Iran		
14							Jamaica		
15							Libya & Egypt		
16							Mozambique		

17							Multi-National		
18							Nepal		
19							Nigeria		
20							Pakistan		
21							Saudi Arabia		
22							South Africa		
23							Switzerland		
24							Tanzania		
25							Tibet		
26							Turkey		
27							UK		
28							USA		
29							Yemen		
30							Zimbabwe		

Key findings and potential impact

General discussion and conclusion

Throughout the previous two articles, the main aim was to synthesize all available evidence on misoprostol treatment for PPH prevention into one comprehensive and informative evidence that addresses and answers areas that has not been adequately studied before.

We set out to answer three questions, namely:

A) In labouring mothers receiving 400µg misoprostol, compared to labouring mothers receiving 600µg misoprostol, is the incidence of postpartum haemorrhage higher?
B) In deliveries outside healthcare facilities, would administering misoprostol to labouring mothers, compared to deliveries inside healthcare facilities, be more protective against postpartum haemorrhage?
C) In labouring mothers who receive misoprostol alone, compared to labouring mothers who receive misoprostol as part of the active management of the third stage of labour, is the incidence of postpartum haemorrhage higher?

Article 1 "Misoprostol Dosage and Side-effects for the Prevention of Postpartum Haemorrhage: A systematic review and network meta-analysis on 400 µg misoprostol vs. 600 µg misoprostol" answers our first question through the utilisation of network meta-analysis under a Bayesian model. This was a necessary due to the paucity of head to head trials comparing these two doses.

The result suggests that there is no difference in the comparative effectiveness of misoprostol 400 µg to misoprostol 600 µg.

Since our findings depends on the lack of statistical significance between the interventions, a discussion of statistical power is important; in many occasions, individual trials are not sufficiently powered to detect specific differences between interventions, and meta-analysis is the only way to have adequate power (1). We have noticed that the topic of power determination, in NMA and conventional pairwise meta-analysis, is a recent emergent issue of debate among experts of evidence synthesis in Canada. The issue of the need for power analysis and a margin for non-inferiority or clinical equivalence does not seem to have been established in the field of evidence synthesis; no mention of its need is yet presented in guidelines for meta-analysis or NMA (1-3).

In developing an RCT, testing if the effect of two interventions is similar would have required prior power analysis with either a non-inferiority margin or a clinical equivalence margin (4-6). Such margin is commonly determined by examining previous trials of each intervention and reaching an agreement with clinical experts and regulators on the margin at which clinical significance is manifested. In the field of evidence synthesis, and especially in NMA, we are including all possible evidence and there is no previous trials of similar or higher level evidence to base the power analysis on. Although, with some outcomes, such as safety outcomes, many of the included trials in a meta-analysis would not have sufficient power to detect a difference, it is unlikely that the same issue would appear with the main outcome of said trials.

Specifically, in our research, one large and well conducted study, that is included in the NMA, has determined an acceptable clinical equivalence margin between two uterotonics at 35% for the outcome of blood loss of 1,000 ml or more, and that, to provide a 90% power for a two sided 5% level, 20,246 women were needed (7). Our network for the outcome of "bleeding 1,000 ml or over" has a population of 42,862. It is also expected that for the outcome of "bleeding 500 ml or over" the clinical equivalence margin would be higher (since the clinical scenario is not as severe), and the frequency of such bleeding would be higher, requiring considerably less sample size to provide sufficient power.

Our finding has the potential to alter the perception that a 600 µg dose is necessary to provide a level of protection against post-partum hemorrhage. As a dose of 400 µg misoprostol consists of two tablets of misoprostol (misoprostol is usually distributed in tablets of 200 µg) which can infer the same protection as the three tablets. A two tablets regimen will be easier to manage by the birth attendant and/or the labouring mother, easier to distribute and keep track of, and cheaper to implement.

Although the side effects of 400 µg were not statistically significantly lower than the 600 µg, the point estimates were consistently lower. It could be assumed that, despite showing no statistically significant differences in the number of mothers with shivering and fever, these side effects might be of lower intensity. Unfortunately, there is no way to measure the intensity of shivering and fever from the trials we identified.

Despite the large number of included studies, our research is not without its limitation, we discussed these limitations that are associated with each article previously. Briefly: lack of sufficient head to head trials comparing different doses of misoprostol, the statistical heterogeneity, and the nature of regression analysis are important limitations.

None the less, our findings can lower the financial and human resources threshold needed to implement a PPH prevention campaign using misoprostol.

Article 2, despite being descriptive in nature, has possible implication on three key areas in women's health; clinical, policy, and research methodology.

The synthesized evidence on the incident of PPH hemorrhage provides an easy to understand measure on how many PPH to expect when using misoprostol for the prevention of PPH. This information is valuable for both policy and clinical decision making.

Article 2 proceeded forward by running a meta-regression using mixed effects model on a large number of predefined potential treatment effects modifiers. Specific to our questions are the settings in which misoprostol was administered and the type of labour management that was practiced during labour. Both of these factors had no effect on the overall heterogeneity of the pooled incidence. Indicating that the type of management (active versus passive) and the setting of administering misoprostol (community versus clinical) both had no effect on the effectiveness on misoprostol for the prevention for PPH.

The finding that labour managements and settings has no effect on the efficacy of misoprostol answers the last two questions of this thesis. It also provides an important piece of information to policy makers that distributing misoprostol to rural areas to be administered without any other measure of labour management is as effective as giving it in a hospital setting under the supervision of a specialised obstetrician who is performing cord traction, early cord clamping, and uterine massage.

It is important to note that, under these findings, we are not advocating the abandoning of proper maternal care and infrastructure. However, we view the need of misoprostol for the prevention of PPH as a bridge to use until proper maternal care and infrastructure are provided for communities who are either suffering from poor resources or geographically isolated.

The value of article 2 extends further to inform on the proper methodological conduct of trials for PPH. Blinding of the trial, induction of labour, and previous history of PPH were three factors that accounted for the majority of observed statistical heterogeneity.

In a predictive model based on the meta-regression, trials that are not blinded were much more likely to underestimate the incident of PPH. This further reinforces the necessity to conduct blinded trials whenever possible to avoid confirmatory bias.

Induction of labour and previous history of PPH are other two factors that have accounted for large amount of the observed statistical heterogeneity. In our predictive model, the higher the percentage of women with induction of labour or previous history of PPH, the higher the incidence of PPH. These factors were recorded in almost half of the studies, indicating the need for better capturing of these variables in future trials.

Also of interest are the factors that did not contribute to the observed statistical heterogeneity in a statistically significant manner. Despite having different approaches in the method to assess bleeding, these differences did not affect the incidence of PPH. It could be that all of these methods are naturally semi-objective and as such are similar in overall effect, another possibility is that we did not have sufficient observations to account for the true effect of the differences in the method of collecting blood.

Similarly, the dose of misoprostol did not have an effect on the outcome. This further supports our finding in article 1 that misoprostol 400 µg is of equal efficacy to 600 µg. In addition to the dose, the route of administration did not exhibit an effect on the outcome.

The potential impact of these two articles lies primarily in it providing evidence that 400 µg can be as effective as 600 µg misoprostol, even in the absence of clinical settings and other aspects of active management of labour. This would allow policy makers and practitioners to provide a lower dose that would give the same effect as the higher dose, and feel confident to provide these pills in resource-poor communities. Thus saving vulnerable mothers in rural and poor communities from PPH, reducing any potential harms with a higher dose and lowering the costs of PPH prevention.

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