# IMPROVING MATERNAL AND FETAL PREGNANCY OUTCOMES

# IMPROVING MATERNAL AND FETAL PREGNANCY OUTCOMES BY PREVENTING POSTPARTUM HAEMORRHAGE AND MOTHER TO CHILD TRANSMISSION OF HIV IN PREGNANCY

**By**

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# TITLE: IMPROVING MATERNAL AND FETAL PREGNANCY OUTCOMES BY PREVENTING POSTPARTUM HAEMORRHAGE AND MOTHER TO CHILD TRANSMISSION OF HIV IN PREGNANCY

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*This thesis is dedicated to the memory of my dear father,* ***Chief Justice Henry NJINJU MORFAW****, who was relentless in his efforts to ensure his children had the very best. Papa, you left us on the 21/03/2017. The vacuum can never be filled. You are my role model forever!!!*

## ABSTRACT

### Background and Objectives:

Postpartum haemorrhage (PPH) and mother to child transmission (MTCT) of the Human Immune Deficiency Virus (HIV) are major threats to maternal and foetal health, especially in low and middle income countries. This thesis addressed two main objectives: 1) to investigate strategies for the prevention of PPH, with a focus on misoprostol; 2) to investigate strategies for prevention of mother to child transmission (PMTCT) of HIV, with a focus on the male partner.

### Methods:

We employed a number of study designs including a cross sectional design, a retrospective chart review, and a systematic review which included Classical and Bayesian approaches of meta-analysis. Key methodological issues addressed include the use of propensity score matching methods to address channeling bias; comparison and combination of evidence from different sources; sensitivity analysis in health research; and methods for developing new tools for measurement in health research.

### Results and Conclusions:

Our findings suggests that an oxytocin-misoprostol combination is better than the current standard of care of oxytocin-only which is recommended by the World Health Organisation for the prevention of PPH. Secondly, effectiveness data from well-designed observational studies may be used to inform clinical decisions on misoprostol in the prevention of PPH. Thirdly, using a new tool we have created, it is possible to objectively identify HIV positive women who lack the support of their male partners in adhering to PMTCT recommendations.

## Publications Related to this Thesis

1. Morfaw F, Fundoh M, Pisoh C, Ayaba BL, Mbuagbaw L, Anderson LN, Thabane L. (2019). "Misoprostol as an adjunct to oxytocin can reduce postpartum-haemorrhage: A propensity score–matched retrospective chart review in Bamenda-Cameroon, 2015-2016". *BMC Pregnancy and Childbirth 2019 Jul 22;19(1):25.*

2. Morfaw F, Miregwa B, Ayaba BL, Mbuagbaw L, Anderson LN, Thabane L. (2019). "Comparing and combining evidence of treatment effects in randomised and non-randomised studies on the use of misoprostol to prevent post-partum haemorrhage". *BMC Systematic Reviews*, potentially acceptable for publication.

3. Morfaw F, Mbuwe C, Ayaba BL, Anderson LN, Mbuagbaw L, Thabane L. (2019). "Development of a scale to assess male partner involvement in the prevention of mother-to-child transmission of HIV". *Maternal and Child Health Journal:* under review

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# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AIDS | Acquired Immune Deficiency Syndrome |
| AMTSL | Active Management of the Third Stage of Labour |
| ANC | Antenatal Care |
| ART | Antiretroviral therapy |
| CD4 | Cluster of differentiation 4 |
| CEM | Coarsened Exact Matching |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CrI | Credible Interval |
| CVR | Content Validity Ratio |
| EMBASE | Excerpta Medica dataBASE |
| HIV | Human Immune Deficiency Virus |
| IHP | International Health Partners |
| IPTW | Inverse Probability of Treatment Weighting |
| IU | International Units |
| LFAM | Life For African Mothers |
| LIC | Low Income Country |
| LMIC | Low and Middle Income Country |
| ln | Natural logarithm |
| MEDLINE | Medical Literature Analysis and Retrieval System Online |
| MTCT | Mother to Child Transmission |
| NRS | Non-Randomised Study |

| | |
|---|---|
| OR | Odds Ratio |
| PMTCT | Prevention of Mother to Child Transmission |
| PPH | Post-partum Haemorrhage |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PS | Propensity score |
| RCT | Randomised Controlled Trial |
| RHB | Regional Hospital Bamenda |
| ROR | Ratio of Odds Ratio |
| RR | Relative Risk |
| SAMPP | Scale Assessing Male Partner Participation |
| SD | Standard Deviation |
| SE | Standard Error |
| SPSS | Statistical Package for the Social Sciences |
| UNAIDS | The Joint United Nations Programme on HIV/AIDS |
| UNICEF | United Nations Children's Fund |
| var | variance |
| WHO | World Health Organisation |

# DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis is prepared as a sandwich thesis of five chapters, three of which (chapters 2-4) are projects prepared for publication in peer reviewed journals. Chapter 1 introduces the research topic, laying out the foundation and rational for the rest of the studies included in the thesis. Frederick Morfaw is the sole author of this chapter, and this chapter is unpublished.

Frederick Morfaw's contribution to chapters 2-4 include: conception of the research ideas, developing of the research questions, designing the studies, developing the protocols and statistical analysis plans, collecting the data, conducting the quantitative analysis, drafting and submitting the manuscripts and responding to the comments from reviewers. Contributions of the co-authors include designing the studies, assisting with data collection providing guidance with data analysis and reviewing several versions of the manuscripts. All authors read and approved the final manuscripts of each study.

Chapter 5 provides a summary of the thesis, and outlines its contribution to health research. FM is the sole author of this chapter, and this chapter is unpublished.

The work in this thesis was conducted between Fall 2017 and Summer 2019.

# CHAPTER 1

# INTRODUCTION

# INTRODUCTION

This thesis is primarily focused on maternal health. Two pillars of maternal health are addressed, namely the prevention of postpartum haemorrhage (PPH) and the prevention of mother to child transmission (PMTCT) of the Human Immune-Deficiency virus (HIV). Several research designs were used to address important research questions in these two areas. In this chapter, an overview of these two clinical issues is provided; the objectives of the thesis are described; key methodological issues addressed in the thesis are discussed; and the thesis outline is provided.

## I. CLINICAL ISSUES ADDRESSED IN THE THESIS

### A. POSTPARTUM HAEMORRHAGE

#### *Introduction*

The death of a woman while pregnant or in childbirth is a devastating experience for the family, the medical team and the community. Bleeding after childbirth or postpartum haemorrhage (PPH) is the leading cause of maternal death worldwide (1), responsible for approximately 35% of all maternal deaths (2). Even though PPH is a well-managed condition in high income countries, the morbidity and mortality from this condition remains high in low and middle income countries (LMIC) where it is estimated to be responsible for about 60% of all maternal deaths (3). In 2015, there were over 303,000 pregnancy-related deaths worldwide, with the majority of these occurring in resource limited settings (4).

#### *Definitions of PPH*

The World Health Organisation (WHO) defines PPH as “blood loss greater than or equal to 500 ml within 24 hours after birth”, and severe PPH is defined as “blood loss greater than or equal to

1000 ml within 24 hours" (5). Other definitions of PPH include bleeding in excess of 500 mL within the first 24 hours following following vaginal delivery or more than 1000 mL following caesarean delivery (6,7). PPH has also been defined as "any blood loss following childbirth (irrespective of the mode of delivery) which is sufficient to cause either a hypovolemia, a 10% drop in the hematocrit or necessitates the transfusion of blood products" (8).

A distinction is usually made between primary PPH which refers to excessive blood loss occurring in the first 24 hours after childbirth, and secondary PPH which refers to excessive blood loss occurring at least 24 hours to 12 weeks after delivery (9). The focus of this thesis is on primary PPH.

***Causes of PPH***

PPH is primarily caused by uterine atony, which refers to inadequate uterine contractions after childbirth (1). Other causes include retained placenta, genital tract lacerations and clotting disorders. Together these four causes are referred to as the "4 Ts", referring to Tone, Tissue, Trauma and Thrombosis respectively (10). It is estimated that 75% to 90% of cases of PPH are due to uterine atony (10). Known risk factors for PPH include, but are not limited to, multiple gestation, grand multiparity (≥5 deliveries at term), a prior history of PPH, and prolonged labour (11). However, the majority of cases of PPH occur in women without any identifiable risk factors (11).

***Symptoms of PPH***

Symptoms of PPH include but are not limited to uncontrolled bleeding after childbirth, hypotension, tachycardia, tenderness and tumefaction of vaginal and perineal tissues, and a drop

in the hematocrit. In the absence of timely interventions, the massive blood loss eventually leads to multiple organ dysfunction and subsequent maternal death (12).

***Prevention of PPH***

The majority of cases of PPH and their associated morbidity could be avoided by the use of safe and effective interventions to prevent PPH. The routine use of uterotonic agents to enhance uterine contractions following childbirth in all women is paramount to the prevention of PPH, especially as its occurrence is usually unpredictable (1). This has to be provided as a package of "good-quality care" which is a basic human right (12). For this to be truly realized, it is important to have adequately trained health personnel with adequate medication throughout the entire health systems (12). In addition, there is a need for the provision of updated evidence-based recommendations to health decision makers and key stakeholders to inform health policy decisions concerning the prevention of PPH (12).

The administration of a prophylactic uterotonic agent is a key component of efforts to prevent PPH, and WHO recommends the use of oxytocin (10 IU, intra venous/intra-muscular) as the uterotonic drug of choice for this purpose (13). Although there exist several other uterotonic drugs which can be used for the prevention of PPH, the use of misoprostol as an affordable and feasible intervention has always been at the forefront of research (14).

Misoprostol is a prostaglandin E1 analog with potent uterotonic properties (14). It is an affordable and stable medication with a long shelf life, which can be administered orally, sublingually, vaginally or rectally (14). The drug is absorbed within 9 to 15 minutes following oral, sublingual, rectal or vaginal administration, and has a half-life of 20-40 minutes (14). Its use in obstetrics is off-label as the drug was developed for the treatment of peptic ulcers (14).

However, given its potent uterotonic effects, easy storage and its easy administration, it has found a wide variety of applications in the field of obstetrics. It is recommended by WHO for the prevention of PPH in settings where oxytocin is either unavailable or its quality cannot be guaranteed (12).

Research is needed not only to develop new interventions, but also to improve upon existing interventions in order to help reduce the burden of PPH (15). Amidst these efforts has been a systematic review of 17 randomised controlled trials (RCTs) involving 29,797 women which compared misoprostol versus injectable uterotonics in the prevention of severe PPH (16). The results showed a higher risk of severe PPH with misoprostol compared to conventional uterotonics (Relative risk (RR) 1.33; 95% confidence interval (CI) 1.16 to 1.52) (16). A Meta-analysis of three trials (3509 women) assessing the use of misoprostol versus placebo in the prevention of PPH in situations without access to conventional uterotonics showed a reduction in the incidence of severe PPH (RR 0.59, 95% CI 0.41 to 0.84) (17). Recently, Gallos et al conducted a network meta-analysis of 140 trials (88, 947 women) aimed at identifying the most effective uterotonic drug for the prevention of PPH, and to clinically rank all available uterotonic treatments (1). Their review permitted the standardising of trial eligibility, risk of bias assessment and outcome reporting which had been a source of discrepancy in previous meta-analyses (15). They concluded on the greater efficacy of ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination in the prevention of PPH than the current standard oxytocin (1).

These efforts notwithstanding, prioritizing the development of evidence for the use of misoprostol in the prevention of PPH is important especially in LMICs who are disproportionately affected by PPH. Its use in these settings seems not only feasible and

acceptable but is probably highly cost effective. It is therefore important to update and consolidate the local evidence-base on the efficiency of this medication in these settings, such that recommendations for change are based more on locally applicable evidence.

## B. MOTHER TO CHILD TRANSMISSION OF HIV

### *Introduction*

Mother to child transmission (MTCT) of the Human Immune Deficiency Virus (HIV), also called "Vertical transmission of HIV" refers to the transmission of the HIV virus from a mother to her infant, during pregnancy, labour, delivery or breastfeeding (18,19). It is estimated that about 95% of the over 3 million children below the age of 15 years living globally with HIV acquired the infection through MTCT (18). The majority of these children live in LMIC, especially sub-Saharan Africa (20). In 2016 alone, it was estimated that 160,000 children got infected with HIV (21), with a slightly higher number of 180,000 in 2017 (22). There has been a progressive rise in the prevalence of HIV in LMICs since the early 80s (23). The Joint United Nations Programme on HIV/AIDS (UNAIDS) established the 90-90-90 targets as a means of ending the HIV pandemic by 2030 (24). This target which aims at diagnosing 90% of all HIV-positive persons; providing antiretroviral therapy (ART) for 90% of those diagnosed; and achieving a 90% viral suppression for those treated by 2020, is achievable via the respect of human rights, mutual respect and inclusion (24). The target prioritizes equity, and specifically seeks to close the treatment gap for children among other key populations (24). Prevention of mother to child transmission of HIV is important if this target is to be met.

### *Timing of mother to child transmission of HIV and risk factors for transmission*

The exact timing of MTCT of HIV remains speculative (25). In the absence of any intervention, the risk of MTCT of HIV is about 15% to 30% during pregnancy and labour, with an added 10% to 20% risk with breastfeeding (19). There is evidence that suggests that this risk of transmission can be reduced to < 2% with the use of appropriate antiretroviral therapy (ART) during gestation, childbirth and the breastfeeding period (25).

Risk factors for MTCT include, but are not limited to, high maternal HIV viral load, low maternal CD4 count, advanced HIV disease, vaginal delivery, genital bleeding, prolonged rupture of membranes, chorioamnionitis, and the presence of other sexually transmitted infections (19). Prolonged breastfeeding (predominantly in mothers not on ART), mixed feeding and maternal seroconversion during the breastfeeding period are additional risk factors for MTCT (19).

### *Prognosis*

The prognosis of infants infected with HIV through MTCT is quite variable. In some cases, about a quarter of these children will rapidly progress to Acquired Immune Deficiency Syndrome (AIDS) or even die within the first year of life, while in other cases, survival up to the age of 12 has been documented even in the absence of ART (26).

### *Prevention of mother to child transmission (PMTCT) of HIV*

Efforts to eliminate new HIV infections among children must support pregnant women to have access to appropriate antenatal care and antiretroviral medication for themselves and their children throughout pregnancy and breastfeeding (21). Prevention of mother-to-child

transmission (PMTCT) of HIV programmes are known to be highly effective, and to potentially be able to improve maternal and child health (27). They are aimed at reducing MTCT of HIV, improving infant survival, while minimising side effect (19). They enabled the prevention of 1.4 million paediatric infections worldwide between 2010 to 2018 (22).

PMTCT programmes are essentially made up of 4 components which include: primary prevention of HIV infection among women of childbearing age; prevention of unintended pregnancies among women living with HIV; prevention of HIV transmission from a woman living with HIV to her infant; and the provision of appropriate treatment, care and support to mothers living with HIV and their children and families (27).

In 2016, the United Nations General Assembly set as target a 95% reduction of new paediatric HIV infections by 2020 (22). Much still needs to be done if this ambitious target is to be achieved, especially in Africa where coverage gaps exists with MTCT rates as high as 20.2% in West and Central Africa (22).

One of the major drivers of PMTCT is the proposal of the Option B+ strategy in the 2012 WHO guideline which recommends lifelong ART for HIV-infected pregnant women irrespective of their CD4 count or clinical stage of disease (28). As well-intentioned as this strategy may be, it is probably limited by the ability of pregnant women to actually access care. If new HIV infections among children are to be prevented, pregnant women need to be supported in their effort to access antenatal care and anti-retroviral medication (21).

The entry point into most PMTCT services is voluntary counselling and testing for HIV (29). There is evidence to suggest that most women tested as part of this routine antenatal care do not inform their male partners of their HIV positive results due to fears of abandonment,

stigmatisation or domestic violence (29,30). One commonality in LMICs is the decisive role of male partners in the utilisation of maternal health care services by their female partners (31). It is believed that the success of PMTCT programs not only depends on the use of anti-retroviral therapy by the mothers in need, but also the amount of support received by these women from their male partners (32).

Evidence suggests that male partner involvement enhances the utilisation of PMTCT services by their female partners (33). This includes increased uptake of prophylactic antiretroviral therapy by their infected female partners during pregnancy (29,34), increased condom use within the couple (29), and improved adherence to recommended PMTCT feeding options (34–36).

Conversely, inadequate involvement of the male partner in the PMTCT cascade has been cited as a major contributor for the reduced effectiveness of PMTCT programmes (32,37). Barriers and facilitators of male partner involvement in the PMTCT cascade have been identified in a bid to facilitate male involvement in PMTCT of HIV (31). Efforts to augment the utilisation of maternal health care services in general must take into consideration the potentially influential role of the male partners, and seek strategies to minimise the barriers and enhance the facilitators of male partner involvement in PMTCT of HIV (31). This is crucial if women are expected to initiate the PMTCT cascade and be retained within the PMTCT programmes after giving birth.

Few attempts have been made to measure the extent of male partner involvement in PMTCT of HIV (38,39). Furthermore, there is a lack of a validated and reliable tool for this purpose. Hence reports of male partner involvement in PMTCT of HIV have been diverse, based on varied personalised items which individual investigators view as relevant.

## II. THESIS OBJECTIVES

This thesis addressed two main objectives: 1) to investigate strategies for the prevention of post-partum haemorrhage, with a focus on the use of misoprostol; 2) to investigate strategies for the prevention of mother to child transmission of HIV, with a focus on the role of the male partner.

The specific research questions addressed in this thesis were:

1. What is the effect of the routine administration of 600-μg misoprostol as an add-on to oxytocin on pregnant women after placental removal in the prevention of PPH?
2. How do the results from RCTs and non-randomised studies (NRS) on the use of misoprostol in the prevention of PPH compare, and what is the geographical location of different sources of evidence?
3. How do the different ways of combining results from RCTs and NRS on the use of misoprostol in the prevention of PPH compare?
4. How do we measure male partner involvement in PMTCT of HIV?

Responses to these questions will help determine better strategies to prevent bleeding after delivery in resource constrained settings, and provide a tool to measure male partner participation in HIV antenatal care, with the overarching aim of improving maternal and foetal outcomes in pregnancy.

## III. KEY METHODOLOGICAL ISSUES ADDRESSED IN THIS THESIS

The following key methodological issues were addressed:

1) The use of propensity score matching methods to address channeling bias;

2) Comparison and combination of evidence from different sources (RCTs and NRS);

3) Sensitivity analysis in health research;

4) Methods for developing new tools for measurement in health research.

The use of observational data to investigate the relationship between exposure and outcomes in real practice settings is subject to confounding bias given that subject characteristics usually influence treatment selection (40). It is important to therefore account for these systematic differences in baseline characteristics between treated and untreated subjects when estimating treatment effects using observational data (40). The first paper in this thesis dealt with this.

The traditional way of accounting for these systematic differences in baseline characteristics has been the use of regression adjustment (40). More recently however, the propensity score (PS) has been used to minimise or eliminate the effect of confounding when using observational data to estimate treatment effects (40). There are numerous ways of using the propensity score (PS) to adjust for confounding in observational data (40,41). We explored each of these methods, comparing the findings with one another.

The second methodological issue addressed in this thesis is the comparison and combination of evidence from different sources (RCTs and NRS). This was dealt with in our second paper.

Comparison of estimates of the same quantity derived from separate analysis has become common practice in clinical research (42). There is a longstanding debate as to whether the results of NRS agree with that of RCTs on the same subject (43). It was therefore important to know how the pooled estimates from NRS on the use of misoprostol in the prevention of PPH compared with that from RCTs.

Increasingly, systematic reviews include NRS of treatment effects (44). It is hypothesised that combining these studies with RCTs, which are generally smaller, may result in the meta-

estimates being weighted towards the NRS estimates given their larger sizes (44). We compared two Classical ways of combining the results of the RCTs and NRS against Bayesian methods of combining results across these two study designs. The classical methods of combining results were a straight forward pooling ignoring study design, and an inverse variance weighted pooling which took into account the greater variability in NRS. The Bayesian method of pooling used a "non-informative" prior distribution, an "informative" prior distribution generated from the NRS and a "sceptical" prior distribution generated from the NRS.

The third methodological issue we addressed was the use of sensitivity analyses in health research.

Simply put, sensitivity analyses are "a critical way to assess the impact, effect or influence of key assumptions or variations on the overall conclusions of a study" (45). This is because during the design and analysis of medical research, certain assumptions are made which may impact the final conclusions (45). If the results of the sensitivity analysis are consistent with that of the main analysis, it reinforces the credibility of the findings (45). In two of the papers included in this thesis, we made certain key assumptions in the main analysis. It was therefore important to use varied analytic methods to assess the robustness of the results and conclusions based on our primary analysis (45).

In our first paper which addressed confounding, we used propensity score matching with conditional logistic regression on the matched pairs as the main method of analysis. Other methods of PS matching as well as multiple logistic regression served as sensitivity analysis. Our reason for comparing the use of multiple logistic regression and propensity score analysis in channeling bias was because each method has its own advantages and drawbacks, and there is

some debate about which of these methods is superior when dealing with confounding in observational data (41).

In our second paper which addressed combining data from different study designs, Classical methods of combining data from different sources served as the main analysis, while Bayesian methods of combining data under different prior assumptions served as sensitivity analysis. These sensitivity analyses helped to assess the robustness of our results and improve upon its overall credibility (45).

The final methodological issue addressed was the method of developing a new tool for measurement in clinical research.

The demand for the development of new and standardised tools for measurement in clinical research is on the rise either due to a lack of tools in general or a lack of reliable and valid tools for a particular setting (46). Key methodological issues needed in the development of measurement tools in clinical research have been summarised elsewhere (46). This thesis focuses on some of the aspects of tool development in clinical research described by Kumar (46) including; provision of a theoretical basis for developing the items in the tool; the design of individual aspects in the tool; piloting the tool; assessment of reliability of the tool using internal consistency and inter-observer reliability; assessment of content validity using expert opinion; and the assessment of concurrent or discriminant validity. These issues were addressed as we developed a tool to measure male partner participation in PMTCT.

## IV. OUTLINE OF THE THESIS

This thesis is written as a "sandwich thesis" of three separate papers (Chapters 2 to 4) which together address the two main objectives of the thesis cited above.

**Chapter 2** reports on the results of a propensity score matched retrospective chart review on the use of misoprostol in the prevention of PPH in Cameroon. The chapter describes Cameroon, which is the main setting of the study, and provides a strong methodological approach to minimise confounding bias in the use of observational data using both propensity score matching methods and multivariable logistic regression. It highlights some of the limitations of the use of matching to control for confounding, and balances it against the benefits of the technic. It provides evidence for the use of misoprostol in the prevention of PPH in resource constrained settings.

**Chapter 3** is built upon the information developed from chapter 2. This chapter provides evidence for the use of data from NRS on the use of misoprostol in the prevention of PPH. The objectives were to compare the results of RCTs and NRS on the use of misoprostol in the prevention of PPH; and to compare Classical and Bayesian approaches of combining the results of RCTs and NRS on the use of misoprostol in the prevention of PPH. A systematic evaluation approach was used to address these two key issues. The conclusions provide a rationale for the use of observational data in clinical and policy decisions on misoprostol in the prevention of PPH in settings where evidence from RCTs is lacking.

**Chapter 4** outlines the creation of a new measurement tool, the first of its kind, to measure male partner involvement in PMTCT of HIV, and documents its psychometric properties. The study was designed in two phases. The first phase was a systematic review to identify items used to describe male partner involvement in PMTCT of HIV (31) (not part of this thesis). The items were used to develop a questionnaire whose content validity was assessed by an expert panel focus group. The second phase, was a cross sectional study to test the different items of the questionnaire and develop the final tool.

**Chapter 5** provides a discussion of the findings from the previous chapters. A summary of the key findings, the key strengths and limitations of the different studies, as well as key implications of the different study findings are provided. This chapter pools the different papers together, highlighting why prevention of PPH and PMTCT of HIV are major pillars of maternal and fetal health which both need to be simultaneously addressed especially in resource constrained settings.

**Overlap in material covered**

Chapters 2 to 4 were developed as independent manuscripts each with independent datasets. However, the research idea for chapter three arose as a potential way forward for chapter two. Consequently, there is some overlap in the introductory material of both chapters. Chapter 4 was conducted in the same settings as chapter 2, but on different participants. Hence there is no overlap in the datasets or material covered in this case.

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# CHAPTER 2

## Misoprostol as an adjunct to oxytocin can reduce postpartum-haemorrhage: A propensity score–matched retrospective chart review in Bamenda-Cameroon, 2015-2016

# Misoprostol as an adjunct to oxytocin can reduce postpartum-haemorrhage: A propensity score–matched retrospective chart review in Bamenda-Cameroon, 2015-2016

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## ABSTRACT

**BACKGROUND**: There is some evidence that suggests misoprostol may supplement the action of oxytocin in preventing post-partum haemorrhage (PPH).

**OBJECTIVES:**

Primary: To determine the effects of the administration of 600μg misoprostol in addition to oxytocin versus oxytocin alone, on the risk of PPH among pregnant women after delivery.

Secondary: To determine the effects of the above combination on maternal death and blood transfusion among pregnant women after delivery. To determine the incidence of PPH, its case fatality, and the maternal mortality ratio in our hospital.

**METHOD**:

*Design and setting*: Retrospective chart review of 1736 women delivering at the Regional Hospital Bamenda Cameroon, between 2015-2016. This was a pre versus post study following a policy change in the prevention of PPH.

*Exposure groups*: One group received oxytocin-misoprostol (January-April 2016: period after policy change), and the second group received oxytocin-only (January-April 2015: period before policy change) after delivery.

*Outcomes*: The primary outcome was PPH, and the secondary outcomes were maternal death and blood transfusion.

*Statistical analysis*: A 1:1 matching with replacement was done with the propensity score (PS). The groups were compared using PS matching with conditional logistic regression on the

matched pairs as the main analysis. A sensitivity analysis was done using other PS adjustment methods and multiple regression.

**RESULTS**: Of the 1736 women included in this study, 1238 were matched and compared. Women who received oxytocin-misoprostol were less likely to have PPH as compared to those receiving oxytocin-only (odds ratio [OR] 0.22, 95% confidence interval [CI] 0.08, 0.59, p=0.003). This reduced odds of PPH was upheld in the different sensitivity analyses. There were no significant differences in the odds of maternal death and the use of blood transfusions between the two groups: OR 3.91, 95% CI [0.44, 35.08], p=0.22, and OR 0.89, 95% CI [0.14-5.63], p=0.91, respectively. Sensitivity analyses showed similar results. The incidence of PPH was 2.9% (before adding misoprostol the incidence was 4.4% and after adding misoprostol it was 1.5%), the case fatality rate of PPH was 1.96%, and the overall maternal mortality ratio in the hospital was 293 maternal deaths/100000 life births.

**CONCLUSION:** Our evidence suggests that using 600μg misoprostol as an add-on to oxytocin in the prevention of post-partum haemorrhage significantly reduces the odds of PPH without affecting other maternal outcomes.

**Key words**: Post-partum haemorrhage, misoprostol, oxytocin, maternal mortality.

# 1. BACKGROUND

Post-partum haemorrhage (PPH) refers to bleeding from the genital tract greater than or equal to 500cc following vaginal delivery, or greater than or equal to 1000cc following a caesarean section (1). PPH is responsible for one maternal death every 4 minutes in low-income countries (2). Most of these maternal deaths occur within the first 24 hours following delivery, but can largely be prevented by the use of prophylactic uterotonics after delivery (3). This is because PPH is primarily due to uterine atony (4).

Active management of the third stage of labour (AMTSL) is an evidence-based intervention which is recommended for all deliveries to prevent PPH (3). The administration of a prophylactic uterotonic agent is a key component of AMTSL, and the World Health Organisation (WHO) recommends the use of oxytocin (10 IU, intra venous/intra-muscular) as the uterotonic drug of choice (3). Despite the widespread use of oxytocin in AMTSL, the high rates of PPH observed in low-income countries is indicative of the fact that this strategy may be lacking in certain aspects, thus justifying the need for add-ons to supplement the uterotonic properties of oxytocin.

One of such potential add-ons is misoprostol which is a prostaglandin E1 analogue with strong uterotonic properties (5). Given its established safety profile in obstetrics, misoprostol is recommended by WHO as an alternative to oxytocin for the prevention of PPH in settings where the latter is unavailable (3). Given their independent pathways of action, one could expect a synergistic effect of both drugs when used in combination to prevent PPH (6). There is strong biological evidence suggesting that misoprostol can augment the effectiveness of injectable uterotonic agents such as oxytocin used in AMTSL (7).

Since October 2015, following a drug donation of misoprostol from the Life for African Mothers Non-Governmental Organisation, there was a policy change in the preventive management of PPH in the Regional Hospital Bamenda (RHB) Cameroon, from the use of oxytocin-only, to the use of an oxytocin-misoprostol combination. Consequently 600μg misoprostol was routinely given in the immediate post-partum period, either orally or rectally, as an add-on to oxytocin in AMTSL, to all women who delivered in the maternity of the Regional Hospital Bamenda, to help in the prevention of PPH. This policy change was based more on biological plausibility than evidence. No study has been done to evaluate the effect of this combination on the prevention of PPH, and consequently the reduction of maternal mortality. It is important to note that the drug donation continues till date, and there are plans for the hospital administration to ensure the continuity of the supply once the donation comes to an end.

The primary objective of this study was therefore to determine whether the routine administering of 600-μg misoprostol to pregnant women after placental delivery in addition to routine AMTSL using oxytocin, was associated with reduced risk of PPH after adjusting for potential confounders.

Our secondary objectives were to determine whether this routine administration of 600-μg misoprostol was associated with reduced risk of maternal death and blood transfusion after adjusting for potential confounders. In addition, we sought to determine the incidence of PPH at the Regional Hospital Bamenda as well as its case fatality rate; and to determine the causes of PPH at the Regional Hospital Bamenda. We equally sought to estimate the maternal mortality ratio at the Regional Hospital Bamenda, and to describe the associated causes of maternal death.

Our research hypothesis was that the use of 600μg misoprostol as an add-on to standard care with oxytocin for AMTSL is protective against PPH, maternal mortality and use of blood transfusions among women after delivery.

## 2. METHODS

### 2.1 Study type

This was a retrospective chart review study.

### 2.2 Setting

This was a hospital-based study conducted at the maternity of the Regional Hospital Bamenda (RHB) in the North West Region of Cameroon. Cameroon is a sub-Saharan West African country. It has an estimated population of about 24 million inhabitants (8). The Regional Hospital Bamenda is the lone referral hospital in Bamenda the capital of the North West Region of Cameroon, and serves a population of about 337,036 inhabitants (9). In this hospital, about 3,360 women give birth annually (9).

### 2.3 Inclusion and exclusion criteria

We included in our study pregnant women who delivered at the maternity of the Regional Hospital Bamenda at a gestational age of 20 weeks or more, and who had complete case records on the evolution of labour from the moment of admission until discharge from the hospital.

We excluded women with incomplete case records during the study period, those with medical records which had been physically damaged, women who delivered before arrival to the hospital.

We equally excluded women who had delivered elsewhere and developed PPH, and were then referred for the management of PPH to the Regional Hospital Bamenda.

### 2.4 Study period

Data for this study was collected between November 2017 to March 2018. Given that the gift of misoprostol was received in October 2015, we could not have a concurrent comparison group, as the drug was routinely administered to all women thereafter. Our comparison group was therefore drawn from a historical cohort of women delivering in the same hospital within a similar time frame (see figure 1). We used a 4-month period within each time frame, that is, from January to April 2015 (period of no misoprostol use), and from January to April 2016 (period of routine misoprostol use). These time frames were chosen to minimise any biases due to differential staffing because during these periods the maternity staff was the same (same 4 Obstetrician Gynaecologists, same midwives in the labour room and postnatal wards, same staff in the theatre). To the best of our knowledge, the quality of care received by the pregnant women during these periods was about the same, and only differed in terms of the routine administration of misoprostol. There were no other changes to clinical practice for PPH over this period.

### 2.5 Study variables

The intervention was the use of misoprostol in addition to standard care for AMTSL. During the period when it was available, 600μg misoprostol was given either orally or rectally to all women who delivered in the maternity of the Regional Hospital Bamenda, irrespective of the mode of delivery. The study group receiving this intervention was referred to as the oxytocin-misoprostol group.

The comparator was standard active management of the third stage of labour using oxytocin-only as the uterotonic drug. The study group receiving this was referred to as the oxytocin-only group.

### 2.6 Study outcomes

The primary outcome measure was PPH defined as vaginal blood loss ≥ 500cc within the first 24 hours following vaginal delivery or blood loss ≥ 1000cc following a caesarean section (1). However rigorous measurement of blood loss was not routinely done in our maternity. For the purpose of this study, we identified potential cases of PPH from diagnoses recorded in the hospital charts. These diagnoses of PPH were based solely on the clinical judgment of the team on duty who made the diagnosis. The records of these potential PPH cases were reviewed by an adjudication team of two obstetrician gynaecologists involved in the routine care of women within the facility. This team used information noted in the records such as reports of PPH, estimates of blood loss after delivery, occurrence of hemodynamic shock after delivery, laboratory results of haemoglobin level before and after deliver as well as the use of blood transfusion after deliver in order to adjudicate whether the primary outcome (PPH) had occurred. The adjudication team was blinded to the treatment option used in each case. PPH was recorded as a dichotomous variable.

Secondary outcome measures included maternal death defined as “the death of a woman whilst pregnant or within 42 days of delivery or termination of pregnancy, from any cause related to, or aggravated by pregnancy or its management, but excluding deaths from incidental or accidental causes”(10); blood transfusions following delivery; the incidence and causes of PPH; the maternal mortality ratio and causes of maternal death. In addition, we tried to collect information

on side effects of misoprostol (such as shivering; fever >38°C; diarrhoea, nausea, vomiting), but these were not routinely noted in the files and thus these outcomes could not be evaluated.

### 2.7 Confounders

Based on a literature review, greater maternal age, higher gravidity, higher parity, a maternal history of postpartum haemorrhage, induced labour, multiple pregnancy, foetal macrosomia, polyhydramnios, increased duration of labour, and delivery by caesarean section are a selection of potential confounders of the relationship between the method used for the prevention of PPH and the occurrence of PPH, and may be associated with increased risk of PPH (11,12). Data was collected on these confounders when possible, and adjustments made for them by matching or during analysis.

### 2.8 Data collection

Baseline demographic data as well as outcome related data was collected on a standardized pretested data abstraction form. The form had no personal identifier other than the numbers assigned during data abstraction. Data was collected from the files of the women, and supplemented where necessary with hospital records from the labour room, wards and theatre registers.

The collected data was transferred into a Microsoft Excel version 13 spread sheet on an independent and secure computer where it was checked for accuracy and completeness. These data were eventually transferred to the Statistical Package for Social Sciences (SPSS) software version 20.0 (13) for analysis. Propensity score matching was done using the R software (version 3.51) (14).

## 2.9 Statistical methods

***Creating the propensity score model****:* It has been noted that in observational studies, there is a tendency for the existence of systematic differences in baseline characteristics between treated and untreated subjects, and it is important to account for such differences when estimating treatment effects (15). In recent times, the propensity score is increasingly being used as a balancing score to minimise such differences (15). The propensity score represents the estimated conditional probability of being assigned to either of the treatment groups given the patients' pre-treatment characteristics (16). We therefore opted to use it in our analysis to balance differences in baseline characteristics between the oxytocin-misoprostol group and the oxytocin-only group.

Our propensity score matching model was created using the Coarsened Exact Matching method with replacement (17). This method was chosen because amongst the multiple methods of matching which we tried out, it resulted in the lowest standardised mean differences between treatment groups for the different matched variables. We did a one-to-one matching with replacement given that it is appropriate in cases where the treatment group is bigger than the control group (18). Furthermore, it provides more unbiased treatment effect estimates relative to a matching without replacement (18). For the matching, we did an automated coarsening, and this provided us with a sufficiently large matched sample.

For the matching, the grouping variable was the use of misoprostol or not, while the covariates matched for were age in years, gravidity, parity, history of delivery of a macrosomic baby in the previous pregnancy, whether or not the woman was referred from a different facility, whether or not labour was induced, the mode of delivery and the birth weight of the child. These variables

were selected among available baseline covariates based on known associations between these and PPH (11,12).

***Comparison of the baseline characteristics***: The characteristics of the study participants in the two study groups, was described using descriptive statistics reported as count (percentage) for categorical variables, and mean (standard deviation [SD]) or median (first quartile, third quartile) for continuous variables depending on the distribution. We directly compared the baseline characteristics between our two treatment groups before and after matching. For each variable compared, we used an absolute standardized mean difference threshold of less than 10% as proof of balance between the groups (15).

***Analysis of primary outcome***: We conducted a propensity score (PS) matched data analysis using conditional logistic regression based on 1:1 matched samples. The use of conditional logistic regression in analysing matched case-control data is increasingly being used as a standard procedure (19), hence the reason we choose it as our primary analysis method.

We conducted sensitivity analyses with the other PS-adjustment methods, multivariable logistic regression analysis and analysis on the unmatched data. Our rationale for using the other PS-methods was that there are several ways of using the PS to adjust for confounding (15), each of them worthy of exploration. These methods are stratification on the propensity score, inverse probability of treatment weighting (IPTW) using the propensity score, and covariate adjustment using the propensity score (15). The rationale for the multivariable analysis comparison was because of the fundamental differences between PS-methods and multivariable regression approaches, with propensity score analysis modelling the relationship between the covariate and the putative cause, while regression adjustment models the relationship between the covariate

and the outcome (20). However, research evidence suggests that the use of multivariable analysis leads to similar results when compared to propensity-score adjusted approaches (21). Our hypothesis therefore was that the results would remain robust under all these methods.

***Analysis of secondary outcomes:*** We conducted a PS matched data analysis using conditional logistic regression based on 1:1 matched samples as the main analysis. A sensitivity analysis was done using the same approaches as with the primary outcome, and for the same reasons.

We presented the results as odds ratio (OR), corresponding 95% confidence interval (CI) and associated p-values for each outcome. All of our statistical analyses were performed using a 2 tailed test, and the level of statistical significance was set at 0.05.

## 3. RESULTS

Figure 1 below summarises the flow of study participants within the study.

### 3.1 Baseline characteristics and assessment of the matching

A total of 1736 women were included in this study. Of these 1736 women, 1238 were matched. Table 1 summarises the characteristics of study participants in the unmatched and matched study populations for the two treatment groups (oxytocin-only vs oxytocin-misoprostol).

Comparison of the standardised mean differences between the variables in the unmatched and matched data samples shown in table 1 indicate an overall lower standardised mean difference in the matched data. The balance was successful for all the covariates except for the birth weight of the babies, for which we did not achieve balance.

### 3.2 Post-partum haemorrhage.

In the unmatched data, PPH was recorded in 1.5% (13/879) of women in the oxytocin-misoprostol group, and in 4.4% (38/857) of women in the oxytocin-only group. In the matched data, PPH was recorded in 0.8% (5/632) of women in the oxytocin-misoprostol group, and in 4.3% (26/606) women in the oxytocin-only group. Figure 2 summarises the odds of PPH between the two treatment groups using different methods of analysis. Women who received oxytocin-misoprostol were less likely to have PPH as compared to those receiving oxytocin-only (main analysis, OR 0.22, 95% CI 0.08, 0.59, p=0.003). This reduced odds of PPH was upheld in the different sensitivity analyses (Figure 2).

### 3.3 Maternal deaths.

In the unmatched data, there were 4 (0.45%) maternal deaths among the 879 women in the oxytocin-misoprostol group, and 1 (0.12%) among the 857 women in the oxytocin-only group. Table 2 summarises the risk of maternal death between the two treatment groups. There was no significant difference in the odds of maternal death between the two treatment groups (OR 3.91, 95% CI [0.44, 35.08]). This result is presented for the unmatched data only as none of the cases of maternal death were matched, hence a propensity score analysis was not possible with this variable (Table 2).

### 3.3 Blood transfusion.

In the unmatched data, 7 of the 879 women (0.79%) in the oxytocin-misoprostol group, and 4 of the 857 women (0.46%) in the oxytocin-only group received a blood transfusion. In the matched data, 2 of the 632 women (0.32%) in the oxytocin-misoprostol group, and 3 of the 606 (0.49%) women in the oxytocin-only group received a blood transfusion. Figure 3 summarises the odds of

blood transfusion between the two treatment groups. There was no significant difference in the odds of blood transfusion between the two treatment groups in both the main and sensitivity analysis (main analysis, OR 0.89, 95% CI [0.14-5.63]) (Figure 3).

### 3.4 Incidence and causes of PPH

Amongst the 1736 women included in the study, there were 51 cases of PPH, giving an overall incidence of PPH of 2.9%. The incidence before the intervention was 4.4% (38/819) and the incidence after the intervention was 1.5% (13/866). Table 3 summarises the causes of PPH in the two study groups. The most common cause of PPH identified in both groups was uterine atony (50% of identified causes).

### 3.5 Maternal mortality ratio and causes of maternal death

Amongst the 1736 women included in the study, there were a total of 1704 life births, with 5 maternal deaths, giving a maternal mortality ratio of 293 maternal deaths/100000 life births. There was one maternal death in the oxytocin only group, and this was due to myocardiac infarction. The 4 maternal deaths in the oxytocin-misoprostol group were due to HELLP syndrome (1 case), pulmonary embolism (1 case), PPH (1 case), and 1 unknown cause. Given the 51 women with PPH in the sample, the case fatality rate of PPH was 1.96%.

## 4. DISCUSSION

Women who received oxytocin-misoprostol were less likely to have PPH as compared to those receiving oxytocin-only (OR 0.22, 95% CI 0.08, 0.59, p=0.003). There were however no significant differences in the odds of maternal death and the use of blood transfusions between the two groups: OR 3.91, 95% CI [0.44, 35.08], p=0.22, and OR 0.89, 95% CI [0.14-5.63],

p=0.91 respectively. Sensitivity analyses showed similar results. The incidence of PPH in the Regional Hospital Bamenda was 2.9% (before adding misoprostol the incidence was 4.4% and after adding misoprostol it was 1.5%), the case fatality rate was 1.96%, and the overall maternal mortality ratio in the hospital was 293 maternal deaths/100000 life births.

Our results contrast with findings from trials conducted in Africa evaluating the use of misoprostol as an add-on to routine uterotonics in the prevention of PPH. Both Fawole et al (22) and Hofmeyr et al (7) did not find any significant reduction in the risk of PPH when misoprostol was used as an add-on to routine uterotonics for the prevention of PPH (relative risk [RR] 0.96, 95% CI 0.63–1.45 and RR 0.64; 95% CI, 0.38–1.07 respectively). It is however not uncommon for the results of propensity score adjusted studies to differ from that of randomised controlled trials (23,24). Despite the higher strength of evidence from the trials of Hofmeyr et al (7) and Fawole et al (22), both evaluated the use of 400μg of misoprostol, contrary to this study which evaluated the effect of a 600μg dose of misoprostol as an add-on to routine oxytocin. Our results therefore suggests that the dose of misoprostol used may be a determinant factor on its efficacy in reducing PPH when it is used as an add-on to oxytocin.

In Pakistan, which is a low-income country like Cameroon, Zuberi et al (25) found 600μg misoprostol given as an adjunct treatment for PPH to be “promising” in reducing PPH, even though they could not measure statistical significance due to a much lower than expected PPH rate. They therefore recommended its continued exploration in women with PPH (25). Our findings support their claim, and substantiate the need for a trial evaluating the use of a 600μg misoprostol dose for prevention of PPH.

The incidence of PPH before the intervention was 4.4%, and we believe this represents the incidence of PPH in our hospital before the start of the study. The reported overall incidence of PPH of 2.9% in this study was much lower than regional estimates of PPH of 25.7% in Africa (26). It was also slightly lower than the 4.1% incidence of PPH found in the Yaounde University Teaching Hospital in Cameroon (27) which is a similar tertiary hospital like the Regional Hospital Bamenda. These differences may be due to differences in study settings (community vs. facility based), differences in labour care, but also the role of misoprostol in reducing PPH in our hospital. The use of an adjudication committee to make the final diagnosis of PPH from the files may equally have limited the number of cases of PPH in this study, hence the low incidence of PPH seen in this study needs to be interpreted with caution.

Given the high case fatality rate of PPH in this study (1.96%) which was higher than the < 1% case fatality rate recommended by the United Nations for women with direct obstetric complications (28), the potentially additive effect of misoprostol to curb PPH is worth considering.

The maternal mortality ratio in this study is comparable to the 287.5 per 100 000 live births reported by Tebeu et al in a tertiary hospital in Yaounde Cameroon (29). It is also comparable to the maternal mortality rate of 239 per 100,000 live births in low-income countries, a value which is 20 times greater than that in high-income countries (30). Mindful of the fact that the overarching aim to curb PPH is to reduce maternal mortality, it is uncertain whether the decrease in odds of PPH with the addition of misoprostol in this study suffices to reduce the risk of maternal death. We failed to show any effect of our intervention on maternal mortality probably because due to the small numbers of maternal death, the study was underpowered to assess the effect of the intervention on this outcome. However, the observed tendency for an increased

maternal mortality in the treatment group was unlikely to be due to the intervention given that the causes of these deaths were well defined, and were unlikely to be linked to the intervention.

Similarly, we failed to show any effect of our intervention on the risk of blood transfusion probably because due to the small numbers of blood transfusion especially after matching, the study was underpowered to assess the effect of the intervention on this outcome as well.

This study is limited by its design. The retrospective assessment of a natural experiment may be subject to bias, including confounding. One potential source of bias which may have played a role in the reduction of PPH in the oxytocin-misoprostol group may have been an increased awareness of the treating staff on PPH following the policy change. We had little control over this potential bias, but believe its effect would have been minimal given that the treating staffs were also not aware that a study will eventually be conducted to compare the outcome before and after the policy change.

Still in terms of bias, assessment of the outcome depended solely on hospital records which may not have been very accurate. However information from medical records for PPH and other maternal outcomes have been used as the gold standard to assess the validity of hospital discharge data (31). We tried to minimise any potential inaccuracies in the diagnosis of PPH by the use of a blinded adjudication team of two obstetrician gynaecologists involved in the routine care of women within the said facility to assert the diagnosis based on the records.

Eight women were excluded from the study because of incomplete records. They were of similar ages as the rest of the sample, and it is unlikely that they would have differed substantially from the rest of the population in terms of other characteristics or the outcome. We therefore suspect that the effect of their exclusion would have been minimal to cause any form of selection bias.

The propensity score matching creates a new often smaller but more balanced data set in which exposed and unexposed participants have a similar distribution of covariates. It was intended as the primary analytical approach in this study. Loss of some data is a limitation of all matching techniques, but the benefits of confounding control outweigh this limitation.

Despite the propensity score matching we used to minimise any potential confounding, this method can only adjust for known confounders which have been measured (32). However, information on other potential confounders such as a maternal history of postpartum haemorrhage, polyhydramnios, and the duration of labour were not available in the records, and were therefore not included in the propensity score model. These may constitute sources of residual confounding, and limit the strength of the causal relationship between the intervention and the outcome in the study. Another potential source of residual confounding was the birth weight of the babies for which we did not achieve balance in the propensity score model (standardised difference 31.7%). This variable was included in the multivariable regression analysis and found non-significant (result not shown).

A further limitation of this study is the fact that we were not able to assess side effects of misoprostol. Consequently, any potential benefits of misoprostol seen in the study must be taken cautiously given that side-effects such as severe hyperthermia may be life-threatening (2). The study is equally limited by the fact that maternal deaths occurring after hospital discharge till 42 days post-delivery were unlikely to be found in the records and therefore not included in the study.

The strengths of our study include the unique ability to evaluate a natural experiment where oxytocin-misoprostol was routinely introduced, and the ability to compare within a short time

frame. Other study strengths include the large sample size and the rigor in statistical analysis. Our findings were robust to extensive sensitivity analysis regarding the methods for propensity score matching analysis associated with a multivariable logistic regression analysis.

The implication of our findings is that there is a potentially beneficial effect in the use of 600μg misoprostol as an adjunct to oxytocin to reduce PPH. While our findings may not be immediately generalizable given the potential for unknown confounding, our study provides a rationale to explore a 600μg dose of misoprostol as an add-on to routine uterotonics for the prevention of PPH in this setting, preferably using a randomised controlled trial. If this hypothesis is backed by future research, it could lay the foundation for generalizability and advocacy for an evidenced-based policy change in the management of PPH especially in low-income settings.

## 5. CONCLUSIONS

Our evidence suggests that using 600μg misoprostol as an add-on to oxytocin in the prevention of post-partum haemorrhage significantly reduces the odds of PPH. This conclusion should be interpreted cautiously given the overall limitations of the study design. Further research is necessary to evaluate the net benefit of this combination in preventing PPH and consequently maternal death.

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## Ethics Approval and Consent to participate

Ethical approval to conduct this study was obtained from the Bamenda Regional Hospital Institutional Review Board decision number 29/APP/RDPH/RHB/IRB. Being a retrospective chart review, we did not have to obtain individual patient consent for the study. Strict patient confidentiality was maintained at all stages of the study.

## Consent for publication

Not applicable.

## Availability of supporting data

Supporting data and the programming code for propensity score matching in R is available upon request from the authors.

## Competing interests

Misoprostol used in this study was donated to the Regional Hospital Bamenda through the Life For African Mothers (LFAM) Charity Organisation in collaboration with International Health Partners (IHP) and Pfizer Drug Company. Neither LFAM, IHP nor Pfizer were involved in the design, execution or write up of this project. The authors do not have any conflicts of interest to declare in relation to any of the above organisations.

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The authors did not receive any external funding for the execution of this project

**Authors' contributions**

FM conceived the research idea. FM, MF, PC, AB, LM, LA and LT jointly designed the study. FM, MF and AB did the data collection. LM, LA and LT provided guidance with data analysis. FM made the first draft. All authors reviewed several versions of the manuscript. All authors read and approved the final manuscript.

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**Table 1: Characteristics of study participants in the unmatched and matched study populations for oxytocin-only vs oxytocin-misoprostol (Coarsened exact method matching)**

| | Unmatched population (n=1736) | | | Matched Population (n=1238) | | |
|---|---|---|---|---|---|---|
| | **Oxytocin-only (n=857)** | **Oxytocin-misoprostol (n=879)** | **Standard difference,%** | **Oxytocin-only (n=606)** | **Oxytocin-misoprostol (n=632)** | **Standard difference,%** |
| Age in years, Mean (SD) | 26.31 (5.17) | 26.25 (5.08) | 1.1 | 25.23 (4.44) | 25.19 (4.27) | 0.9 |
| Gravidity, Mean (SD) | 2.58 (1.51) | 2.57 (1.55) | 0.9 | 2.25 (1.19) | 2.20 (1.21) | 3.6 |
| Parity, Mean (SD) | 1.29 (1.32) | 1.29 (1.37) | 0.3 | 1.09 (1.09) | 1.07 (1.23) | 2.1 |
| History of macrosomic baby n (%) | 94 (11.0) | 62 (7.10) | 13.7 | 47 (7.8) | 37 (5.9) | 7.6 |
| Patient referred n (%) | 27 (3.20) | 20 (2.30) | 5.4 | 3 (0.5) | 3 (0.5) | 0.3 |
| Induction of labour in indexed pregnancy n (%) | 30 (3.50) | 45 (5.10) | 8.0 | 3 (0.5) | 5 (0.8) | 3.7 |
| Mode of delivery caesarian section n (%) | 125 (14.6) | 83 (9.4) | 15.9 | 46 (7.6) | 36 (5.7) | 7.6 |
| Birth weight of babies in the indexed pregnancy in grams, Mean (SD) | 3393.9 (516.7) | 3182.6 (481.1) | 42.3 | 3362.42 (419.83) | 3230.66 (412.77) | 31.7 |

SD: Standard Deviation

**Table 2: Association between maternal death and the type of drug used for PPH prevention**

| **Main Analysis** | **Odds ratio (95% CI)** | **p-value** |
|---|---|---|
| Unmatched analysis (n=1238) | 3.91 (0.44 -35.08) | 0.223 |
| Analysis with multivariable logistic regression on the unmatched data (n=1238) [a] | 5.32 (0.095 – 298.58) | 0.416 |
| ***Analysis with the matched data was not conducted as there were no cases of maternal death in the matched data*** | | |

a: Analysis adjusted for age, gravidity, parity, referral status, induction of labour, history of a macrosomic baby, mode of delivery, birth weight.

**Table 3: Causes of Postpartum haemorrhage in the two treatment groups**

| | **Oxytocin-only group (N=20): n (%)** | **Oxytocin-Misoprostol group (N=10) : n (%)** | **Total* (N=30): n (%)** |
|---|---|---|---|
| Uterine atony | 9 (45.0) | 6 (60.0) | 15 (50.0) |
| Retained placental tissue | 6 (30.0) | 1 (10.0) | 7 (23.3) |
| Genital laceration | 5 (25.0) | 2 (20.0) | 7 (23.3) |
| Coagulopathy | 0 (0.0) | 1 (10.0) | 1 (3.3) |

* missing cases = 21

# LIST OF FIGURES CHAPTER 2

## Figure 1: Flow chart of study participants

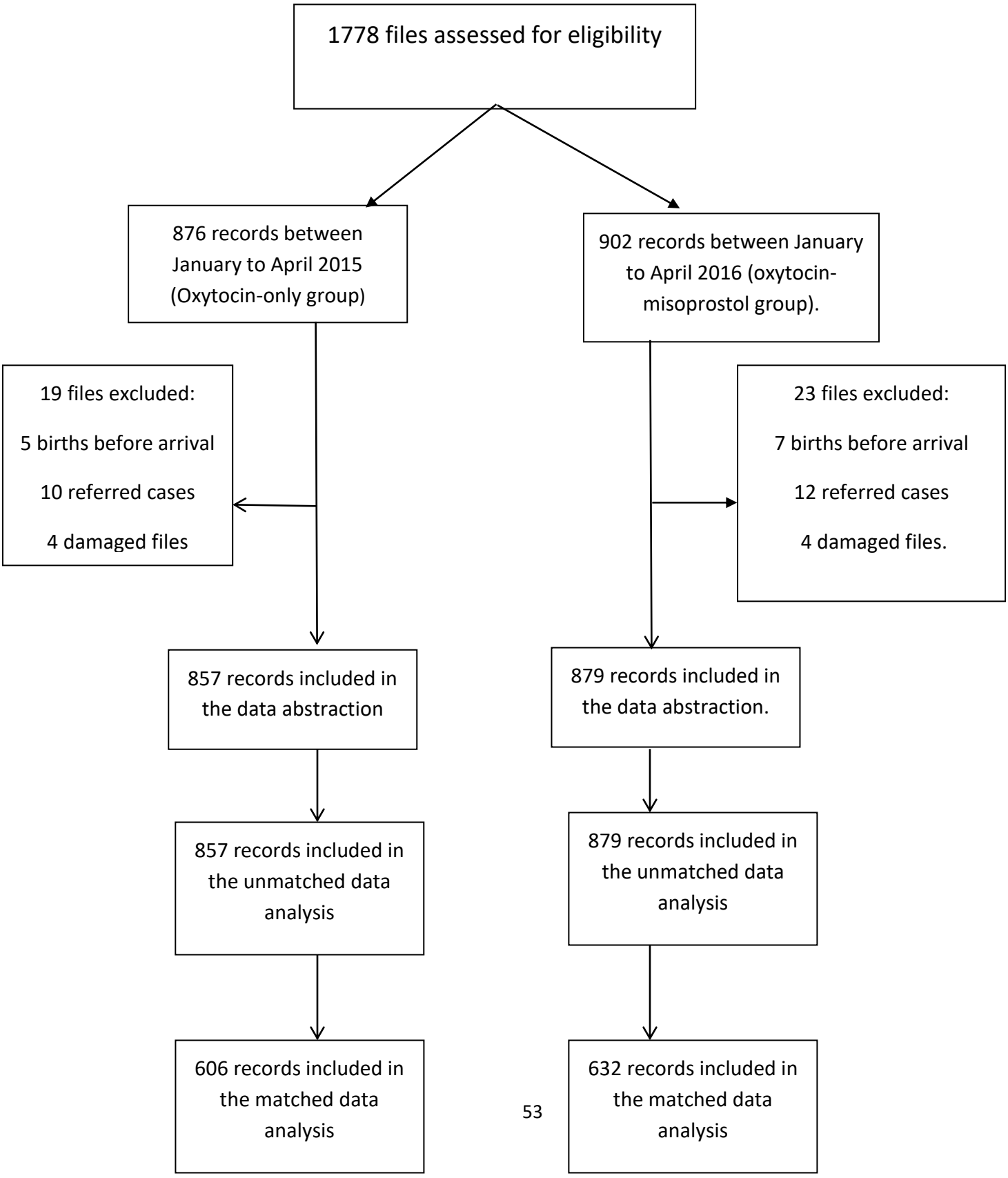
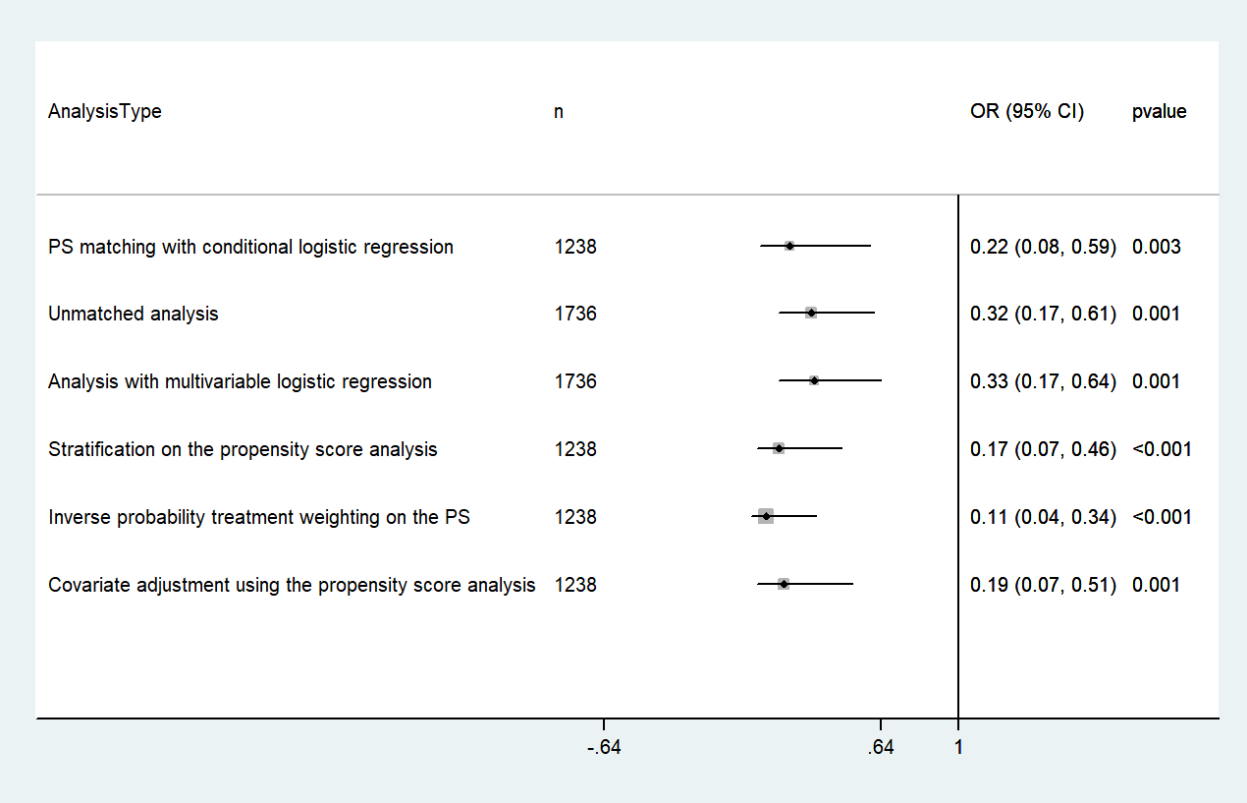
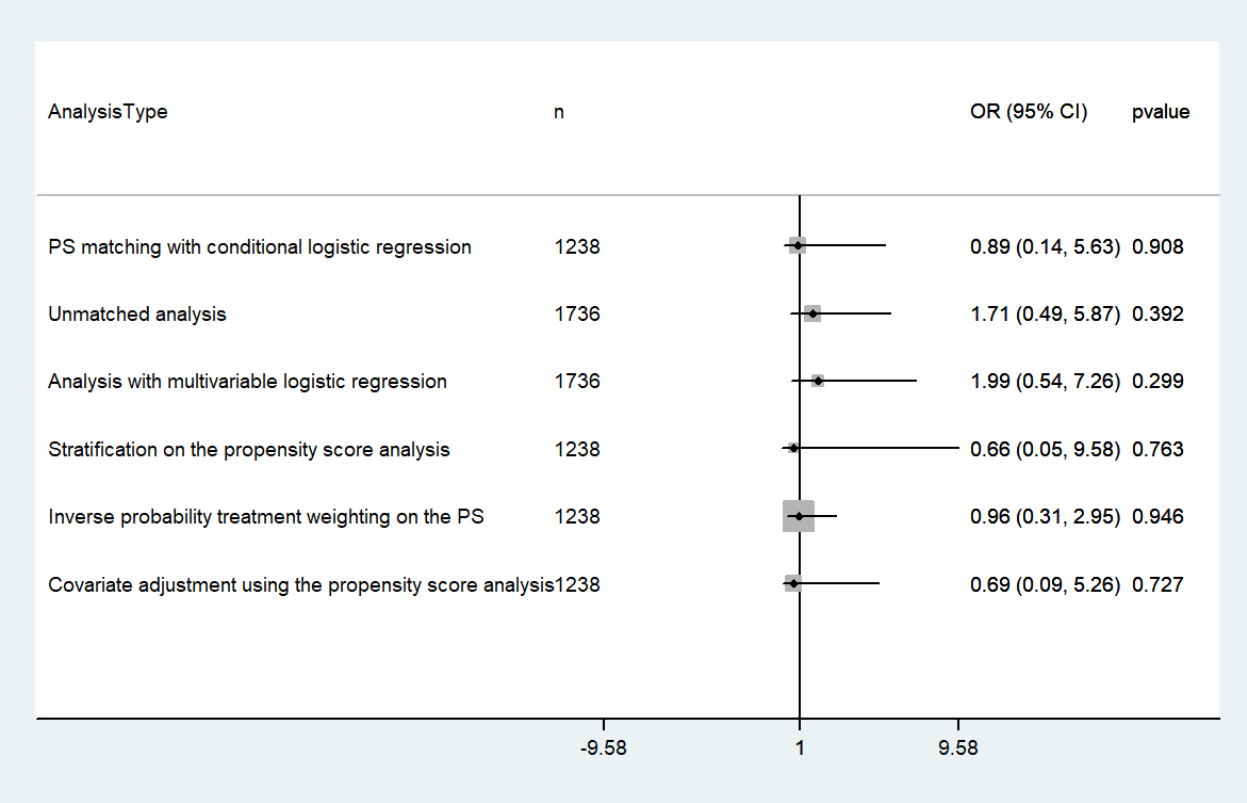


**Figure 2: Comparing the odds of post-partum haemorrhage between oxytocin-misoprostol vs oxytocin only using different methods of analysis (Main analysis and sensitivity analysis)**




**Multivariable Analysis adjusted for age, gravidity, parity, referral status, induction of labour, history of a macrosomic baby, mode of delivery, birth weight.**
**Acronyms: PS (Propensity score); n (sample size); OR (Odds Ratio); CI (Confidence Interval).**

**Figure 3: Comparing the odds of blood transfusion between oxytocin-misoprostol vs. oxytocin only using different methods of analysis (Main analysis and sensitivity analysis)**




**Multivariable Analysis adjusted for age, gravidity, parity, referral status, induction of labour, history of a macrosomic baby, mode of delivery, birth weight. Acronyms: PS (Propensity score); n (sample size); OR (Odds Ratio); CI (Confidence Interval)**

# CHAPTER 3

## Comparing and combining evidence of treatment effects in randomised and non-randomised studies on the use of misoprostol to prevent post-partum haemorrhage

# Comparing and combining evidence of treatment effects in randomised and non-randomised studies on the use of misoprostol to prevent post-partum haemorrhage

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## ABSTRACT

### Background

Postpartum haemorrhage (PPH) is a preventable condition and the main cause of maternal death worldwide. Evidence on the effectiveness of misoprostol in the prevention of PPH has been generated from both randomised controlled trials (RCTs) and non-randomised studies (NRS). The missing link is a synthesis of all the evidence to check whether the evidence from both sources is consistent, and if so, how it can be combined.

### Objectives

*Primary objective*: To compare the results of randomised and non-randomised studies on the use of misoprostol versus placebo or no treatment in the prevention of PPH.

*Secondary objective*: To compare Classical and Bayesian approaches of combining the results of RCTs and NRS on the use of misoprostol in the prevention of PPH; To geographically map, according to study design the income level of the countries that generate the evidence on the use of misoprostol in the prevention of PPH.

### Methods

We conducted a systematic evaluation of the evidence from RCTs and NRS assessing the efficacy of misoprostol versus placebo/no treatment in the prevention of PPH. We searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials for appropriate studies. Data were pooled using a random effects meta-analysis of odds ratios (OR). Treatment effect estimates (OR) were compared between the two study designs using a z score for interaction, and sensitivity analyses were conducted using the ratio of odds ratios (ROR). Results

from the two study designs were combined using classical and Bayesian random effects meta-analysis.

**Main results**

A total of 34 studies (20 RCTs and 14 NRS) involving 74,204 participants were identified. The summary OR from RCTs for the use of misoprostol in the prevention of PPH was 0.69 (95% confidence interval (CI): 0.59 -0.80) with moderate heterogeneity ($I^2$ = 43.5%, 20 studies, 17,314 participants). The summary OR from non-randomised studies was 0.46 (95% CI: 0.36 -0.63) with considerable heterogeneity ($I^2$ = 79.9%, 14 studies, 56,890 participants). The overall z test for interaction showed a discrepancy between the two estimates (z=2.68, threshold for discrepancy z >1.96 or z <-1.96). Sensitivity analysis showed similar results. Classical and Bayesian approaches of combining the two study designs both showed benefit of misoprostol in preventing PPH, with similar pooled estimates. The majority of the the RCTs (57.1%) were conducted in high income settings, while the majority of the NRS (92.9%) were conducted in low and middle income settings.

**Conclusions:**

Both RCTs and NRS show significant benefit for the use of misoprostol in the prevention of PPH. The results from both study designs are comparable, with NRS tending to overestimate the treatment effect. Different methods of pooling across both study designs all show significant benefit of misoprostol in preventing PPH.

**Keywords:** Misoprostol, Post-partum haemorrhage, randomised controlled trials, non-randomised studies, comparisons, interaction, Bayesian.

## BACKGROUND

Postpartum haemorrhage (PPH) is a preventable condition and the main cause of maternal death worldwide, responsible for over 100,000 maternal deaths annually (1,2). The vast majority of these deaths occur in Sub-Saharan Africa (3). Inadequate uterine contractions after delivery (uterine atony) is the main cause of PPH (4) and it is responsible for over 70% of cases of primary PPH (5). The importance of generating holistic evidence on solutions for PPH cannot be overemphasized, and research on strategies to reduce, if not eliminate, this potentially fatal complication of childbirth is on-going. One of such strategies is the use of misoprostol in the prevention of PPH.

Numerous studies have assessed the role of misoprostol in the prevention of PPH (6). These have varied in their designs from randomised (7,8) to non-randomised studies (9,10). Even though randomised controlled trials (RCTs) are widely considered as the gold standard for causal effect estimation, they may in reality be a "bronze standard" given that they may not always be well conducted (11). Non-randomised studies have the advantage of better mimicking usual clinical practice than RCTs (12) and are usually a more practical source of evidence given that they are less resource-intensive than RCTs. Nevertheless, the use of non-randomised studies for causal inference is subject to confounding bias (13), and RCTs remain the best method for causal effect estimation.

Whether the results from non-randomised studies are consistent with those from RCTs on the same topic has always been debated (14). Even though efforts have been made to compare the results from these two major study designs on different medical topics, the approach has been broad, simultaneously addressing different topics (14). Consequently, conclusions have been more in terms of broad statements without addressing specific clinical topics (14,15). The list of

topics addressed so far is not exhaustive and include the use of trial of labour in breech delivery and screening mammography in breast cancer amongst others (14). Continued research and comparisons are necessary to build upon this evidence.

The evidence from non-randomised studies on the use of misoprostol in the prevention of PPH has never been compared against RCTs. We recently concluded a retrospective chart review in a low income setting on the use of misoprostol in the prevention of PPH (10). Given the lack of local evidence from RCTs, we were faced with the dilemma of limiting our evidence to just hypothesis generation or using it for policy recommendations as well. We found it challenging to make clinical and policy recommendations based on this evidence given that we lacked evidence to show its comparability with results from RCTs. This challenge is commonly encountered by researchers and policy makers in low and middle income countries (LMIC) who may have plenty of evidence from non-randomised studies on this topic, and wonder whether it should simply be ignored.

Comparing the evidence from RCTs and non-randomised studies on the use of misoprostol in the prevention of PPH is important for two reasons. Firstly, such a comparison will provide better rationale for using evidence from non-randomised studies, at least at a local policy level. This is potentially relevant especially in LMICs who may lack the resources to conduct RCTs, and who may need to rely on “external evidence” from RCTs despite potentially having a plethora of potentially informative evidence from non-randomised studies on this topic. Secondly, most summary evidence on the use of misoprostol in preventing PPH includes only RCTs, often conducted in high income countries (6,16–18).This further reinforces the use of “external evidence” in low and middle income settings.

The missing link in the evidence of misoprostol in the prevention of PPH is a synthesis of all the evidence to check whether the evidence from both sources is consistent, and if so, how it can be combined to fully understand the effects of misoprostol in the prevention of PPH. The non-integration of operational evidence from non-randomised studies with clinical evidence from RCTs on the use of misoprostol in preventing PPH may actually limit the realisation of the full potential of misoprostol in this indication (19). This needs to be addressed.

## OBJECTIVES

The primary objective was to compare the results of randomised and non-randomised studies on the use of misoprostol versus placebo or no treatment in the prevention of PPH in order to inform clinical and policy decision makers on the strength of the evidence from non-randomised studies on the use of misoprostol in preventing PPH.

The secondary objective was to compare Classical and Bayesian approaches of combining the results of RCTs and non-randomised studies on the use of misoprostol in the prevention of PPH. We also sought to geographically map out the income level of the countries that generate the evidence on the use of misoprostol in the prevention of PPH according to study design (RCTs versus non-randomised studies).

The research hypothesis was that the treatment effects will be similar between randomised and non-randomised studies on this topic.

## METHODS

This was a systematic evaluation of randomised and non-randomised studies assessing the efficacy of misoprostol versus placebo or no treatment in the prevention of PPH.

**Study inclusion criteria:**

**Types of studies:** We included RCTs and non-randomised studies (prospective, retrospective and cross sectional) that evaluated the use of misoprostol compared to either placebo or no treatment in the prevention of PPH. We also included randomised and non-randomised studies that evaluated the use of misoprostol plus oxytocin versus oxytocin alone in the prevention of PPH. We excluded single arm non-randomised studies.

**Types of participants:** Our study population included pregnant women delivering within hospital settings or in the community, who received misoprostol for the purposes of preventing PPH. Any studies with only a subset of the relevant participants were included and data was specifically extracted only for this subset of women.

We excluded studies on women who received misoprostol for induction of labour or for the treatment of confirmed PPH.

**Type of intervention:** We assessed the use of misoprostol given either orally, rectally or sublingually for the prevention of PPH, and this irrespective of the dose used.

**Comparisons:** The control groups were expected to receive standard of care for the prevention of PPH applicable within the settings of the study. In cases where misoprostol was combined with oxytocin, the comparison group must have received an equal dose of oxytocin, and the only difference between the two treatment groups being the addition of misoprostol in the treatment group.

**Outcomes:** The primary outcome was the number of cases of PPH as described by the authors in the different studies, irrespective of the criteria they used in ascertaining the outcome.

**Electronic searches**

Using the OVID search platform, we searched MEDLINE and EMBASE from 1946 to 8th February 2019, and the Cochrane Central Register of Controlled Trials (CENTRAL) through the Cochrane Library (Issue 12 of 1, January 2019). We set no limitations on language or the publication status of the studies. (See supplementary file 1 for the MEDLINE search strategy).

**Searching other resources**

We hand-searched the reference list of relevant studies and previous reviews identified through the electronic searches as supplemental sources for studies that may have been missed in searches. We also searched the World Health Organisation International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), in order to identify on-going trials or completed but unpublished trials. We searched for grey literature on the website of the International Federation of Gynaecology and Obstetrics in order to identify on-going studies or completed but unpublished studies. Finally, we contacted experts in the field by email for any on-going studies or relevant but unpublished studies.

**Data collection**

***Study selection:*** Two review authors (FM and BM) independently screened the titles and abstracts of the studies identified through the electronic searches in order to identify possible articles for inclusion, while excluding duplicates. Following this screening, the full texts of eligible articles were obtained and assessed by both reviewers based on the inclusion criteria cited above. Disagreements were sorted out by discussion or by consultation with a third author (LM). Figure 1 is a PRISMA flow diagram describing the study selection process. A list of the

excluded studies with a reason for their exclusion is provided in the "Characteristics of excluded studies" (Supplementary file 2).

***Data Extraction and management:*** Data extraction from the included studies was done using a pre-designed and pre-tested data extraction form created using the web-based systematic review software DistillerSR (20). We extracted data on the study period, the country of conduct of the study, the language, the design, the sample size, the participant characteristics, the dose of misoprostol used, the route of administration, the adjunctive use of oxytocin, and the primary outcome PPH. In cases of incomplete data, missing data or uncertainty, we contacted the authors of the principal studies by email for clarifications. Data extraction was done independently and in duplicate by the two review authors (FM and BM). We resolved any discrepancies in data extraction by discussion.

***Assessment of risk of bias in included studies:*** Assessment of risk of bias in RCTs was done using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (21). The risk of bias table was completed for each outcome by two review authors (FM and BM) working independently of each other. Studies were rated as being at either "high", "low" or "unclear" risk of bias. As much as possible, we avoided the term "unclear" in describing the risk of bias, except in the rare situations when the review authors could not make any judgment.

We used the "Risk Of Bias In Non-randomised Studies - of Interventions" (ROBINS-I) tool (13) to asses risk of bias in the non-randomised studies. Studies were rated as being at either "Low risk", "Moderate risk", "Serious risk" and "Critical risk" of bias. For the purposes of this review, we merged the last three categories into a single category of "high risk of bias" for ease of

comparability with the RCTs. We resolved any discrepancies in risk of bias by discussion or by consultation with a third author (LM).

**Statistical analysis**

***Measures of treatment effect and data synthesis:*** The unit of analysis was the individual. We used the odds ratio (OR), or the adjusted odds ratio if reported, to measure the effect of the intervention between the two groups in both the RCTs and the non-randomised studies. Data were computed such that an OR < 1 indicated a beneficial effect of the experimental intervention.

STATA statistical software version 13 (22) was used to meta-analyse results from the included studies. Meta-analysis was conducted using a random-effects model (DerSimonian–Laird) to obtain a summary estimate of treatment effect in the RCTs and non-randomised studies. A random effects model was used to incorporate between study variance (23). We used the summary estimates from each study category for the different comparisons. The Review Manager version 5 (Revman 5) software (24) calculator was used to compute standard errors (SE) from the odds ratios and 95% confidence intervals (CI) generated from the meta-analysis.

***Comparison of effect estimates: Main and sensitivity analysis.***

The main method of analysis used to compare the estimates of the odds ratios between the RCTs and non-randomised studies was a z test of interaction (25). This is the ratio of the difference between the log odds ratio and the standard error of this difference. By comparing the value of z to the standard normal distribution, this test provides a test of the null hypothesis that the difference between the two estimates is zero i.e., a test of the null hypothesis that RCT and non-randomised study estimates are equal (25). We chose this method for our main analysis as it

takes into account the variance of the difference between two estimates, and it is a validated method to compare two estimates of the same quantity derived from separate analyses (25).

The z test for interaction is obtained using the formula below:

$$z=\ln(OR_{RCT}) - \ln(OR_{NRS})/\{var[\ln(OR_{RCT})] + var[\ln(OR_{NRS})]\}^{1/2}$$

where $\ln(OR_{RCT})$ refers to the natural logarithm of the odds ratio in randomised controlled trials, $\ln(OR_{NRS})$ refers to the natural logarithm of the odds ratio in non-randomised studies, and *var* represents the variance (25). Based on this formula, z score >1.96 or <-1.96 implies the difference between the odds ratios of the two study designs is beyond what will be expected by chance alone at the 0.05 significance level (25). All tests were two-tailed, implying a difference in either direction was interpreted.

A sensitivity analysis for assessment of discrepancy between the two study designs was done using the difference in magnitude of treatment effect. This was done by assessing the ratio of the odds ratio (ROR) with the threshold of discrepancy defined as the OR of the RCT being at least twice or less than half the OR of the non-randomised studies (14). This method was chosen given that it is also commonly used in the comparison of treatment estimates, and the magnitude of treatment effect helps show to what extent a treatment works (14). Comparison of the two ORs was done using the software WINPEPI (26).

***Combining treatment estimates between RCTs and non-randomised studies***

We compared Classical or Frequentist approaches of combining study estimates with Bayesian approaches of combining study estimates between RCTs and non-randomised studies.

The Classical approach of combining the estimates was done using STATA statistical software version 13 (22), and this was done in two ways,. The first approach was a straight forward pooling of all treatment estimates within the meta-analysis model ignoring study type.

The second approach was a stratified pooling according to study design, which consisted of weighting by an estimation of the inverse variance of each effect size. This was done using the following formula (27):

Pooled OR = $(E_1*W_1 + E_2*W_2)/ (W_1 + W_2)$

Where $E_1$= Estimate of odds ratio from RCTs, $E_2$= Estimate of odds ratio from non-randomised studies, $W_1$=1/variance of RCTs, $W_2$=1/variance of non-randomised studies, and the variance of the pooled estimate = $W_1 + W_2$ (27).

These two methods were chosen as they are commonly used approaches for pooling different estimates in classical meta-analysis.

The Bayesian approach of combining the estimates from the two study designs was done using a hierarchical Bayesian random-effects model. This analysis was performed using the statistical software OpenBUGS version 3.2.3 (28). A hierarchical Bayesian random-effects model was chosen given that it has been proposed as a means to combine evidence from different study designs (29,30). Furthermore, it permits us to incorporate not only prior beliefs, but to capture the variability inherent in different sources, and to make a probability statement of the treatment effect (31). Synthesis of data from RCTs with that from non-randomised studies within this model was done in 3 different ways: using a “non-informative” prior distribution (32); using an “informative” prior distribution generated from the non-randomised studies (33): and using a

"sceptical" prior distribution generated from the non-randomised studies but discounted for the potentially lower quality of non-randomised studies (34).

The "non-informative" prior distribution was developed by setting the odds ratio at 1, with a very large variance. In this case, the pooled trial data dominates the posterior distribution, providing a result similar to that obtained from a non-Bayesian meta-analysis (31). For the "informative prior" we used a random effects Bayesian meta-analysis model to obtain prior estimates and variances from the observational studies. Using Bayes rule, we then added randomised studies in order to obtain our posterior distributions (31). Our "sceptical" prior distribution was developed on the premise of a 10-20% decrease in the risk of major clinical outcomes following clinical interventions (35). We prescribed a highly sceptical 5% probability of the odds ratio being below 0.43 as was observed from the Bayesian meta-analysis of the non-randomised studies. This permitted us to calculate a "sceptical" prior distribution of the log odds ratio centred around zero (see supplementary file 4).

### Mapping the sources of evidence

Data on where the studies were conducted was obtained during data extraction. We used the online interactive tool MapChart (36) to map out the countries where the different studies were conducted.

## RESULTS

### Description of the search outcome

The electronic databases and other resource search gave us a total of 1232 records after removal of duplicates. The PRISMA diagram (Figure 1) summarises the process of screening and

selecting studies for inclusion in the review, and the number of studies retained at each stage. A total of 34 studies were retained for data extraction and included in the data synthesis.

**Included studies**

Twenty of the included studies were randomised controlled trials (37–56), while the remaining 14 were non-randomised studies (9,10,57–67), and together involved a total of 74,204 participants. Most of the non-randomised studies were prospective cohort studies, with sample sizes ranging from 400 to 34,631 participants. Supplementary file 3 (characteristics of included studies) summarises the key features of the included studies.

**Excluded studies**

Forty four studies were excluded after full text review. Studies were excluded because based on our inclusion criteria, they either had the wrong design, the wrong comparison or did not report the outcome of interest. Supplementary file 2 (characteristics of excluded studies) summarises the key features of the excluded studies.

**Risk of bias in included studies**

We included an assessment of the risk of bias of each of the individual studies in the characteristics of included studies table (Supplementary file 3). About 24% of the RCTs were considered to be at high risk of bias while 27% of the non-random studies were considered to be at high risk of bias for the primary outcome of PPH.

**Estimates of treatment effects and between study heterogeneity**

Figure 2 summarises the pooled odds ratios for RCTs and the non randomised studies for treatment effects of misoprostol in the prevention of PPH. The pooled OR for RCTs was 0.69

(95% CIs: 0.59 -0.80) with moderate heterogeneity ($I^2$ = 43.5%, 20 studies, 17,314 participants). The pooled OR for non-randomised studies was 0.46 (95% CIs: 0.36 - 0.63) with considerable heterogeneity ($I^2$ = 79.9%, 14 studies, 56,890 participants).

**Comparison of treatment effects**

Table 1 summarises the comparison of the treatment effects using the z test for interaction and the ratio of odds ratio. The z test of interaction showed a discrepancy in the two estimates (z=2.68, threshold for discrepancy z >1.96 or z <-1.96). Sensitivity analysis showed similar results.

**Combining of treatment estimates**

Table 2 provides the Bayesian estimates obtained from combining results from RCTs with that of non-randomised studies using different priors, and provides a probability statement of the treatment effects in each case. Irrespective of the prior used, the probability statement of a benefit in using misoprostol to prevent PPH was almost 1.

Figure 3 summarises the odds ratios obtained from pooling the treatment estimates using classical and Bayesian approaches for combining the studies. Pooled estimates are similar across all the methods.

**Mapping the sources of evidence**

Figure 4 represents the geographical location where the different studies were conducted. The majority of the the RCTs (57.1%) were conducted in high income settings, while the majority of the non-randomised studies (92.9%) were conducted in low and middle income settings.

## DISCUSSION

### Summary of main results:

A total of 34 studies (20 RCTs and 14 NRS) involving 74,204 participants were identified. The summary OR from RCTs for the use of misoprostol in the prevention of PPH was 0.69 (95% confidence interval (CI): 0.59 -0.80) with moderate heterogeneity ($I^2$ = 43.5%, 20 studies, 17,314 participants). The summary OR from non-randomised studies was 0.46 (95% CI: 0.36 -0.63) with considerable heterogeneity ($I^2$ = 79.9%, 14 studies, 56,890 participants). The overall z test for interaction showed a discrepancy between the two estimates (z=2.68, threshold for discrepancy z >1.96 or z <-1.96). Sensitivity analysis showed similar results. Classical and Bayesian approaches of combining the two study designs both showed benefit of misoprostol in preventing PPH, with similar pooled estimates. The majority of the the RCTs (57.1%) were conducted in high income settings, while the majority of the NRS (92.9%) were conducted in low and middle income settings.

### Comments

To the best of our knowledge, this is the first study comparing treatment effects on the use of misoprostol in the prevention of PPH among RCTs and non-randomised studies, and to pool treatment effects across both study designs. The z test of interaction is a test of the null hypothesis that the RCTS and non-randomised study estimates are equal (25). The results show that though not equal, the estimates from the two study designs are comparable as both suggest a benefit of misoprostol in preventing PPH, with non-randomised studies overestimating the protective effect. Overestimation of treatment effects by observational studies has previously been reported (14,68).

Mapping of the sources of evidence highlights the fact that most of the evidence from RCTs on this topic is from high income countries. This is pertinent given that the persistence of PPH in LMICs since 1990 (69). Consequently, a reliance on evidence from RCTs on this topic for policy and decision making in these settings will largely ignore any form of internal or local evidence. Our results suggest that local evidence from non-randomised studies is probably telling us the right message, and we should seek ways of including it in clinical and policy decisions rather than ignoring it. One may argue about the validity of this evidence from non-randomised studies, but ignoring it altogether in favour of external evidence is probably not the right approach. Adequate methodological approaches of incorporating this evidence as highlighted in this study, is probably the way forward.

We explored varied approaches of combining evidence from RCTs with that of non-randomised studies on this topic, each with its merits and demerits. Intuitively, a direct pooling of treatment effects using a classical approach makes us wonder whether we are not actually "mixing apples and oranges". This approach has the potential drawback of assigning more weight to the observational studies given their larger sample sizes. However, by comparing different methods of pooling the two study designs together, we were able to better assess the robustness of our conclusions. Our results remained robust to the different approaches of combining the different study designs, showing strong benefit of misoprostol in preventing PPH in each of the analysis.

Our use of a Bayesian approach to pool data from the different sources has two fundamental advantages. Firstly, it permitted us to combine prevailing internal evidence with valid external evidence on this topic in order to arrive at the conclusion that the use of misoprostol in isolation or in combination with oxytocin is beneficial in preventing PPH. This incorporation of external evidence into the pooled trial data provides a more precise treatment effect estimate (31).

Secondly, it allowed us to give a probability statement about the certainty of our conclusions (31). Irrespective of the prior that was used in the analysis, the probability of a benefit when using misoprostol in preventing PPH was almost 1. This further supports the convergence of evidence from the different sources. We believe that the use of a Bayesian meta-analysis in this study was not only appropriate, but better helped us understand the evidence.

**Strengths of this study**

The broad search strategy without language restrictions permitted capturing a wide range of studies thereby ensuring that most relevant studies were included. This provides a higher applicability of the conclusions to clinical practice. The use of two independent reviewers for screening, data extraction and risk of bias assessment adds to the strengths of the study in ensuring data accuracy and adequacy. We employed a rigorous methodology with sensitivity analysis permitting adequate conclusions to be drawn from the data collected. By comparing classical and Bayesian approaches of pooling data, this study provides a more integrated approach to combining data between different study designs. The use of a random-effects meta-analysis to pool data helped to account for between study variation (31).

**Potential limitations**

The study is limited by the methodological limitations of the studies included in this review, especially the non-randomised studies. This is partially reflected by the high level of unexplained heterogeneity observed among these studies ($I^2$=79.9%), but was unavoidable given the design of the study. A drawback of Bayesian meta-analysis is that the results depend on the prior used (31). Our results however remained robust despite using three different prior assumptions.

### Study implications

This work has important implications for policy and research on the prevention of PPH using misoprostol. Misoprostol given in isolation or as an adjunct to oxytocin is beneficial in reducing PPH. Our results from the mapped sources of evidence suggest that in LMICs, there is a lot of evidence on the use of misoprostol in the prevention of PPH from non-randomised studies as compared to evidence from RCTs. In the absence of evidence from RCTs, local evidence from non-randomised studies can be used either in isolation or in combination with "external evidence" for clinical and policy decisions, rather than relying solely on "external evidence" from RCTs for this purpose.

## CONCLUSION

Both randomised and non-randomised studies on the use of misoprostol in the prevention of PPH show benefit. The results from both study designs are comparable, with non-randomised studies tending to overestimate the treatment effect. Different methods of pooling across both study designs all show benefit of misoprostol in preventing PPH.

## LIST OF ABBREVIATIONS

PPH (Post-partum haemorrhage), RCT (Randomised Controlled trial), NRS (Non-Randomised Study), MEDLINE (Medical Literature Analysis and Retrieval System Online), EMBASE (Excerpta Medica dataBASE), CENTRAL (Cochrane Central Register of Controlled Trials) PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), OR (Odds Ratio), ROR (Ratio of Odds Ratio), CI (Confidence Interval), SE (Standard Error), *var* (variance), *ln* (Natural logarithm), CrI (Credible Interval).

## DECLARATIONS

### Ethics Approval and Consent to participate

Being a systematic evaluation of already published literature, we did not need any ethical approval nor patient consent in order to conduct this study.

### Consent for publication

Not applicable.

### Availability of supporting data

Data analysed during the current study is available upon request from the authors. A list of additional material is found in the appendix, and references made to them within the manuscript.

### Competing interests

None

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**Authors' contributions**

FM conceived the research idea. FM, BM and AB did the study searches and title and abstract screening. FM and BM did the data extraction, while LM helped with arbitration of discrepancies. LT provided input for statistical analysis. FM developed the statistical models and ran the initial analyses. FM made the first draft. All authors reviewed several versions of the manuscript. All authors read and approved the final manuscript.

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# LIST OF TABLES IN CHAPTER 3

**Table 1: Comparison of treatment effects, main and sensitivity analysis**

| **Comparison** | **$OR_{RCT}$ (95% CI)** | **$OR_{NRS}$ (95% CI)** | **Main analysis (z test for interaction)$_a$** | **Sensitivity analysis (Ratio of odds ratios $OR_{RCT}/OR_{NRS})_b$(95% CI)** |
|---|---|---|---|---|
| All studies (20 RCTs, 14 NRS) | 0.69 (0.59-0.80) | 0.46 (0.36-0.63) | 2.68 | 1.5 (1.09 - 2.06) |

RCT = Randomised controlled trials; NSR = Non-randomised studies; $OR_{RCT}$ = Odds ratio randomised controlled trials; $OR_{NRS}$ = Odds ratio in non randomised studies; 95% CI = 95% confidence interval; a = threshold for discrepancy, absolute z > 1.96; b = threshold for discrepancy, $0.5 \leq OR_{RCT}/OR_{NRS} \geq 2$.
All data are based on a random-effects calculation

**Table 2: Results of Bayesian approaches to combining randomised and non-randomised studies**

| Source of Assumptions | Prior distribution | Odds ratio (OR) (95% credible interval) | Probability of OR < 1 | Between study variance on log odds ratio scale |
|---|---|---|---|---|
| Non-randomised studies only | Non-informative prior distribution | 0.43 (0.27,0.63) | 0.99 | 2.49 |
| RCT data only | Non-informative prior distribution | 0.57 (0.45, 0.69) | > 0.99 | 3.97 |
| Synthesis of RCT data with non-randomised studies | Informative prior distribution from observational studies [a] | 0.49 (0.38, 0.63) | > 0.99 | 2.14 |
| | Sceptical prior distribution from observational studies [b] | 0.57 (0.422, 0.75) | 0.99 | 2.16 |

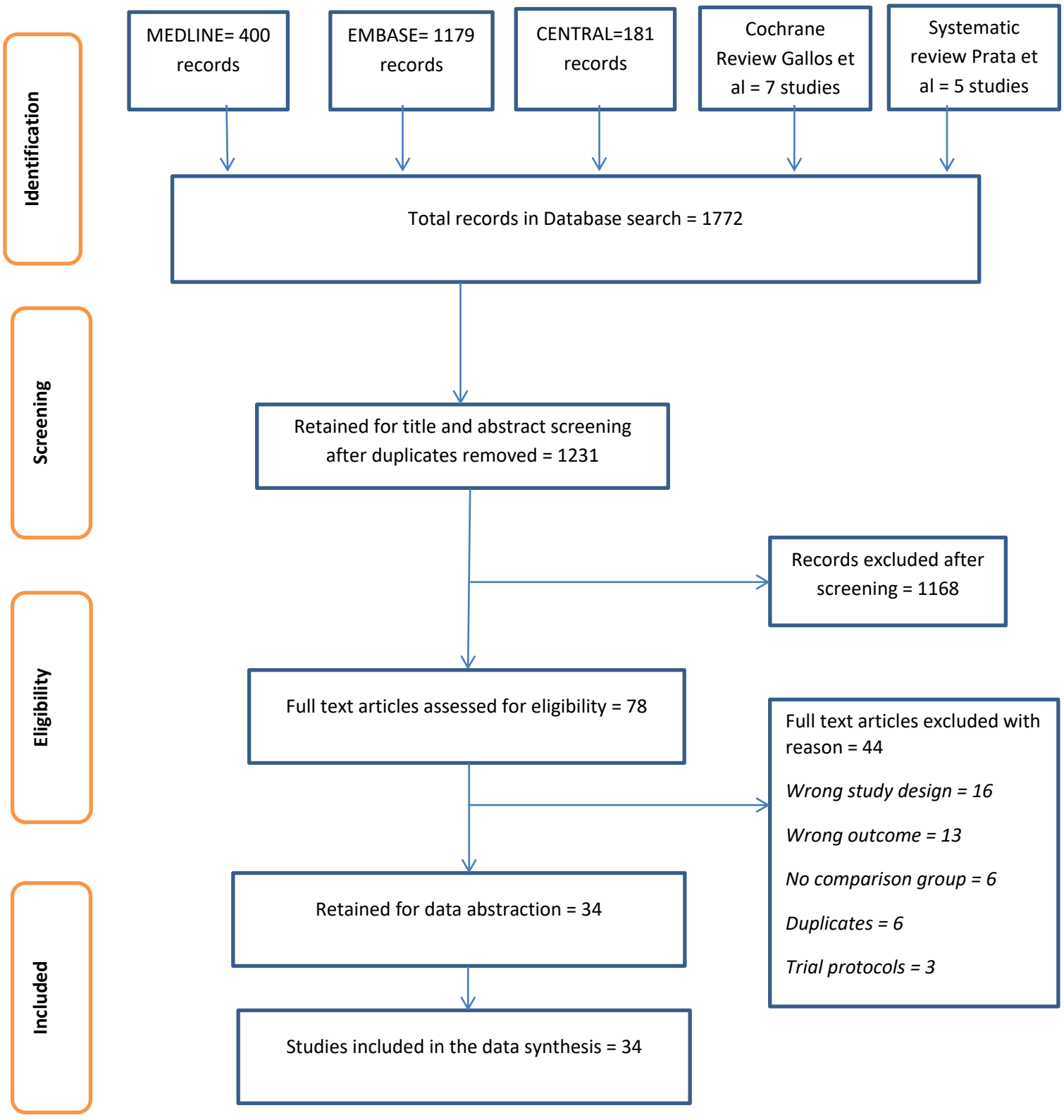
[a] The Bayesian estimate obtained from the 14 non-randomised studies are: log odds ratio (log OR) = -0.873 (95% Credible interval [Cr.I] -1.298, -0.456) standard deviation (SD) of log OR = 0.211, therefore the within study variance = 0.044 and precision = 22.48

[b] Mean=0; variance = 0.263 * 0.263: precision = 3.79 such that the prior probability that the true odds ratio is > 0 is 0.05; between study standard deviation is adopted from Bayesian estimate from observational studies.

RCT = Randomised controlled trial

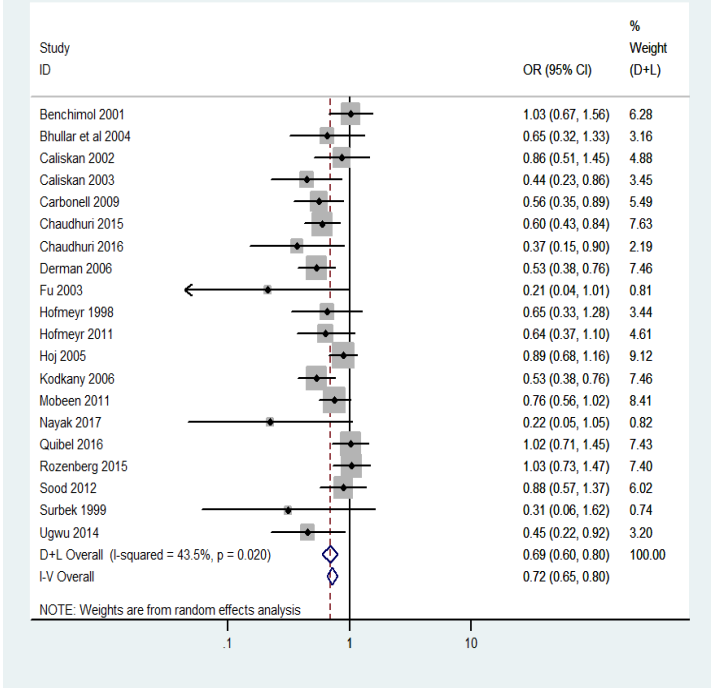
# LIST OF FIGURES CHAPTER 3

## Figure 1: PRISMA Flow Diagram

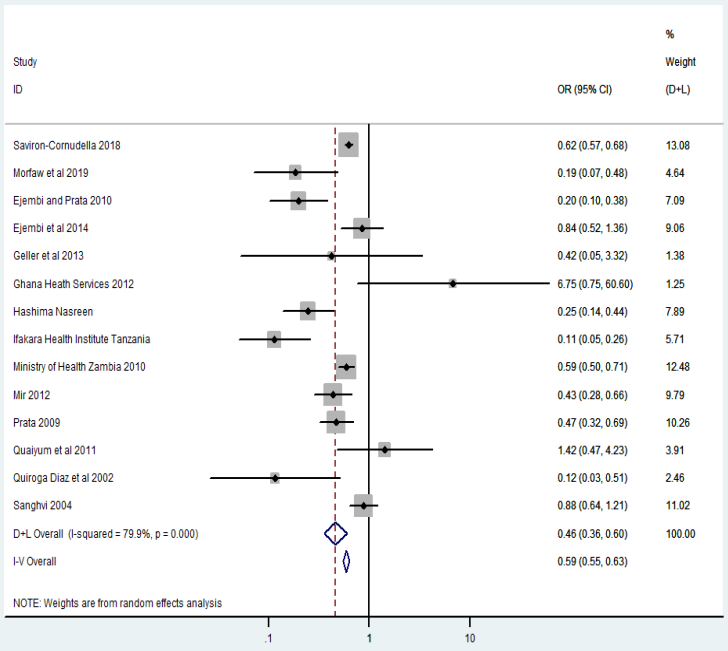


# Figure 2: Overall summary meta-analysis for randomised controlled trials and observational studies

**Randomised controlled trials**

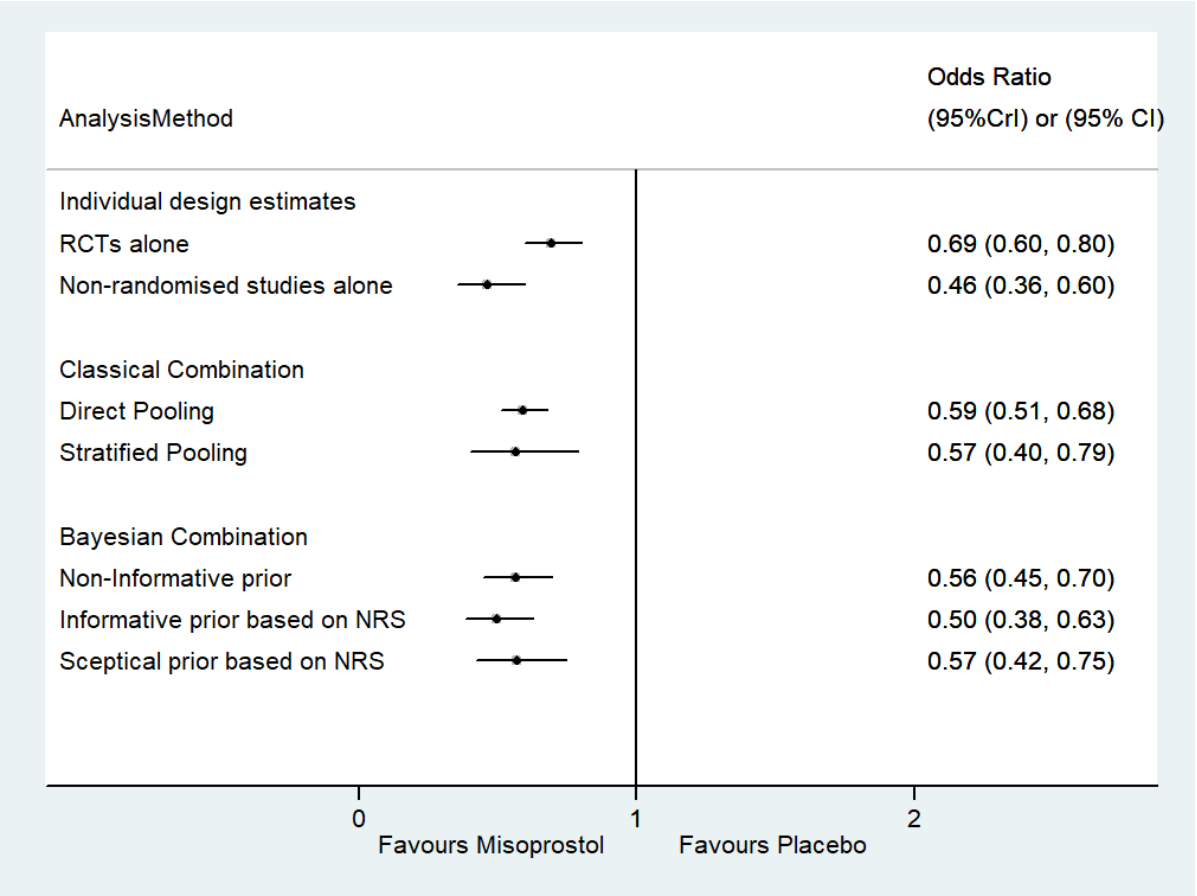



**Non-randomised studies**



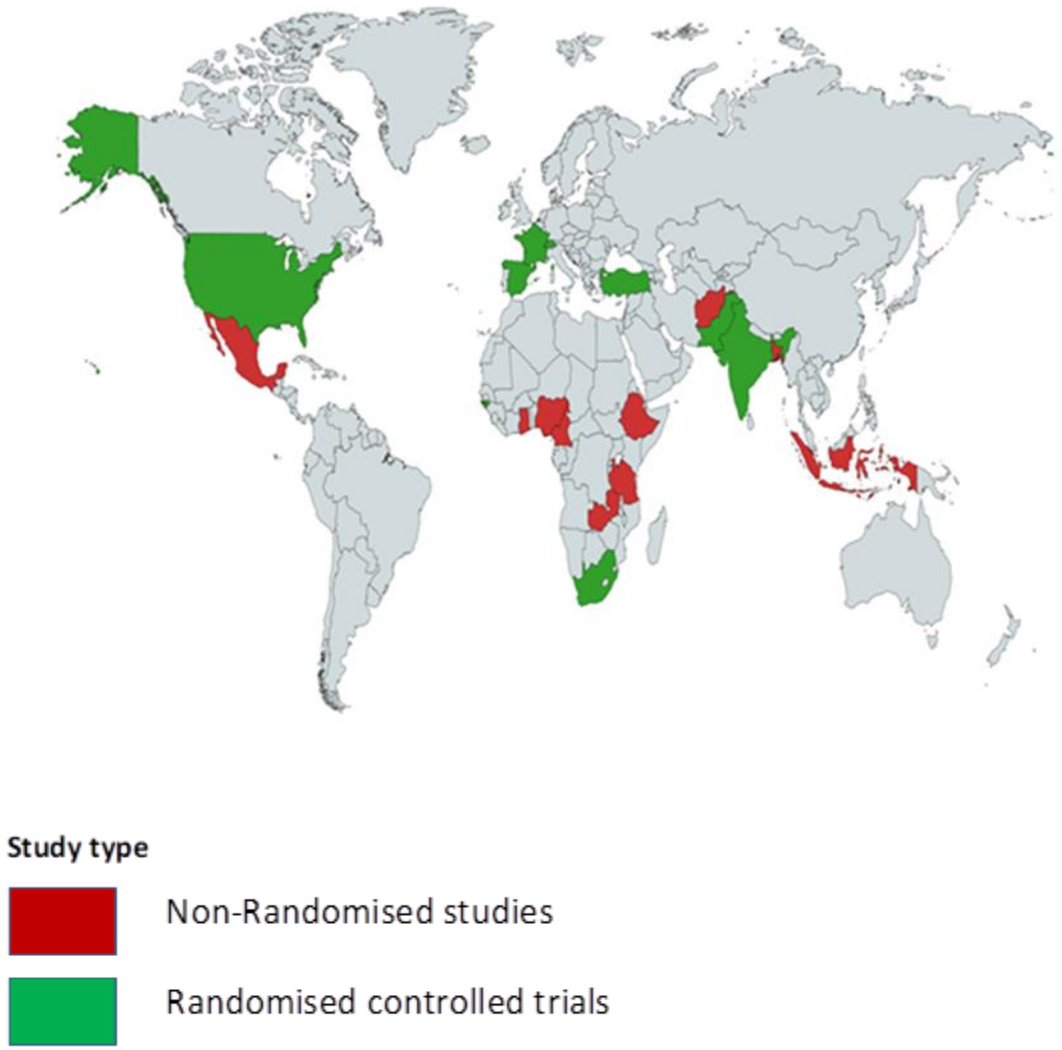

OR= Odds Ratio; 95% CI = 95% Confidence interval

## Figure 3: Comparing Classical and Bayesian approaches to combining randomised and non-randomised studies




RCT=randomised controlled trial; NRS= Non-randomised studies; 95% CrI = 95% credible intervals (applicable for the Bayesian estimates only); 95% CI = 95% confidence interval (applicable for non-Bayesian estimates)

**Figure 4: Mapping of source of research evidence on misoprostol on the prevention of postpartum haemorrhage according to study design**



# SUPPLEMENTARY FILES CHAPTER 3

## Supplementary file 1, Medline search strategy

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | misoprostol.mp. or Misoprostol/ | 5152 |
| 2 | cytotec.mp. or exp Misoprostol/ | 3935 |
| 3 | exp Postpartum Hemorrhage/ | 6513 |
| 4 | Postpartum Hemorrhage/ or PPH.mp. | 10334 |
| 5 | exp Postpartum Hemorrhage/ or postpartum bleeding.mp. | 6661 |
| 6 | 1 or 2 | 5160 |
| 7 | 3 or 4 or 5 | 10474 |
| 8 | 6 and 7 | 400 |

## Supplement 2: Characteristics of excluded studies

| Study | Reason for exclusion |
|---|---|
| Gulmezoglu et al 2001 (1) | Wrong comparator: Misoprostol vs oxytocin |
| Anderson 2005 (2) | Background article |
| Walraven et al 2005 (3) | Trial protocol |
| Weeks 2012 (4) | Trial protocol |
| Weeks et al 2013 (5) | Wrong outcome |
| Bamigboye, et al 1998 (6) | Wrong outcome, blood loss >1000cc |
| Weeks et al 2015 (7) | Wrong outcome. Drop in hemoglobin after 5days |
| Mir et al 2012 (8) | Duplicate article |
| Aleem-Abdel et al 2001 (9) | Wrong outcome |
| Aleem-Abdel et al 2001 (9) | Wrong outcome/Duplicate article |
| Misprostol as postpartum oxytocic?. South African Medical Journal. 2001 (10) | Background article |
| Nielsen et al. 2006 (11) | Wrong outcome, treatment |
| Kodkany et al 2004 (12) | This is a trial protocol |
| Carpenter. 2003 (13) | Background article |
| Durocher et al 2011 (14) | Duplicate of article Mobeen et al 2011 |
| El-Refaey, et al 1996 (15) | No comparison group |
| El-Refaey, et al 1997 (16) | No comparison group |
| Amant 2001 (17) | Background article |
| Hofmeyr et al 2001 (18) | Wrong outcome |

| | |
|---|---|
| El-Refaey et al 1996 (19) | No comparisongroup |
| Sanghvi et al 2010 (20) | Duplicate article |
| Hofmeyr, et al 2001 (18) | Duplicate article, Wrong outcome |
| Hofmeyr, et al 2011/12//. 16:180 (21) | Wrong publication type. Commentary on a different article |
| Khan et al 2002 (22) | Commentary |
| Bellad et al 2012 (23) | Background article |
| Mir et al 2012 (8) | Duplicate article |
| O'Brien et al 1997 (24) | No comparison group |
| Ramsey et al 1999 (25) | Commentary |
| Rani, et al 2013 (26) | Commentary |
| Khan et al 2002 (22) | Commentary/Background article |
| Rozenberg et al 2015 (27) | Duplicate article |
| Rani et al, 2013 (26) | Background article |
| Rajbhandari, et al 2006 (28) | No comparison group |
| Anderson, T 2005 (2) | Background article/Duplicate |
| Udofia et al 2008 (29) | Background article |
| Uncu, et al 2015 (30) | Wrong study outcome |
| Walder, J. 1997 (31) | Background article |
| Wang, S. 2010 (32) | No comparison group |
| Weeks et al 2015 (33) | Wrong study outcome |
| Amant 2001 (17) | Background article/ Duplicate article |
| Song et al, 2001 (34) | Background article |

| | |
|---|---|
| Hofmeyr et al 2008 (35) | Background article |
| Prata et al 2009 (36) | Duplicate article |
| Weeks et al 2013(5) | Duplicate article/ Wrong study outcome, drop in hemoglobin 3 - 5 days post partum |

**References for the excluded studies**

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# Supplement 3: Characteristics of included studies

| Study | Study period | City/country | Design | Comparison type | Dose of misoprostol | Route of misoprostol | Sample size | ROB |
|---|---|---|---|---|---|---|---|---|
| Saviron-Cornudella 2018 (1) | 2007 - 2014 | Zaragosa / Spain | Historical control studies | Misoprostol + oxytocin vs oxytocin | 600mcg | Rectal | 34631 | Low |
| Morfaw et al 2019 (2) | 2015 - 2016 | Bamenda/Cameroon | Historical control studies | Miso + Oxy vs Oxy | 600mcg | oral | 1238 | Low |
| Ejembi and Prata 2010 (3) | 2009 | Zaria/Nigeria | Prospective nonrandomised studies | Misoprostol vs placebo/nothing | 600mcg | Oral | 1796 | Low |
| Ejembi et al 2014 (4) | 2009 | Zaria/Nigeria | Prospective nonrandomised studies | Misoprostol vs placebo/nothing | 600mcg | Oral | 1500 | Low |
| Geller et al 2013 (5) | 2011 - 2012 | Bonsaaso Millenium Village/Ghana | Prospective nonrandomised studies | Misoprostol vs placebo/nothing | 600mcg | Oral | 484 | Serious |
| Ghana Heath Services 2012 (6) | 2009 - 2011 | Ghana | Prospective nonrandomised studies | Misoprostol vs placebo/nothing | 600mcg | Oral | 978 | Serious |
| Hashima Nasreen 2011 (7) | 2009 - 2010 | Bangladesh / Nilphamari district (intervention) and Naogaon district (control) | Prospective nonrandomised studies | Misoprostol vs placebo/nothing | 400mcg | Oral | 2017 | Low |
| Ifakara Health Institute Tanzania 2011 (8) | 2009 - 2010 | Tanzania | Prospective nonrandomised studies | Misoprostol vs placebo/nothing | 600mcg | Oral | 2073 | Low |
| Ministry of Health Zambia 2010 (9) | 2009 - 2010 | Zambia | Prospective nonrandomised studies | Misoprostol vs placebo/nothing | 600mcg | Oral | 1989 | Serious |
| Mir 2012 (10) | 2009 - 2010 | Pakistan/ Khanewal and Dadu districts | Prospective nonrandomised studies | Misoprostol vs placebo/not | 600mcg | Oral | 1367 | Serious |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | hing | | | | |
| Prata 2009 (11) | 2005 - 2007 | Ethiopia/Tigray | Prospective nonrandomised studies | Misoprostol vs placebo/nothing | 600mcg | Oral | 966 | Low |
| Quaiyum et al 2011 (12) | 2009 - 2010 | Bangladesh | Prospective nonrandomised studies | Misoprostol vs placebo/nothing | 600mcg | Oral | 2524 | Low |
| Quiroga Diaz et al 2002 (13) | 1999 - 2001 | Monterrey/Mexico | Prospective nonrandomised studies | Miso + Oxy vs Oxy | 800mcg | Vaginal | 400 | Low |
| Sanghvi 2004 (14) | 2002 - 2003 | Indonesia/West Java | Prospective nonrandomised studies | Misoprostol vs placebo/nothing | | Oral | 1494 | Low |
| Benchimol 2001 (15) | 1999 - 2000 | Amiens/France | RCT | Misoprostol vs placebo/nothing | 600mcg | Oral | 602 | High |
| Bhullar et al 2004 (16) | 2000 - 2002 | Orlando Florida | RCT | Miso + oxy vs oxy only | 200mcg | Oral | 756 | Low |
| Caliskan 2002 (17) | 2000 | Ankara/Turkey | RCT | Miso + oxy vs oxy only | 600 | Rectal | 808 | Low |
| Caliskan 2003 (18) | 2000 | Ankara/Turkey | RCT | Miso + oxy vs oxy only | 600mcg | Oral | 788 | Low |
| Carbonell 2009 (19) | 2007 - 2008 | Valencia/Spain | RCT | Miso + oxy vs oxy only | 600mcg | Oral + rectal | 1400 | High |
| Chaudhuri 2015 (20) | 2012 - 2013 | Kolkata/India | RCT | Miso + oxy vs oxy only | 400mcg | Oral | 396 | Low |
| Chaudhuri 2016 (21) | 2012 - 2014 | Kolkata/India | RCT | Miso + oxy vs oxy only | 400mcg | Oral | 288 | Low |
| Derman 2006 (22) | 2002 - 2005 | Karnataka state/ India | RCT | Misoprostol vs placebo/nothing | 600mcg | Oral | 1620 | Low |
| Fu 2003 (23) | | | RCT | Misoprostol vs placebo/nothing | | | 156 | High |
| Hofmeyr 1998 | | South Africa/Johanes | RCT | Misoprostol vs | 400mcg | Oral | 500 | Low |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (24) | | burg | | placebo/not hing | | | | |
| Hofmeyr 2011 (25) | 2006 - 2007 | East London/ South Africa | RCT | Miso + oxy vs oxy only | 400mcg | Oral | 1099 | Low |
| Hoj 2005 (26) | 203-2004 | Guinea Bissau/Bissau | RCT | Misoprostol vs placebo/not hing | 600mcg | Oral | 661 | Low |
| Kodkany 2006 (27) | | India | RCT | Misoprostol vs placebo/not hing | 600mcg | Oral | 1620 | High |
| Mobeen 2011 (28) | 2006 - 2008 | Pakistan/ Chikral | RCT | Misoprostol vs placebo/not hing | 600mcg | Oral | 1119 | Low |
| Nayak 2017 (29) | | Burla/India | RCT | Miso + oxy vs oxy only | 400mcg | Oral | 200 | High |
| Quibel 2016 (30) | | Paris/France | RCT | Miso + oxy vs oxy only | 400mcg | Oral | 1603 | Low |
| Rozenberg 2015(31) | | France/Poissy | RCT | Miso + oxy vs oxy only | 400mcg | Oral | 1721 | Low |
| Sood 2012 (32) | | New delhi/ India | RCT | Miso + oxy vs oxy only | 400mcg | Oral | 174 | Low |
| Surbek 1999 (33) | 1997 - 1998 | Basel, Switzerland | RCT | Misoprostol vs placebo/not hing | 600mcg | Oral | 65 | Low |
| Ugwu 2014 (34) | 2011 - 2012 | Ibadan/Nigeria | RCT | Miso + oxy vs oxy only | 400mcg | Oral | 120 | Low |

**References for the included studies**

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# Supplementary file 4: Codes for Bayesian Model

1. **Code of Bayesian model, initial values, number of iteration and burn-in model used for non-randomised studies and non-informative randomised controlled trial model**

```
model
    {
        for( i in 1 : Num ) {
            rc[i] ~ dbin(pc[i], nc[i]) ;                    # Binomial structure
            rt[i] ~ dbin(pt[i], nt[i]) ;
            logit(pc[i]) <- mu[i]
            logit(pt[i]) <- mu[i] + delta[i] ;              # Define log (odds ratio)
            mu[i] ~ dnorm(0.0,1.0E-5);                      # Prior for mu
            delta[i] ~ dnorm(d, tau)                        # Random effects
        }
        d ~ dnorm(0.0,1.0E-6)                               #Non informative prior for mean
        tau~dunif(0,10)                                     # Non informative prior for between
study standard deviation
        delta.new ~ dnorm(d, tau)                           # predicted effect
        sigma <- 1 / sqrt(tau)
        w.var<- (sigma*sigma)   # within study variance
      tau.sq<-tau*tau           # between study variance
      prec<-1/(tau.sq)
    OR <- exp(d)            # Convert to odds ratio
    prob <- step(0-d)   # Posterior probability of odds ratio less than 1
    }
list(d = 0, delta.new = 0, tau=1, mu = c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0),
        delta = c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0))
```

Using non-informative prior probabilities

Iteration=100,000

Thin=1

Burn-in=10,000

Seed=91000

**2. Code of Bayesian model, initial values, number of iteration and burn-in model used for RCTs informative prior**

```
model
    {
        for( i in 1 : Num ) {
            rc[i] ~ dbin(pc[i], nc[i])
            rt[i] ~ dbin(pt[i], nt[i])
            logit(pc[i]) <- mu[i]
            logit(pt[i]) <- mu[i] + delta[i]
            mu[i] ~ dnorm(0.0,1.0E-5)
            delta[i] ~ dnorm(d, tau)
        }
        d ~ dnorm(-0.873, 22.48)    # informative prior for mean from NRS, with variance 0.0445
        tau~dunif(0, 3.47)          # Informative prior for between study standard deviation with tau square = 12.1
        delta.new ~ dnorm(d, tau)
      tau.sq<-tau*tau           # between study variance
      prec<-1/(tau.sq)          # precision
    OR <- exp(d)            # Convert to odds ratio
    prob <- step(0-d)   # Posterior probability of odds ratio less than 1
    }
```

For the non informative analysis, we did 101000 iterations and discarded the first 10000 values following model convergence. Seed 91000

For the informative analysis using NRS prior, we did 105471 iterations and discarded the first 10000 values following model convergence. Seed 95492 Iteration=100,000 (Thin=1, Burn-in=10,000, Seed=95492)

### 3. Code of Bayesian model, initial values, number of iteration and burn-in model used for RCTs sceptical prior

```
model

    {

        for( i in 1 : Num ) {

            rc[i] ~ dbin(pc[i], nc[i])

            rt[i] ~ dbin(pt[i], nt[i])

            logit(pc[i]) <- mu[i]

            logit(pt[i]) <- mu[i] + delta[i]

            mu[i] ~ dnorm(0.0,1.0E-5)

            delta[i] ~ dnorm(d, tau)

        }

        d ~ dnorm(0, 3.79)    # skeptical prior for between study standard deviation such as only a 5% chance to detect the alternative hypothesis

        tau~dunif(0, 3.47)        # Informative prior for between study standard deviation from Non randomised studies

        delta.new ~ dnorm(d, tau)

      tau.sq<-tau*tau          # between study variance

      prec<-1/(tau.sq)         # precision

    OR <- exp(d)           # Convert to odds ratio

    prob <- step(0-d)   # Posterior probability of odds ratio less than 1

    }
```

For the sceptical prior analysis, we did 117576 iterations and discarded the first 10,000 values following model convergence. Seed 107508. (Thin=1, Burn-in=10,000, Seed=107508)

# CHAPTER 4

## Development of a scale to assess male partner involvement in the prevention of mother-to-child transmission of HIV

# Development of a scale to assess male partner involvement in the prevention of mother-to-child transmission of HIV

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**ABSTRACT**

**Background:** Male partner participation in the prevention of mother to child transmission (PMTCT) of the Human Immuno-Deficiency virus (HIV) is recognized as being critical for the success of a PMTCT program. Limited attempts have been made to measure it and a validated tool is lacking.

**Objectives:** To develop a tool to measure male partner involvement in PMTCT of HIV, and determine its internal consistency and validity.

**Methods:** Our study was designed in two phases. The first phase was a systematic review to identify items used to describe male partner involvement in PMTCT. The items were used to develop a questionnaire. The second phase, was a cross sectional study to test the different items of the questionnaire on 266 participants. Principal component analysis was used to group items that measured the same construct. Cronbach's alpha was used to test internal consistency. Multiple linear regression analysis was used to test construct validity.

**Results:** The final scale with 20 items consisted of two subscales: supportive and non-supportive domains of male partner involvement in PMTCT. Estimates of Cronbach's alpha for internal consistencies of the subscales were 0.91 (95% confidence interval [CI]: 0.89, 0.92) and 0.89 (95% CI: 0.87, 0.91), respectively. Scores on the scale varied from 20 to 100. Based on the 50th and 90th percentile scores of the study participants, a male partner can be considered as being "uninvolved" (score ≤67 ), "partially involved" (score 68 to 88) or "involved" (score≥ 89) in the PMTCT cascade. The results of the regression indicated that older age of the woman (estimated β=0.29 [95% CI: 0.06, 0.53], p=0.016), and living together with the male partner (estimated β=4.35, [95% CI: 1.60, 7.11], p=0.002), were found to be positive predictors of male partner

PMTCT involvement, and associated with higher scores. The fear of the male partner to know his HIV status was associated with significantly lower scores (estimated β=-16.36, [95% CI: -20.40, -12.32], p<0.001).

**Conclusion:** We have developed a tool to measure an attribute we call "Male partner involvement in PMTCT", and have assessed its internal consistency and validity. More research still remains to validate the tool.

**Key words:** Male, spouse, partner, PMTCT, participation, involvement, scale

## 1. BACKGROUND

According to the United Nations Children's Fund (UNICEF), there were about 1.4 million pregnant women living with the Human Immuno-Deficiency Virus (HIV) worldwide by 2016 (1). About 33% of children born to women who are HIV-positive will acquire the infection in the absence of any preventive efforts (2). Prevention of mother to child transmission of HIV has been described as a "key pillar in the worldwide response to the AIDS epidemic" (3). Interventions aimed at preventing mother to child transmission (PMTCT) of HIV, are considered to be highly effective, and have the potential to improve the health of mothers and their children (3).

Many services make up PMTCT interventions, including counseling and testing for HIV, the provision of prophylactic or therapeutic antiretroviral drugs to pregnant women, provision of facilities for safe deliver, and possibilities for safe infant feeding amongst others (2). A critical look at most PMTCT programmes highlights the fact that they are designed as though their clients have total liberty of action and decision making capacity regarding the use of their services (4). However, this is probably not always the case, and a woman's capacity to make decisions about her pregnancy and health is modeled by her community, her partner, as well as societal norms and beliefs with respect to HIV (5). The role of the male partner's involvement in PMTCT has consequently been the subject of research.

Despite evidence in certain contexts pointing out that male partner involvement may hinder a woman's ability to adhere to PMTCT recommendations (6,7), the vast majority of the evidence strongly favour male partner support in the overall success of the PMTCT program, highlighting its benefits in HIV prevention within the couple by enhancing spousal communication (8);

facilitating condom use within the couple (9); approval of HIV testing by the pregnant woman (10) ; the initiation or retention in HIV prophylaxis and treatment (11); or adherence to recommended infant feeding options (12). Consequently, male partner involvement may ameliorate adherence to PMTCT program recommendations and improve program outcomes (12). Nevertheless, getting the male partners 'involved' is not without its challenges and the barriers and facilitators of male partner involvement in PMTCT have been reviewed (13).

Challenges in the definition and interpretation of male partner involvement in PMTCT have been highlighted, and emphasis laid on the lack of an appropriate operational definition of male partner involvement in PMTCT as well as the lack of a validated tool for its measurement (14). An extensive literature review by the World Health Organisation (WHO) to identify possibilities of promoting constructive male engagement in PMTCT further reiterated the methodological challenges in definition of male partner PMTCT involvement and the lack of a standardized way to measure male involvement in PMTCT (4). Therefore the question of participation in what aspects of PMTCT by men constitutes involvement has been asked, and remains a methodological challenge in research addressing male involvement in PMTCT (4). A validated tool for the measurement of male PMTCT involvement is needed.

Limited attempts have been made to measure the level of male involvement in PMTCT. Byamugisha et al used an ad hoc male involvement index comprising six equally weighted variables (15). However, there was no justification for the use of these variables, nor was there any mention of their internal or external validity (4). In addition, they provided no justification for their categorization into "high" and "low" male involvement. Peltzer et al (16) used 6 items in measuring male involvement among HIV-positive women attending antenatal care in Nkangala district in South Africa. They however reported only two of these items. Similar to

Byamugisha et al (15), they did not justify the choice of the items used. They provided a Cronbach alpha value of 0.71 for male involvement within the sample (16), but this value lacked a justification as well. These examples highlight the research gap in the development of a tool to measure male partner involvement in PMTCT. Moreover, none of these previous attempts were primarily geared at developing a tool for measuring male partner involvement in PMTCT.

In this study, we report the development of a tool to measure male partner participation in PMTCT and assess its internal consistency and validity.

## 2. METHODS

### 2.1 Study design

Our study was designed in two phases. The first phase was item identification, done through a systematic review of published literature of male involvement in PMTCT, and is reported elsewhere (13). In the second phase of the study which is reported in this paper, expert consultation was used to determine the face and content validity of the items identified in the systematic review, with irrelevant items being discarded. Retained items were used to develop a questionnaire which was administered in a cross sectional study.

#### 2.1.1 Item identification

Based on a systematic review whose aim was to identify the facilitators of and barriers to male partner involvement in PMTCT (13), two authors (FM and LM), independently identified different attributes of male PMTCT involvement used across studies. The initial list of 40 items is summarised in Appendix 1.

### 2.1.2 Face and content Validity

The initial list of items was reviewed by an external panel of ten experts involved in the management of HIV in pregnancy for face validity. This included 4 physicians, 2 nurses, 2 social workers and 2 patients working in the HIV Accredited Treatment Centre of the North West Regional Hospital Bamenda Cameroon. The expert panel was asked to review the different items for relevance and to provide subjective assessment of whether or not they represented the different facets of male partner involvement in PMTCT. The expert panel was also asked to identify any other aspects of male PMTCT involvement that was not captured by the list. We used Lawshe's content validity ratio (CVR) to quantify the content validity of each of the selected items (17). Following this process, 13 items were eliminated, while no new items were added.

### 2.1.3 Item testing, domains and selection for the final scale

The selected 27 items (see appendix 2) were used to develop an orally administered questionnaire. The questionnaire was structured with any potentially sensitive or controversial items towards the end of the questionnaire to minimise drop-outs. We did not have any initial distinction into domains. The questionnaire was administered in a cross sectional study. Based on the obtained responses, we used principal component analysis and item-total correlation to guide the selection of items for the final scale.

### 2.1.4 Administering the initial questionnaire

The initial questionnaire was pilot tested on a sample of 10 patients to ensure it was not unnecessarily burdensome. It took on average about five minutes to administer. No changes were

made to the questionnaire after the pilot test. The final questionnaire was administered on paper and in person by a trained research assistant.

#### *2.1.4.1 Study setting*

The cross sectional phase of our study was conducted primarily at the Obstetrics and Gynaecology Unit of the Bamenda Regional Hospital, and five other primary healthcare facilities in the North West Region of Cameroon.

#### *2.1.4.2 Study Population and method of sampling for the cross sectional study*

We used a convenience sample of HIV positive pregnant women presenting for antenatal care or delivering at any of the study sites. This sample of patients was chosen because it was easily accessible to us. We used a consecutive sampling strategy, recruiting every eligible patient until our desired sample size was achieved. By choosing patients from these sites, we hoped to get a representative sample of patients both urban and rural. We included in our sample pregnant women and early postpartum women aged 16 years or older, with a confirmed HIV diagnosis, and who had been on prophylactic antiretroviral therapy for at least 4 weeks during the indexed pregnancy. We judged that four weeks was a minimal time frame to assess the impact of male partner support. We excluded pregnant women who did not meet our eligibility criteria. For the purpose of the study, the male partner was the man identified as the biological author of the indexed pregnancy.

#### *2.1.4.3 Patient recruitment and sample size for the cross sectional study:*

Data were collected from November 2017 to February 2018. Based on the recommendation of between 100 and 200 participants to perform a comprehensive item analysis (18,19) we targeted

a total of 250 participants. During the study period, all pregnant women who fulfilled the eligibility criteria were approached. The study objectives were explained to them, and informed written consent to participate in the study was sought. Consenting participants were interviewed individually in a private room by a trained research assistant.

#### *2.1.4.4 Data collection and management*

Data were collected using the interviewer-administered questionnaire. The questionnaires had no personal identifiers. An independent data entry person retrieved the data collection forms from the research assistants at each site at the end of each week. He then transferred their content into a Microsoft Excel version 10 spreadsheet on an independent and secure computer. The principal investigator ensured quality control by checking Excel spreadsheets against the filled questionnaires. Incomplete questionnaires with less than 50% responses were discarded.

### 2.1.5 Data analysis methods

All data collected were transferred to the Statistical Package for Social Sciences (SPSS) software version 20.0 (20) for analysis.

#### 2.1.5.1 Development of the scale

***Item testing***

For the purpose of data analysis and ease of interpretation, given that some of the items were negatively worded, we reversed the coding of the responses of these questions such that all answers were now going in the same direction before analysis. Hence the final responses in the analysis were graded on a Likert scale of 1 to 5 reflecting strong disagreement to strong agreement of male spousal involvement in PMTCT respectively. Two of the questions had

yes/no responses, and were also graded such that the higher scores reflected greater male spousal involvement in PMTCT.

***Item selection:***

Principal component analysis with varimax rotation was used to maximize the variance of the squared loadings of a factor on all items, as we presumed our initial items to be independent of each other. The elbow of a Scree plot and the Eigen values greater than 1 were used to determine principal components. Factor loadings greater than 0.5 on the principal components (21) was used to guide the selection of items. In addition, we used the item-total correlation to determine any items that had no correlation with the scale. Any items with an item-total correlation value of 0.2 or less were eliminated (22,23).

**2.1.5.2 Assessment of internal consistency**

We used Cronbach's alpha to estimate the internal consistency within each domain (24). Our interpretation was guided by the premise that high values of alpha (>0.8) indicate a high correlation between the items all of which may not be necessary. Conversely lower values of alpha (<0.2) indicated that the items in the subscale are unrelated and are assessing different constructs (22).

***2.1.5.3 Assessment of validity***

***Face and content validity***

Thematic variables generated from the systematic review were verified by the expert panel for face validity. We used Lawshe's content validity ratio (CVR) to quantify the content validity of

each of the selected items (17). The content validity ratio was computed using the formula below:

$$\text{CVR} = \frac{ne - (N/2)}{N/2}$$

where $n_e$ is the number experts indicating the item as "essential," and N is the total number of experts in the panel (17). For our panel of 10 experts, we used a critical value of 0.620 as recalculated by Wilson et al (17), to ensure that the expert's judgments exceeded chance expectation at a two-tailed alpha level of 0.05 (17). Hence only items with a CVR value greater than 0.620 were included in the initial questionnaire.

***Construct validity***

We used multiple linear regression analysis to evaluate the association between specific variables and the male partner PMTCT score after adjusting for covariates. Variables assessed for construct validity included age of the woman, place of residence, the role of relationship status (specifically living together), level of partner education, attendance of antenatal visits, and male partner employment. Older age of the woman (25), urban residence of the woman (26), living together (27), higher level of male partner education, attendance of antenatal care with the male partner (28) and government employment status (29), have been found to be positive predictors of male partner PMTCT involvement. We expected these to be associated with higher scores. We also assessed the fear of the male partner to know his HIV status, as this has been shown to be a negative predictor of male partner PMTCT involvement (27,28), and thus expected to be associated with lower scores. We ran a single regression model including all of these variables as covariates. We created dummy variables for categorical variables, and

emphasized the reference categories in the analysis. We report the β coefficients, corresponding 95% confidence interval [CI] and associated p values of each of the variables. We assessed model fit using the coefficient of determination (adjusted $R^2$).

## 3. RESULTS.

### 3.1 Study population

In total, 350 pregnant women were approached in the six recruitment centres, of which 266 were included in the final analysis. Figure 1 summarises the flow of the pregnant women within the study. Characteristics of these women are summarised in Table 1.

### 3.2 Item generation

A total of 40 items were initially identified from the systematic review as reflecting different constructs of male partner participation in PMTCT (Appendix 1). Following consultation with experts in the field, this list was reduced to 27 items (Appendix 2).

### 3.3 Item selection:

After principal component analyses, 4 principal components were identified that explained 58.9% of the variance (see Table 2). These results are also reported on the scree plot in figure 2 which shows the elbow at 4 components. We selected items with factor loadings of 0.5 or higher on any of the principal components (see appendix 3), and ended up with 24 items which we grouped into two domains: supportive (components 1 and 4: 15 items) and non-supportive (components 2 and 3: 9 items) male partner attitudes. This domain distinction was based on the different questions that fell into each domain.

We verified the item total correlation of these 24 items (see appendix 4). Four Items with an item total correlation of less than 0.2 were removed leaving us with 20 items (13 supportive and 7 non-supportive male partner attitudes) (see appendix 4).

### 3.4 Internal consistency

The internal consistency (Cronbach's alpha) of the two subscales (supportive and non-supportive) are summarised in table 3. Neither the internal consistency nor the variance could be modified greatly by removing any of the items. The overall internal consistency (Cronbach's alpha) of the 20 items was 0.85 (95% CI 0.82 – 0.87).

### 3.5 Construct validity

A multiple linear regression analysis was used to assess construct validity (see table 4). A significant regression equation was found ($F(84.94, 1520.94) = 17.91$, $p<0.001$), with an adjusted $R^2$ of 0.458. The results of the regression indicated that older age of the woman ($\beta=0.29$ [95% CI: 0.06, 0.53], $p=0.016$), and living together with the male partner ($\beta=4.35$, [95% CI: 1.60, 7.11], $p=0.002$), were found to be positive predictors of male partner PMTCT involvement, and associated with higher scores. The fear of the male partner to know his HIV status was associated with significantly lower scores ($\beta=-16.36$, [95% CI: -20.40, -12.32], $p<0.001$). Place of residence ($\beta=-0.51$ [95% CI: -3.7, 2.6], $p=0.75$), male partner educational status (university education vs. no education $\beta=0.88$, [95% CI: -12.46, 14.23], $p=0.89$), the male partner accompanying the woman to antenatal care (all the time vs. never $\beta=-3.08$, [95% CI: -7.1, 0.90], $p=0.13$) and government employment status ($\beta=-1.19$, [95% CI: -3.80, 1.43], $p=0.37$) were not associated with scores after adjusting for covariates.

### 3.6 The Final tool

The first iteration of the Scale Assessing Male Partner Participation in PMTCT (SAMPP-PMTCT) is presented in Table 5. Scores on the SAMPP-PMTCT are computed by adding the score rating for each of the individual items of the two subscales. Items 1 to 11 on the supportive subscale, and items 1-7 on the non-supportive subscale are each scored from 1-5. These 18 items will score from 18 to 90. Items 12 and 13 on the supportive subscale are scored thus: No=1, Do not know=3, Yes 5. Scores of these two items will range from 2 to 10. The minimum total score will therefore be 20 and the maximum will be 100. The higher the score, the more involved the male partner is in the PMTCT cascade.

Figure 3 summarises the final scores of the pregnant women included in the study based on the newly developed scale. The mean score was 74.4 (SD 12.5), with the $25^{th}$, $50^{th}$, $75^{th}$ and $90^{th}$ percentile scores being 67, 76, 82 and 89.3 respectively.

## 4. DISCUSSION AND CONCLUSION

### 4.1 Discussion

In this study, we have developed a tool that measures the level of male partner involvement in PMTCT activities. This tool is made up of two domains: Supportive and non-supportive domains of male partner involvement in PMTCT. The complete tool has 20 items grouped into these two domains. Each of the items within this tool carries the same weight and the overall score is a summation of the score of each of the individual items, and can range from 20 to 100. Based on the $25^{th}$, $50^{th}$, $75^{th}$ and $90^{th}$ percentile scores of the patients used in developing this scale, we propose that male partners of clients with scores less than or equal to the $50^{th}$ percentile (score $\leq$67 ) should be considered as “uninvolved” in the PMTCT cascade. Those with scores between

the 50$^{th}$ and 90$^{th}$ percentile (score between 68 to 88 inclusive), should be considered as "partially involved" in the PMTCT cascade. Male partners of women with scores greater than or equal to the 90th percentile (score ≥ 89) should be considered as "involved" in the PMTCT cascade. This guideline will help us identify women mostly in need of male spousal support for PMTCT adherence, and possible strategies for improving this support by identifying aspects in which the woman needs male spousal support, with an overarching aim of a successful PMTCT implementation.

A comparison with similar studies provides some support to the importance of these domains as determinants of male PMTCT involvement. Five of the six items in the adhoc male involvement index developed by Byamugisha et al (15) were retained in this scale. The only item not retained was attendance of ANC visit by the male partner which was equally listed Peltzer et al (16), and which was in our initial questionnaire but later eliminated for a low factor loading. Intuitively, attendance of antenatal care by the male partner seems strongly suggestive of male partner involvement in PMTCT, but it is probably reflected in other items. The second item listed by Pelzer et al (16) concerning knowledge of use of antiretroviral drugs by the partner is also captured by our scale. Consequently, the SAMPP-PMTCT incorporates a good proportion of the known items that have been used to measure male involvement in PMTCT, and this is one of the strengths of our tool. It provides robust evidence why these items should be used for this purpose. In addition, it expands the repertoire of the multifaceted concepts viewed as forms of male involvement in PMTCT, and which at times may be neglected when considering this topic. If health resources are to be allocated to improve male partner involvement in PMTCT, this tool provides an objective assessments of the situation.

Further strengths of this study includes the identification of items based on a comprehensive search of the literature, its large sample size (266 clients), the recruitment of clients from six different health centres providing a rich source of diverse data, and the robust quantitative methodology used in developing the tool.

Our study has some limitations. This scale assumes that all pregnant women have a male partner who is the biological author of the indexed pregnancy. However, the scale will not be applicable to women whose partners are women, or women conceiving by sperm donation, or those who have deliberately kept their male partners unaware of the pregnancy. A second limitation is that in the two questions where a possible answer is "do not know" (questions 12 and 13, subscale 1), this response is rated higher than "no" and lower than a "yes". This may actually bias the results for or against male partner involvement depending on the true underlying response. Nonetheless, we judged this as the best possible way to score this response. A third limitation of our study is the fact that we used Lawshe's CVR to quantify the content validity of each of the selected items (17). However, recalculations have suggested that the critical values used by Lawshe for item inclusion were more conservative than necessary (17), thus minimising the chance of including an unnecessary item in our final scale.

This scale was developed using a sample of Cameroonian women. Hence depending on the population, maybe certain items may have more relevance than others, and the perception of male partner support may vary greatly among regions. However the use of a systematic review of published literature to identify the initial items included in the scale increases the chance of capturing all aspects of male PMTCT participation from different regions among different populations of women.

### 4.2 Implications for practice and research.

This tool was developed on the premise that male partner involvement in PMTCT is beneficial to adhering to the PMTCT cascade. The implications is the reinforcement of strategies to improve male partner involvement in the PMTCT cascade for women with partners categorized as "partially involved" or "uninvolved" in the PMTCT cascade. However, in certain societies, the reverse has been shown to be true (6,7). Intuitively therefore, one can imagine that this scale may be used in such societies to identify women with "involved" male partners, and strategies devised to discourage their involvement in PMTCT. We cannot assert that this scale may fulfill such a purpose, but recommend cautious use and interpretation for users who may wish to use the scale in this manner.

This tool should be used for objective assessment of the level of male partner participation in the PMTCT cascade at the patient level, and comparability of male partner participation in the PMTCT cascade across communities. Based on the context and settings, strategies to improve male partner involvement in the PMTCT cascade can be devised if background research in such communities shows that male partner involvement will be additive rather than detrimental to the PMTCT cascade.

Given that scores on this scale are continuous; our categorization into "uninvolved', "partially involved" and "involved" is somewhat arbitrary, especially when direct comparisons between communities are being made. In such cases, the differences in mean scores will better reflect the relative discrepancy between the two communities than the arbitrary categorization.

A key implication for research for our study would be to determine if higher male partner involvement score is associated with better pregnancy outcomes. This may inform the development of better cut-off points as our present cut-off points are based on percentiles.

### 4.3 Conclusion

We have developed a tool to measure an attribute we call "Male partner participation in PMTCT" and assessed its internal consistency and validity. More research still remains to validate the tool in different settings.

## LIST OF ABBREVIATIONS

UNICEF (United Nations Children's Fund), HIV (Human Immune Deficiency Virus), MTCT (Mother to Child Transmission of HIV) PMTCT (Prevention of Mother to Child Transmission of HIV), AIDS (Acquired Immune Deficiency syndrome) UNAIDS (United Nations Agency for International Development), WHO (World Health Organisation), ART (Anti-retroviral therapy), ANC (Antenatal Care), SAMPP (Scale Assessing Male Partner Participation), SD (Standard Deviation), CI (confidence interval), FM (Frederick Morfaw), LM (Lawrence Mbuagbaw), LA (Laura Anderson) LT (Lehana Thabane), MC (Mbuwe Crescentia), AB (Ayaba Bi).

## DECLARATIONS

### Ethics Approval and Consent to participate

Being a systematic review of published literature, we did not need any ethics approval or patient consent in order to conduct the systematic review phase of the study. Ethics approval to conduct the cross-sectional phase of the study was obtained from the Bamenda Regional Hospital Institutional Review Board decision number 30/APP/RDPH/RHB/IRB. All clients included in the cross-sectional phase of the study provided written informed consent for participation, and strict patient confidentiality was maintained at all stages of the study. In the case of minors, informed consent was obtained from the parents or legally authorized representatives, while assent was obtained from the patients.

### Consent for publication

All participants involved in this the cross-sectional phase of the study provided written informed consent for publication of study findings.

## Availability of data and materials

The dataset used in the development of this tool can be made available upon reasonable request from the corresponding author. A list of additional material used in the current study is found in the appendix, and references made to them within the manuscript.

## Competing interests

None.

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## Authors' contributions

FM conceived the research idea. FM, LM and LT jointly designed the study and developed the initial questionnaire. MC and AB assisted in patient interview and data collection. LM and LA provided guidance with data analysis. FM made the first draft. All authors reviewed several versions of the manuscript. All authors read and approved the final manuscript.

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**Table 1 Socio-demographic characteristics of the 266 participants involved in item testing.**

| **Variable (N=266)** | **Statistic** |
|---|---|
| **Age (Years)**: Mean (SD) | 30.6 (4.9) |
| **Marital status: n (%)[a]** | |
| Single | 43 (16.2) |
| Monogamous | 149 (56.0) |
| Polygamous | 26 (9.8) |
| Cohabiting | 16 (6.0) |
| Divorced | 3 (1.1) |
| Widow | 4 (1.5) |
| **Level of education: n (%)[b]** | |
| None | 3 (1.2) |
| Primary | 77 (30.0) |
| Secondary | 148 (57.6) |
| University | 29 (11.39) |
| **Employment status: n (%)** | |
| Unemployed | 87 (32.7) |
| Self-employed | 118 (44.4) |
| Government employed | 61 (22.9) |
| **Place of residence: n(%) [c]** | |
| Urban | 40 (15.3) |
| Rural | 221 (84.7) |
| **Time (months) since HIV diagnosis: Mean (SD) [d]** | 3.4 (2.9) |
| **Age of partner (Years): Mean (SD) [e]** | 38.5 (5.2) |
| **Partner Level of education: n (%)** | |
| None | 2 (0.8) |
| Primary | 58 (21.8) |
| Secondary | 165 (62.0) |
| University | 41 (15.4) |
| **Partner Employment status: n (%)** | |
| Self-employed | 150 (56.4) |
| Government-employed | 116 (43.6) |
| **Age differential within couple (years): Mean (SD)[f]** | 7.9 (4.5) |

a: 25 (9.4%) missing. b: 9 (3.4%) missing. c: 5 (1.9%) missing. d: 15 (5.63%) missing. e: 16 (6.0%) missing. SD: Standard deviation

**Table 2: Total variance explained for each of the 4 principal components**

| **Component** | **Initial Eigenvalues** | | |
|---|---|---|---|
| | **Total** | **% of Variance** | **Cumulative %** |
| 1 | 8.097 | 29.990 | 29.990 |
| 2 | 5.080 | 18.813 | 48.803 |
| 3 | 1.429 | 5.294 | 54.097 |
| 4 | 1.295 | 4.796 | 58.892 |

**Table 3: Estimates of Cronbach alpha for internal consistency statistics of the scale**

| **Subscale** | **Statistic (95% CI)** |
|---|---|
| Supportive male partner attitudes subscale | 0.91 (0.89, 0.92) |
| Non-supportive male partner attitudes subscale | 0.89 (0.87, 0.91) |
| Overall scale | 0.85 (0.82, 0.87) |

95 % Confidence Interval

**Table 4: Multivariable analysis for assessing construct validity of the scale**

| | Adjusted β (95% CI) | P-value |
|---|---|---|
| Age of the woman (years) | 0.29 (0.06, 0.53) | 0.016 |
| Place of residence (reference=Urban) | -0.51 (-3.67, 2.64) | 0.749 |
| Living together with partner (reference=No) | 4.35 (1.60, 7.11) | 0.002 |
| Partner level of education (Reference=No education) | | |
| Primary | 3.29 (-10.03, 16.59) | 0.627 |
| Secondary | 1.56 (-11.54, 14.66) | 0.815 |
| University | 0.88 (-12.46, 14.23) | 0.896 |
| Male partner attending antenatal care with the female partner (Reference= Never) | | |
| All time times | -3.08 (-7.06, 0.90) | 0.129 |
| Most of the times | -4.56 (-9.72, 0.59) | 0.083 |
| Sometimes | 1.38 (-2.69, 5.46) | 0.505 |
| Rarely | 0.506 (-3.71, 4.73) | 0.813 |
| Government Employment status (reference=employed) | -1.19 (-3.80, 1.43) | 0.372 |
| Male partner afraid to know his HIV status (reference=No) | | |
| Yes | -16.36 (-20.40, -12.32) | <0.001 |
| Do not know | -15.03 (-18.79, -11.27) | <0.001 |

$R^2$= 0.458. Covariates adjusted for included age of the woman, place of residence, the role of relationship status (living together with partner), level of partner education of male partner (partner level of education), male partner attending antenatal care with the female partner, male partner government employment status (government employment status), and the fear of the male partner to know his HIV status (Male partner afraid to know his HIV status). 95% CI: 95% confidence interval

**Table 5: The Scale assessing male partner participation in PMTCT (The SAMPP-PMTCT).**

Subscale 1: Supportive domains of male partner involvement in PMTCT

(Use for responses to questions 1 to 10) 1- Strongly disagree 2- Disagree 3- Neither agree nor disagree 4- Agree 5- Strongly agree

(Use for response to question 11) 1- Never 2- Rarely 3- Sometimes 4- Most of the time 5- All the time

(Use for responses to questions 12 and 13) 1- No 3- Do Not know 5- Yes

| | | **1** | **2** | **3** | **4** | **5** |
|---|---|---|---|---|---|---|
| 1 | Your partner supports antenatal testing for HIV in pregnancy | | | | | |
| 2 | Your partner accepts to participate in couple counselling for HIV | | | | | |
| 3 | Your partner provides you with moral support since testing for HIV | | | | | |
| 4 | Your partner provides you with financial support since testing for HIV | | | | | |
| 5 | Your partner helps you to do physical work at home since testing for HIV | | | | | |
| 6 | Your partner prays for you and supports you spiritually | | | | | |
| 7 | Your partner portrays an understanding attitude towards your HIV status | | | | | |
| 8 | Your Partner communicates with you concerning HIV and the prevention of mother to child transmission of HIV | | | | | |
| 9 | Your partner supports your usage of antiretroviral drugs | | | | | |
| 10 | Your partner supports infant nevirapine use | | | | | |
| 11 | Your partner uses condoms with you during sexual relationships since your testing for HIV? | | | | | |
| 12 | Would/did your partner accept to get tested for HIV? | | | | | |
| 13 | Would/did your partner accept to disclose his HIV status to you? | | | | | |

Subscale 2: Non-supportive domains of male partner involvement in PMTCT

(Use for responses to questions 1 to 7) 1- Strongly agree 2- Agree 3- Neither agree nor disagree 4- Disagree 5- Strongly disagree

| | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| 1 | Partner portrays an attitude of shock and anger towards your HIV test result | | | | | |
| 2 | Partner blamed you for not consulting him before testing for HIV | | | | | |
| 3 | Partner accuses you of infidelity since testing for HIV | | | | | |
| 4 | Partner abuses you verbally because of your HIV status | | | | | |
| 5 | Partner threatens and intimidates you because of your HIV status | | | | | |
| 6 | Partner is physically violent towards you because of your HIV status | | | | | |
| 7 | Partner ill-treats you because of your HIV status | | | | | |

# Total score (addition of individual scores in subscales 1 and 2):

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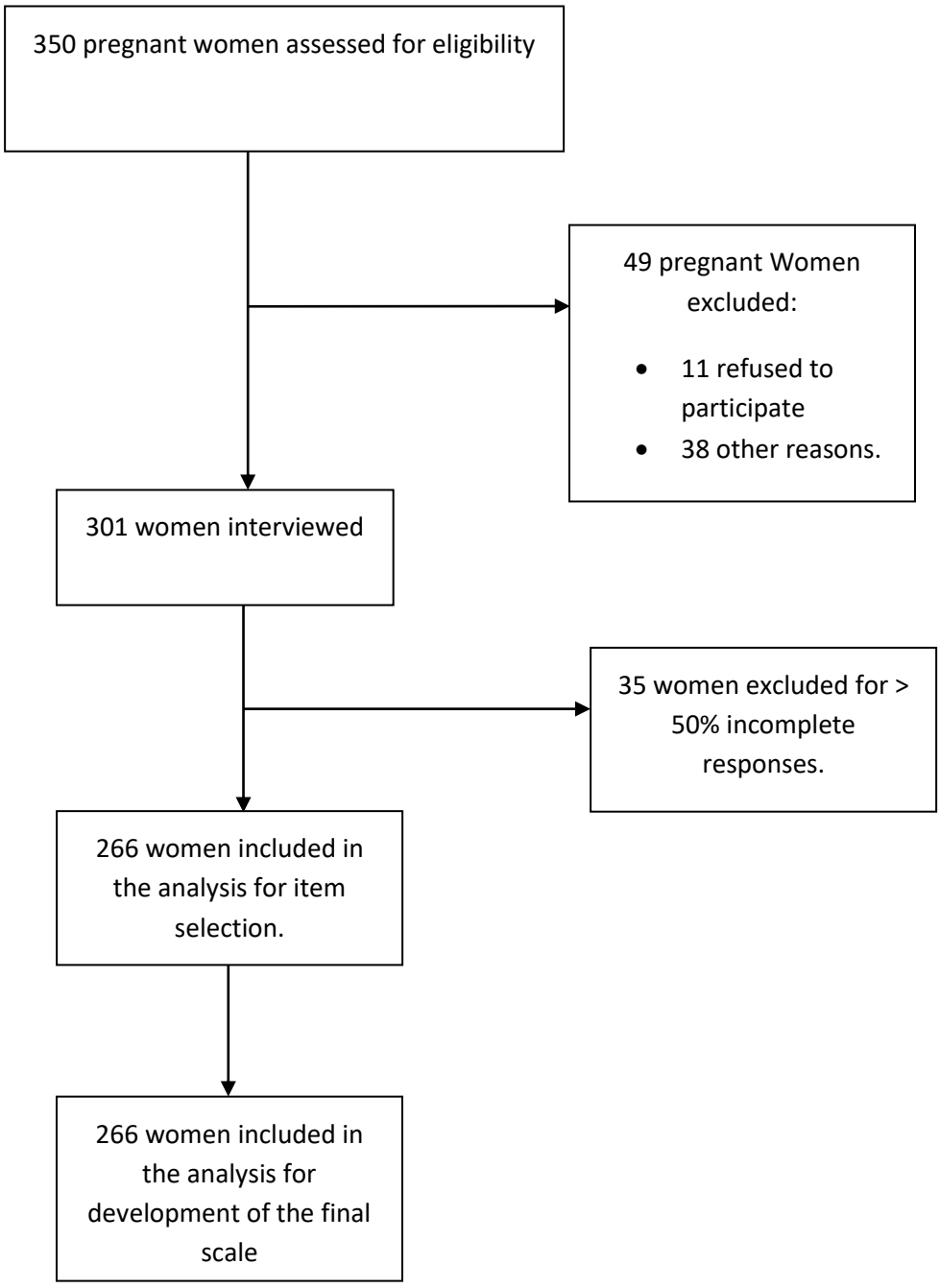
## Figure 1: Flow chart of pregnant women included in the study



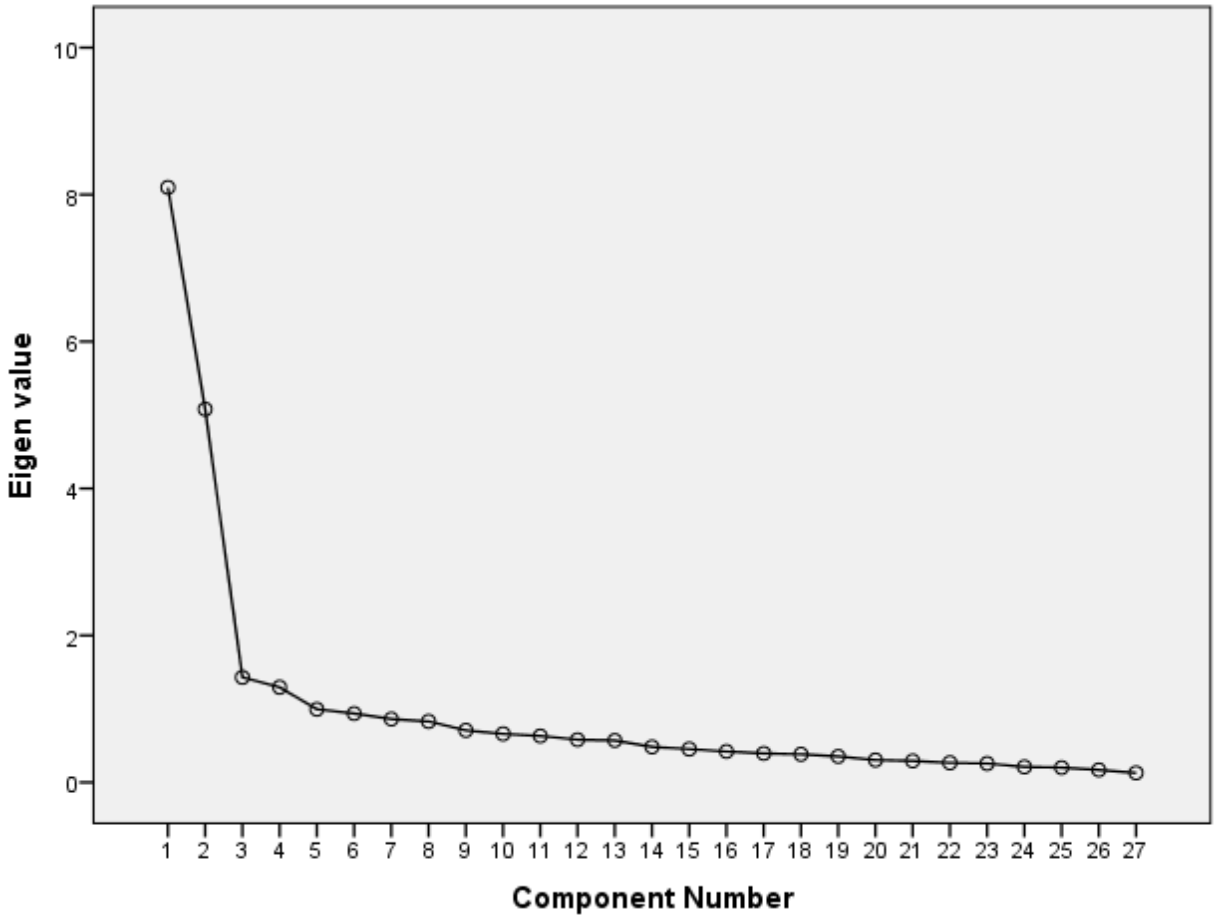



**Figure 2: Scree plot showing elbow at 4 components**

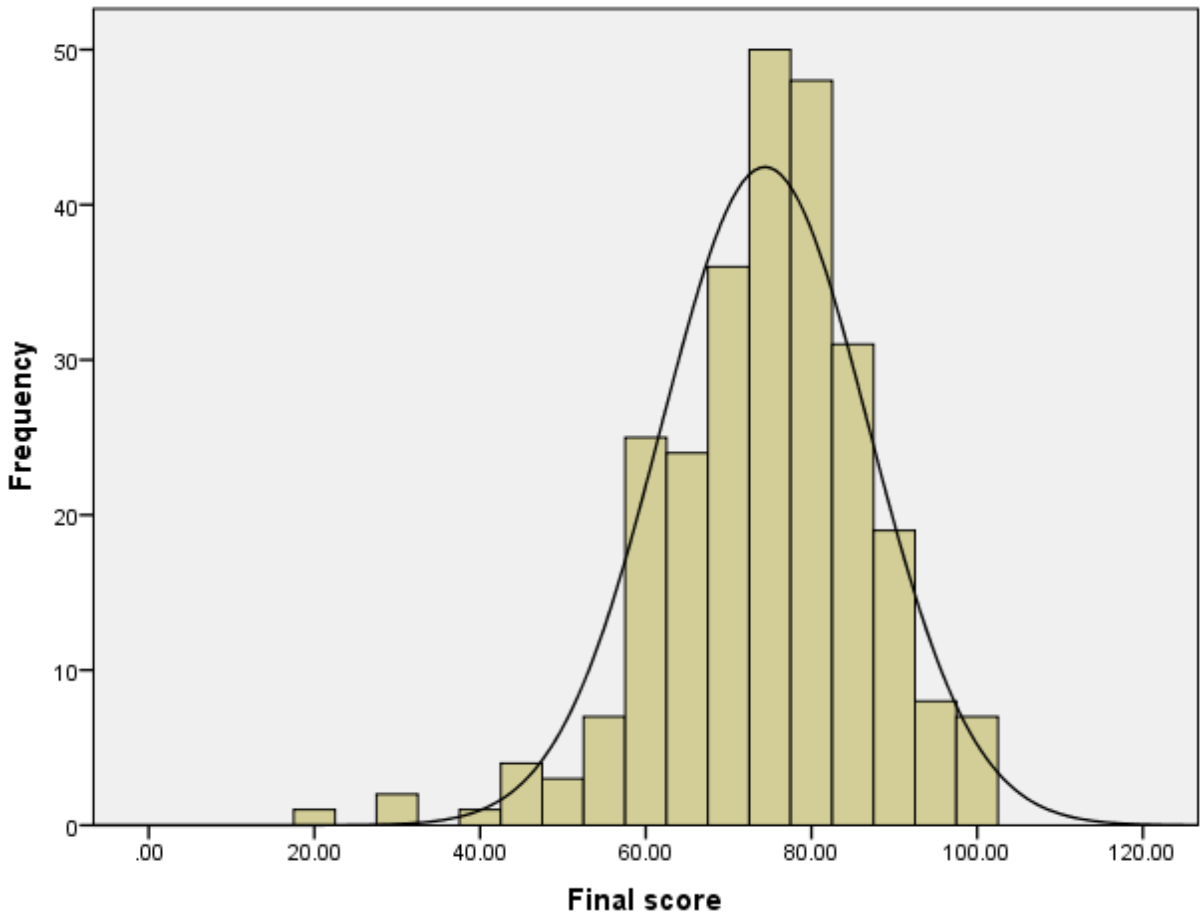



**Figure 3: Frequency distribution of the final score of the pregnant women included in the study**

# SUPPLEMENTARY MATERIAL IN CHAPTER 4

## Appendix 1: Attributes of male partner PMTCT involvement used across studies

1. Accompanying the woman to the antenatal clinic,
2. Supporting of HIV testing in pregnancy,
3. Acceptance to participate in couple counselling of HIV,
4. Accepting to get tested for HIV,
5. Accepting to disclose one's HIV status,
6. Providing moral support
7. Providing physical support
8. Providing spiritual support
9. Providing financial support,
10. portraying an understanding attitude towards the spouses HIV status,
11. Accepting sexual relationships since testing for HIV,
12. Accepting the use of condoms during sexual relationships,
13. remaining faithful to the spouse during the indexed pregnancy,
14. Communicating about HIV and PMTCT,
15. Supporting the use of antiretroviral therapy for the mother
16. Supporting the use of antiretroviral therapy for the infant,
17. Supporting non-breastfeeding,
18. Supporting the use of artificial milk for the infant,
19. Denial of the spouses HIV status,
20. Portrayal of shock and anger towards the spouse's HIV results,
21. Blaming the spouse for not consulting him before testing for HIV,
22. Accusations of infidelity since testing for HIV,
23. verbally abusing the spouse because of her HIV status,
24. Threatening or intimidating the spouse because of her HIV status,
25. Domestic violence towards the spouse since testing for HIV,
26. Ill treatment by the male partner
27. Whether or not the relationship had ended since the spouse was diagnosed with HIV.
28. Accepting voluntary counselling and testing activities in bars
29. Accepting voluntary counselling and testing activities in churches
30. Accepting community sensitization activities about HIV and PMTCT
31. Cooking and caring for the family when the wife is pregnant
32. Acceptance of invitation letter to attend antenatal care
33. Acceptance to attend antenatal care for voluntary counselling and testing at non-working hours
34. Acceptance of PMTCT knowledge sharing by male peers
35. Acceptance of disclosure of HIV results assisted by health personnel
36. Acceptance of disclosure of HIV results assisted by family
37. Acceptance of guidance from elders about HIV and PMTCT
38. Showing love to the female partner
39. Stigmatization of the spouse because of their HIV results
40. Condom use in extra-conjugal relationships

# Appendix 2: Item selection process on the 27 items retained after expert consultation:

| | | Removed for low factor loadings <0.5 | Removed for item total correlation less than 0.2 | Retained |
|---|---|---|---|---|
| 1 | Partner accompanies to ANC | x | | |
| 2 | Partner supports ANC HIV testing | | | x |
| 3 | Partner participates in couple counselling | | | x |
| 4 | Partner accepts to take HIV test | | | x |
| 5 | Partner discloses his status to you | | | x |
| 6 | Partner provides moral support | | | x |
| 7 | Partner provides financial support | | | x |
| 8 | Partner helps do physical work | | | x |
| 9 | Partner prays and supports you spiritually | | | x |
| 10 | Partner provides an understanding attitude | | | x |
| 11 | Partner rejects and refuses sex | | x | |
| 12 | Partner uses condoms during sex | | | x |
| 13 | Partner remains faithful | x | | |
| 14 | Partner communicates with you on HIV PMTCT | | | x |
| 15 | Partner supports usage of ARV drugs | | | x |
| 16 | Partner supports infant nevirapine use | | | x |
| 17 | Partner supports avoidance of breastfeeding | | x | |
| 18 | Partner supports use of artificial milk | | x | |
| 19 | Partner denies your HIV results | | x | |
| 20 | Partner portrays and attitude of shock and anger | | | x |
| 21 | Partner blamed you for not consulting him | | | x |
| 22 | Partner accuses you of infidelity | | | x |
| 23 | Partner abuses you verbally | | | x |
| 24 | Partner threatens and intimidates you | | | x |
| 25 | Partner is physically violent towards you | | | x |
| 26 | Partner ill-treats you | | | x |
| 27 | Has your relationship ended | x | | |

## Appendix 3: Factor loadings for each of the 27 items on the 4 principal components identified

| | Items | Component | | | |
|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 |
| 1 | Partner accompanies to ANC | 0.361 | 0.012 | 0.438 | -0.139 |
| 2 | Partner supports ANC HIV testing | 0.698 | -0.123 | -0.065 | -0.093 |
| 3 | Partner participates in couple counselling | 0.756 | -0.029 | 0.008 | 0.004 |
| 4 | Partner accepts to take HIV test | 0.765 | 0.006 | -0.072 | -0.085 |
| 5 | Partner discloses his status to you | 0.718 | -0.044 | -.0184 | -0.113 |
| 6 | Partner provides moral support | 0.786 | 0.002 | 0.126 | 0.143 |
| 7 | Partner provides financial support | 0.747 | -0.009 | 0.061 | 0.074 |
| 8 | Partner helps do physical work | 0.722 | -0.099 | 0.306 | 0.175 |
| 9 | Partner prays and supports you spiritually | 0.767 | -0.149 | 0.213 | -0.020 |
| 10 | Partner provides an understanding attitude | 0.662 | -0.068 | 0.417 | 0.271 |
| 11 | Partner rejects and refuses sex | -0.309 | 0.511 | 0.156 | 0.428 |
| 12 | Partner uses condoms during sex | 0.076 | 0.176 | -0.060 | 0.548 |
| 13 | Partner remains faithful | 0.463 | 0.098 | 0.337 | 0.469 |
| 14 | Partner communicates with you on HIV PMTCT | 0.724 | -0.044 | 0.209 | 0.348 |
| 15 | Partner supports usage of ARV drugs | 0.810 | 0.047 | 0.200 | 0.076 |
| 16 | Partner supports infant nevirapine use | 0.780 | -0.059 | 0.148 | 0.064 |
| 17 | Partner supports avoidance of breastfeeding | 0.156 | -0.102 | -0.430 | 0.619 |
| 18 | Partner supports use of artificial milk | 0.107 | 0.056 | 0.755 | -0.080 |
| 19 | Partner denies your HIV results | -0.351 | 0.569 | 0.042 | 0.240 |
| 20 | Partner portrays and attitude of shock and anger | -0.120 | 0.649 | -0.082 | -0.001 |
| 21 | Partner blamed you for not consulting him | -0.062 | 0.724 | 0.005 | 0.257 |
| 22 | Partner accuses you of infidelity | 0.118 | 0.765 | 0.075 | -0.068 |
| 23 | Partner abuses you verbally | 0.097 | 0.839 | -0.034 | -0.079 |
| 24 | Partner threatens and intimidates you | 0.055 | 0.802 | 0.039 | -0.053 |
| 25 | Partner is physically violent towards you | -0.085 | 0.860 | 0.028 | 0.061 |
| 26 | Partner ill-treats you | -0.044 | 0.844 | 0.064 | 0.115 |
| 27 | Has your relationship ended | -0.483 | -0.049 | -0.390 | -0.075 |

# Appendix 4: Item total statistics of Remaining 24 items.

| | Item-Total Statistics | | | | |
|---|---|---|---|---|---|
| | | **Scale Mean if Item Deleted** | **Scale Variance if Item Deleted** | **Corrected Item-Total Correlation** | **Cronbach's Alpha if Item Deleted** |
| 1 | Partner denies your HIV results [a] | 80.38 | 157.765 | .090[a] | .823 |
| 2 | Partner portrays and attitude of shock and anger | 80.23 | 155.080 | .209 | .817 |
| 3 | Partner blamed you for not consulting him | 79.93 | 149.300 | .374 | .810 |
| 4 | Partner accuses you of infidelity | 79.60 | 148.063 | .440 | .807 |
| 5 | Partner abuses you verbally | 79.62 | 147.018 | .471 | .805 |
| 6 | Partner threatens and intimidates you | 79.62 | 149.765 | .412 | .808 |
| 7 | Partner is physically violent towards you | 79.78 | 149.819 | .390 | .809 |
| 8 | Partner ill-treats you | 79.83 | 146.867 | .439 | .806 |
| 9 | Partner rejects and refuses sex [a] | 80.30 | 154.497 | .162[a] | .821 |
| 10 | Partner supports ANC HIV testing | 78.79 | 153.148 | .308 | .812 |
| 11 | Partner participates in couple counselling | 78.83 | 149.050 | .431 | .807 |
| 12 | Partner accept to get tested | 80.35 | 154.699 | .458 | .810 |
| 13 | Partner discloses his status | 80.40 | 156.039 | .374 | .812 |
| 14 | Partner provides moral support | 78.81 | 148.030 | .552 | .803 |
| 15 | Partner provides financial support | 78.81 | 149.137 | .481 | .806 |
| 16 | Partner helps do physical work | 79.30 | 146.325 | .488 | .804 |
| 17 | Partner prays and supports you spiritually | 79.18 | 148.651 | .401 | .808 |
| 18 | Partner provides an understanding attitude | 79.19 | 147.191 | .503 | .804 |
| 19 | Partner uses condoms during sex | 80.08 | 152.453 | .234 | .817 |
| 20 | Partner communicates with you on HIV PMTCT | 79.25 | 145.036 | .567 | .801 |
| 21 | Partner supports usage of ARV drugs | 78.87 | 145.496 | .585 | .801 |
| 22 | Partner supports infant nevirapine use | 78.82 | 147.577 | .497 | .804 |
| 23 | Partner supports avoidance of breastfeeding [a] | 79.63 | 158.266 | .050[a] | .828 |
| 24 | Partner supports use of artificial milk [a] | 80.12 | 152.587 | .180[a] | .822 |

[a] Removed from scale

# CHAPTER 5

# CONCLUSIONS

# CONCLUSIONS

This thesis brings together a series of investigations focused on improving maternal and foetal outcomes in pregnancy. In this chapter, I summarise the key research findings by addressing the specific research questions that guided the entire thesis. I discuss the strengths and limitations of the thesis as a whole. I provide implications for practice and research, including some final remarks.

## I. ADRESSING THE RESEARCH QUESTIONS

### *A. What is the effect of the routine administration of 600-µg misoprostol as an add-on to oxytocin on pregnant women after placental delivery in the prevention of PPH?*

The results of our retrospective chart review with adjustment for confounding using the propensity score suggest that the use of a 600-µg dose of misoprostol as an add-on to oxytocin is protective against PPH, and is more effective than the use of oxytocin alone in the prevention of PPH.

This finding agrees with recent findings from a meta-analyses of RCTs suggesting that the use of an oxytocin-misoprostol combination is more effective than the current standard of care of an oxytocin-only regimen in the prevention of PPH (1). Our data suggest that by using this combination in settings where oxytocin only is the standard of care in the prevention of PPH, we can reduce the risk of PPH by 78%. We however call for caution in the interpretation of this finding as it was not balanced against the potential side effects and potential misuses of misoprostol.

***B. How do the results from RCTs and non-randomised studies (NRS) on the use of misoprostol in the prevention of PPH compare, and what is the geographical location of the different sources of evidence?***

Based on a systematic review and meta-analysis of published literature, we identified 34 studies which had evaluated the effect of misoprostol compared to placebo/no treatment in the prevention of PPH. Both RCTs and NRS show significant benefit for the use of misoprostol in the prevention of PPH. The results from both study designs are comparable, with NRS tending to overestimate the treatment effect. Overestimation of treatment effects by observational studies has previously been documented (2,3).

The majority of the RCTs on the use of misoprostol in the prevention of PPH were conducted in high income settings, while the majority of the NRS were conducted in low and middle income settings.

***C. How do the different ways of combining results from RCTs and NRS on the use of misoprostol in the prevention of PPH compare?***

Despite methodological differences and key differences in underlying assumptions, Classical and Bayesian methods of pooling estimates of treatment effect across RCTs and NRS all show an overall significant benefit of misoprostol in preventing PPH, providing comparable pooled estimates.

***D. How do we measure male partner involvement in PMTCT of HIV?***

Using a systematic review and cross sectional study design, we found that male partner involvement in PMTCT is a multifaceted concept which is summarily captured in two main

domains namely: supportive and non-supportive. Supportive domains of male partner involvement in PMTCT include the following: supporting antenatal HIV testing, accepting couple counselling for HIV, providing moral, spiritual and financial support to the female partner following HIV testing, assisting the female partner to do physical work, portraying an understanding attitude towards the female partner's HIV status, communication regarding PMTCT, supporting the use of ART for the mother and the infant, accepting condom use, accepting to get tested for HIV, and accepting to disclose his HIV status.

Non-supportive domains of male partner involvement in PMTCT include the portrayal of shock and anger towards the female partner's HIV status, blaming the female partner for doing an HIV test without his consent, accusing the female partner of infidelity, being verbally abusive towards the female partner because of her HIV status, threatening and intimidating the female partner because of her HIV status, being physically violent and ill-treating the female partner because of her HIV status.

The extent of these attributes can be measured using a Likert scale to obtain an overall summary score which tells us the extent of involvement of a particular male partner in PMTCT programmes, with higher scores suggesting greater male partner involvement in PMTCT.

## II. STRENGTHS AND LIMITATIONS

### *A. Strengths*

The strength of this thesis lies in its diverse methodological approach and its innovation. We use a variety of methodological approaches to highlight potentially useful evidence for the improvement of maternal and foetal outcomes in pregnancy. Furthermore, this thesis is

innovative because it develops a novel tool, the SAMPP-PMTCT, for measurement of male partner involvement in PMTCT, thereby fulfilling a critical research gap.

In addition, the thesis provides a platform for integrating knowledge from NRS with that from RCTs in clinical and potentially policy decision-making on the use of misoprostol in the prevention of PPH. This ensures that subsequent decisions on the use of misoprostol in the prevention of PPH can integrate efficacy data from RCTs with effectiveness data from observational studies.

The research setting of two of the included papers in this thesis was in a low income country (LIC), Cameroon. Its strength lies in the fact that these results are probably generalizable to other LICs who bear the brunt of PPH and MTCT of HIV.

### *B. Limitations*

Beyond the limitations identified in the individual papers which were mostly linked to their design, a potential limitation of this thesis is the risk of residual confounding given the design of some of the studies which made it impossible to eliminate all sources of confounding bias.

Specifically, our first study is limited by the fact that we were not able to identify and match all known potential confounders of the relationship between treatment received and PPH. These include uterine fibroids, a history of PPH, the duration of labour, singleton or multiple pregnancy, polyhydramnios and instrumental delivery. Uterine fibroids is highly prevalent among women of African descent and is a known risk factor of PPH. Matching for these risk factors in our propensity score model would have help to further decrease the potential of residual bias within our study. We however lacked data for these.

We recognise that the width of the confidence intervals associated with each predictor in our first study was quite wide, thereby suggesting a low precision. This was probably due to a low prevalence of PPH in our cohort. A larger sample may increase the precision of the estimates.

Our second study which compared different methods of pooling data could be improved upon by assessing other competing approaches of synthesising evidence in systematic reviews such as mixture meta-regression. We could have used this method as an additional sensitivity analysis to further determine the robustness of our conclusions.

In our third paper on developing the SAMPP-PMTCT tool, we acknowledge the longstanding debate on whether Likert scale data can ever be used as continuous, hence the appropriateness of use of principal component analysis rather than factor analysis. The items in our tool have five points and there is some indication that the interval between the points is approximately equal. The underlying concept of all Likert scale data is continuous hence the reason why we used principal component analysis. The use of factor analysis may have served as an additional sensitivity analysis.

Still in the third paper, we were limited by the absence of a previous validated scale or objectively assessed criterion measuring construct validity. Our next best bet was to compare our scale against previously reported criteria that measure the same construct. These criteria were obtained from a broad literature review of reported constructs associated with male partner involvement in PMTCT. Our linear regression model helped establish which of these reported constructs our scale agreed with. We judged this to be the best option to assert any form of construct validity in the absence of an established scale.

## IMPLICATIONS

### *A. Implications for research*

The implication of our findings from the retrospective chart review is that there is probably a beneficial effect in the use of 600μg misoprostol as an adjunct to oxytocin to reduce PPH. The methodological rigor both in the design and analysis of this study provides reassurance to its quality and trustworthiness. The evidence is robust and consistent when viewed from the broader perspective of RCTs and NRS put together. Further research is unlikely to change this conclusion.

The study comparing Classical and Bayesian methods of combining treatment estimates from different study designs leads to the question of which method was better. We must emphasise that one cannot tell which method was better based on these empirical analyses because there is no way of objectively defining "better". Both methods could be correct or wrong (because we really do not know where the "truth" is). One would need to run simulation studies (where we know the truth from the model we are using to simulate the data) and compare the performance of different methods based on estimates of bias, coverage, precision, etc. This is one potential direction of future research.

Research is needed to validate the SAMPP-PMTCT tool in different settings and to assess whether improved male involvement in PMTCT will ultimately lead to better pregnancy outcomes in general, not just PMTCT of HIV. The SAMPP-PMTCT only tells us to what extent the male partner is involved in PMTCT of HIV, without telling us strategies to use in order to improve involvement. More research is therefore needed on the best possible interventions to get male partners involved in PMTCT care.

### *B. Implications for clinical practice*

The quality and trustworthiness of the evidence in this thesis is such that it could potentially be used to inform guidelines for clinical practice.

We highlight three potential implications of our findings for clinical practice.

Firstly, the current WHO-recommended standard for the use of oxytocin in the prevention of PPH can be improved by using misoprostol as an add-on to oxytocin for this purpose.

Secondly, effectiveness data from well-designed observational studies may be used to inform clinical decisions on misoprostol in the prevention of PPH, especially in situations where trial evidence is scarce or difficult/expensive to obtain. The robustness and consistency of the evidence from RCTs and NRS on this particular topic is reassuring.

Thirdly, it is possible to objectively identify HIV positive women who lack the support of their male partners in adhering to PMTCT recommendations. These women can be the focus of additional support within the clinical settings to help them in their efforts to adhere to the PMTCT cascade.

## III. FINAL COMMENTS

Prevention of postpartum haemorrhage and prevention of mother to child transmission of HIV are two pillars of maternal health with a huge potential of influencing maternal and foetal outcomes in pregnancy and beyond. This thesis provides potentially useful evidence which can be used to minimise these two issues.

Our research aligns with recently developed evidence which suggests that an oxytocin-misoprostol combination is better than the current standard of care of oxytocin only as

recommended by WHO for the prevention of PPH (1). This combination should therefore be considered especially in LMICs which bear the brunt of PPH and maternal death.

We created new knowledge by developing the SAMPP-PMTCT. This will help in harmonising subsequent research assessing the level of male partner involvement in PMTCT of HIV in different communities, and improve the integration of men in the PMTCT cascade.

We employed a number of study designs including a cross sectional design, a retrospective chart review, and a systematic review which included Classical and Bayesian approaches of meta-analysis. We used varied but complimentary methodological approaches within these study designs to address our research objectives while reducing bias and potential confounding.

Collectively, the information contained within this thesis can be used to improve maternal and foetal outcomes from different perspectives.

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