A SYSTEMATIC REVIEW ON THE EFFECT OF MISOPROSTOL IN THE PREVENTION OF POST-PARTUM HEMORRHAGE IN SUB-SAHARAN AFRICAN WOMEN OF REPRODUCTIVE AGE

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ABSTRACT

Background: Maternal mortality ratio (MMR) is a significant healthcare marker used to evaluate the quality of health in a population. The wide range of MMR (from 5 to more than 500 deaths per 100,000 births) indicates that there is still a robust global effort in reducing maternal death in developing countries, especially sub-Saharan Africa, where the MMR burden is the highest. Postpartum hemorrhage (PPH), defined as a blood loss of 500 ml or more within 24 hours after delivery is the leading cause of maternal death worldwide. In developed countries, the natural physiologic action of oxytocin, a uterotonic hormone, has been used in reducing PPH during the third stage of labor. Since 2011, misoprostol has been added to the Essential Medicines List by the WHO. The WHO guidelines also recommended misoprostol, a prostaglandin E1 analog as a favorable alternative in settings where oxytocin is not available.

Objective: This scholarly project is a systematic review with a focus on the administration of misoprostol (200-1000 μg PO, sublingually or rectally) during the third stage of labor in Sub-Saharan African women of reproductive age (age 15-44). It is hypothesized that the implementation of misoprostol during the third stage of labor is a valuable alternative of oxytocin and will reduce the incidence or severity of PPH in Sub-Saharan Africa (with an outcome primarily measured in estimated blood loss (EBL) in mL).

Methods: PubMed and the International Journal of Obstetrics and Gynecology were the main databases of this systematic review. The main inclusion criterion in the search was region of interest (Sub-Saharan Africa). The initial 35 primary articles were then further evaluated and the final seven articles were selected based on their primary outcomes (EBL in mL), region (Sub-Saharan Africa) and purpose (comparing (1) misoprostol with the gold-standard, oxytocin or with a controlled placebo and (2) two different doses of misoprostol).

Results: Three meta-analyses using a Cohen's D scale were generated from the data collected in this study. The overall result of the first meta-analysis favors the use of oxytocin over misoprostol [-0.13 (95% CI -0.26, 0.01)]. The two main conclusions drawn from this meta-analysis are, (1) there is a tendency for oxytocin to have a positive effect on blood loss but (2) since the overall result is not statistically significant, misoprostol also have a positive effect on blood loss. In the second meta-analysis, the effect of two different doses of misoprostol (400 and 600 mcg) on blood loss are compared. The results demonstrated that there is an effect modification on the overall population and dosage was found to be a confounder in blood loss [-0.13 (95% CI -0.26, 0.01)]. Lastly, the third meta-analysis compared the effect that adding oxytocin to misoprostol to control postpartum blood loss, has on EBL. Overall, the main conclusion drawn from this meta-analysis is that there is no statistical significance in adding oxytocin to a misoprostol regimen and in this case, the addition of oxytocin does not have a confounding effect on misoprostol [-0.13 (95% CI -0.26, 0.01)].

Conclusion: Based on the results of this systematic review, it was supported that oxytocin should remain the gold-standard drug in settings where it is available. However, it was also proven that misoprostol remains a valuable alternative in places where oxytocin is unavailable.

Keywords: Maternal mortality, post-partum hemorrhage, oxytocin, misoprostol, sub-Saharan Africa

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INTRODUCTION, SIGNIFICANCE, RATIONALE

Sub-Saharan Africa and the burden of Maternal Mortality

Maternal mortality is one of the significant healthcare markers used to evaluate the quality of care in a population. Based on the World Health Organization, it is estimated that approximately 800 women die every day due to preventable causes related to pregnancy and childbirth. As of November 2015, 303,000 women worldwide died annually during or following childbirth[1]. 66.3% (201,000) of these deaths occurred in **Sub-Saharan Africa alone, carrying the heaviest burden of Maternal Mortality Ratio (MMR)[1]**. Globally in 2015, Maternal mortality ratios ranged from 5 deaths per 100,000 lives in developed nations (e.g. in Finland, Sweden and Greece) to 546 deaths per 100,000 in developing countries (e.g. in Cameroon, Cote d'Ivoire, Somalia and Kenya)[1]. These statistics clearly highlight the global disparity in maternal mortality. To this day, significant effort is still required to decrease maternal mortality in many countries.

Since 2000, reducing maternal health is one of the eight Millennium Development Goals (MDG5). Countries worldwide were devoted to reduce their MMR by three quarters over a 25-year period (from 1990 to 2015)[1-2]. By the end of 2015, maternal death dropped by 43.9% worldwide, with an annual decline of approximately 2.3% (from 1990 – 2015)[1]. Despite the mobilized efforts, MMR was **only halved in Sub-Saharan African** countries[1]. A new global Sustainable Development Goal (SDG) was recently established, with an ambitious projected MMR of less than 70 maternal deaths per 100,000 live births by 2030[1]. To meet this requirement, identifying and targeting the main causes of maternal deaths need to be reinforced and will inevitably require a much more robust global effort[1].

The main causes of maternal deaths worldwide include postpartum hemorrhages (PPH, 27%), hypertensive disorders during pregnancy (pre-eclampsia and eclampsia, 18.5%), postpartum infections (11%) and complications during pregnancy and unsafe abortions (approximately 18%). Such conditions are aggravated with indirect socioeconomic factors such as poverty, malnutrition, anemia and the high prevalence of pre-existing infectious diseases (primarily malaria, hepatitis and HIV/AIDS).[3]

This systematic review will specifically focus on PPH, the leading cause of maternal death in Sub-Saharan Africa.

Post-Partum hemorrhages and risk factors

PPH is a medical condition that can occur up to 24 hours after birth. PPH is defined as a vaginal blood loss of 500 ml or more during this timeframe. Severe PPH is blood loss of 1000 ml or more also within the first 24 hours postpartum. The number one cause of maternal death worldwide, PPH can lead to other medical emergencies including shock and organ dysfunction.[4]

After a normal childbirth and upon placental delivery, uterine bleeding is controlled by two mechanisms, (1) the contraction of the myometrium, which eventually compresses the blood supply of the placental bed, causing mechanical hemostasis, (2) initiation of the clotting cascade regulated by local decidual hemostasis factors. A pathogenic event that causes a disturbance in one of these two mechanisms (e.g. genital tract trauma, bleeding diathesis, incomplete placental separation or defective myometrial contraction) results in PPH. Uterine atony accounts for at least 80 percent of PPH. Risk factors associated with PPH include multiple gestation, prolonged labor, infection, and multiparity, even though most PPH cases occur in women with no significant past medical history. Women with additional co-morbidities (such as pre-existing anemia) have higher risks of morbidity and mortality after PPH[4].

The Active Management of the Third Stage of labor (AMTSL) and Misoprostol

Active management of the third stage of labor (AMTSL) has proven to reduce PPH by 66%. The three key actions of AMTSL consist of (1) administrating uterotonic drugs to the new mother within one minute of childbirth, (2) a controlled placental delivery by cord traction and (3) a uterine massage. The use of recommended uterotonic drugs (oxytocin, ergometrine or the combination of both) right after delivery is very critical in preventing PPH. Failure of the uterus to contract properly after childbirth will cause bleeding from the genital tract of 500 mL or more within the first 24 hours postpartum, leading to PPH[4].

Oxytocin (IM/IV, 10 UI)[4], a hormone that induces uterine contractions after birth is the drug of choice for the AMTSL[4]. The use and feasibility of oxytocin in developing countries remains very limited because of its storage and administration protocols (i.e. requires a skilled health provider, cold chain storage and sterile syringes and needles)[6-7].

These storage and administration challenges with oxytocin have led to increased interest in misoprostol, a synthetic prostaglandin E1 analogue, as a practical alternative in developing areas where oxytocin is not accessible. One of the most important advantages of Misoprostol over oxytocin is the possibility of oral administration, in addition to reasonable cost, and a long shelf life at room temperature[8]. Additionally, administering misoprostol (400 – 600 μg) sublingually allows a faster onset of action and a greater bioavailability by avoiding first-pass metabolism[6].

Despite these WHO guidelines and the evidence that misoprostol is a convenient alternative in settings where oxytocin is not available, implementing the use of uterotonic drugs is still a challenge. Perhaps this could be due to difficulty in facilitating the distribution of misoprostol or the proper use of the medication in settings where the targeted population is not trained to do so.

Rationale and Significance

A number of studies have been done in different Sub-Saharan countries (e.g. Nigeria, Liberia, Tanzania and Uganda) to evaluate the benefits and efficacy of Misoprostol in preventing PPH. A systematic review that analyses the outcomes of such studies has not yet been performed.

Based on the statistics discussed above, the robust effort necessary to significantly reduce maternal deaths by 2030, in addition to the pharmaceutical and clinical promises of misoprostol, this Global Health systematic review proves itself to be extremely relevant to women's health. Positive findings of this study would support the use of misoprostol as a gold-standard alternative of oxytocin and encourage operationalization of implementation programs.

METHODS

Since this is a new research, there is no preliminary data collected. However, as further discussed in the subsequent sections, there are 35 preliminary selected articles for this review (23 are primary articles) [All references to Figure 1].

Databases

PubMed is my main research source. Access to the International Journal of Obstetrics and Gynecology online was obtained through my mentor.

Inclusion/Exclusion criteria

The main inclusion criterion was the medical condition (postpartum hemorrhage), misoprostol and the region of interest (sub-Saharan Africa).

Keyword search strings

- PubMed Terms: Misoprostol postpartum hemorrhages: **380 results**
    - Misoprostol postpartum hemorrhages:

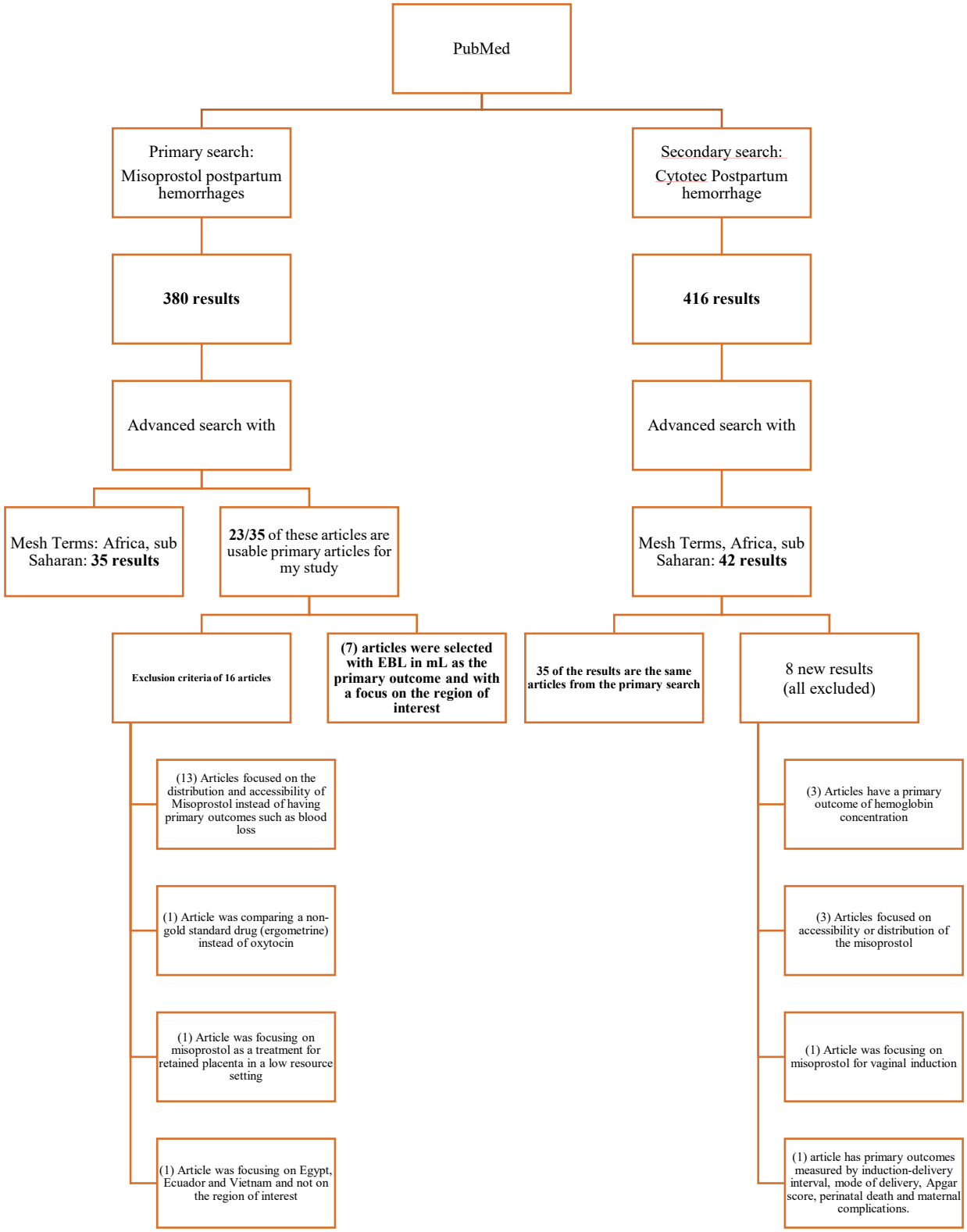
      → Advanced search with:
        - Mesh Terms: Africa, sub Saharan: **35 results**
        - **23/35 of these articles are usable primary articles for my study.**

- Additional keyword search String (PubMed): Cytotec Postpartum hemorrhage: **416 results**
    - Cytotec Postpartum hemorrhage:
        - Advanced search with:
            - Mesh Terms, Africa: **42 results**
                - **35 of the results are the same as articles from the original search (see above)**
                - **8/42 were new results and did not qualify for this study.**

Analyses and outcomes

The identified studies from the selected studies all have measurable outcomes. Such outcomes include but are not limited to blood loss (in mL), blood hemoglobin concentration after birth, feasibility, acceptability, effectiveness of distribution mechanisms and uterotonic coverage. However, for the original purpose of this systematic review and the emphasis on PPH, estimated blood loss (EBL) in mL is the primary outcome used for results and data analysis. Tables, figures and data analysis were all performed by using Excel and Stata version 14 and reviewed by Paul Kang, a biostatistician.

Figure 1. Key search strings



RESULTS

The seven selected articles for this systematic review were categorized based on the authors' names, the country of the study, the dose and route of misoprostol, the population size and demographic characteristics (e.g. gestational age, parity, birthweight of the newborn, etc.) [Table 1]. The primary outcome used for analysis is estimated blood loss (EBL). When available, Effect size blood loss as well as relative risk or odds ratio were used for analysis.

Table 1. Characteristics of articles, primary outcome (EBL) and statistical values

Author	Country	Misoprostol Usage (dose, route, includes oxytocin, etc.)	Population (sample size)	Study Design (Cohort, CC, or RCT)	Demographic characteristics (gestational age, # of children etc.)	Outcomes (blood loss) Means (SD) for misoprostol and not misoprostol	Effect Size Blood Loss - Mean difference between misoprostol vs no misoprostol /oxytocin	Odds Ratio - Relative Risk
Atukunda et al.	Uganda	600 ug, Sublingual	1,140, 38 – 41 weeks pregnant women	Double blind randomized non-inferiority trial	**Misoprostol** (n = 570) Mean age: 29.3 (SD 3.4) Mean gestational age (weeks): 39.2 (SD 0.8) Parity: 1: 249, 43.7% 2-4: 273, 47.9% 5+: 47, 8.3% Mean birthweight (kg): 3.1 (SD 0.4) **Oxytocin** (n= 570) Mean age: 29.7 (SD 3.1) Mean gestational age (weeks): 39.3 (SD 0.8) Parity: 1: 219, 38.4% 2-4: 286, 50.2% 5+: 64 (11.3%) Mean birthweight (kg): 3.2 (SD 0.5)	At 24 h PP, **primary PPH** occurred in 163 (28.6%) participants in the misoprostol group and 99 (17.4%) participants in the oxytocin group (relative risk [RR] 1.64, 95% CI 1.32 to 2.05, p,0.001; absolute risk difference 11.2%, 95% CI 6.44 to 16.1). **Severe PPH** occurred in 20 (3.6%) and 15 (2.7%) participants in the misoprostol and oxytocin groups, respectively (RR 1.33, 95% CI 0.69 to 2.58, p = 0.391; absolute risk difference 0.9%, 95% CI 21.12 to 2.88)	Mean measured blood loss was 341.5 ml (standard deviation [SD] 206.2) and 304.2 ml (SD 190.8, p = 0.002) at 2 h and 484.7 ml (SD 213.3) and 432.8 ml (SD 203.5, p,0.001) at 24 h in the misoprostol and oxytocin groups, respectively.	RR for PPH (blood loss > or equal to 500ml): 1.64 (1.32 to 2.05)

Hofmeyr et al.	South Africa, Uganda, Nigeria	400 ug sublingual	**1103 women:** 547 misoprostol group - 546 analyzed 556 placebo group - 553 analyzed	Randomized placebo-controlled, double-blind trial	**Misoprostol** (n = 547) Mean age (year): 25 (SD 5.6) Primiparous (n=543): 145, 26.70 **Placebo** (n = 556) Mean age (year): 28 (SD 6.0) Primiparous (n=553): 146, 26.40	There was no significant difference in the primary outcome, (500 mL or more within 1 hour of administration of the trial medication**), with relative risk [RR], 0.64; 95% confidence interval [CI], 0.38–1.07),** which occurred in 22/546 (4.03%) women allocated to misoprostol and in 35/553 (6.33%) women allocated to placebo.	There was no significant difference in mean blood loss occurring within 1 hour of taking the tablets (weighted mean difference, –9.58; 95% CI, –22.3 to 3.14), or in the incidence of blood loss of 1000 mL or more (RR, 3.70; 95% CI, 0.61–22.4).	RR for PPH (blood loss > or equal to 500ml): 0.64 (0.38 to 1.07)
Geller et al.	Ghana	600 ug oral	999 doses distributed to midwives: 646 given to women during third trimester ANC: 529 returned because the woman delivered at an institution 96 used at home 7 used at the facility 9 returned despite delivering at home → 102 total used miso	"Operation research study"	**Misoprostol** (n = 102) Mean Age (year): 24.4 (SD 6.56) Mean Gravidity: 3.82 (SD 2.23) Mean Parity: 2.50 (SD 2.05) Mean # of prenatal visits: 3.70 (SD 0.57) **No Misoprostol** (n = 107) Mean Age (year): 26.58 (SD 7.02) Mean Gravidity: 3.93 (SD 2.17) Mean Parity: 2.34 (SD 2.01) Mean # of prenatal visits: 3.35 (SD 0.98)	**Misoprostol** (n = 82) Blood loss: <350 ml: 71, 86.6% 350 – 499 ml: 10, 12.2% +500 ml: 1, 1.2% **No Misoprostol** (n = 92) Blood loss: <350 ml: 83, 90.2% 350 – 499 ml: 6, 6.5% +500 ml: 3, 3.3%	-	-

Abdulkarim O. Musa et al.	Nigeria	600 ug oral	Oral misoprostol (n= 100) Oxytocin (Intramuscular during Active Management of the third stage of labor) n= 100	Double blind randomized controlled trial	**Misoprostol** (n= 100) Mean age (year): 29.60 (SD 4.71) Mean Gestational age (weeks): 39.38 (SD 1.70) Mean Parity: 2.22 (SD 1.10) Mean Birth weight (g): 3004.3 (SD 430.1) **Oxytocin** (n= 100) Mean age (year): 29.50 (SD 4.37) Mean Gestational age (weeks): 39.39 (SD 1.43) Mean Parity: 2.22 (SD 1.09) Mean Birth weight (g): 3013.3 (SD 47.3)	**Misoprostol** (n= 100): Postpartum blood loss (ml): 325.85 (SD 164.72) PPH (+500 ml): 15, 15% Oxytocin (n= 100): Postpartum blood loss (ml): 303.95 (SD 163.33) PPH (+500 ml): 14, 14% 20% of women given misoprostol had a measured blood loss of at least 500 mL, compared with 14% of those given oxytocin (RR 1.44, 95% CI 1.35–1.54; P b 0.001). Additionally, 15% of women in the misoprostol group and 11% in the oxytocin group required additional uterotonics (RR 1.40, 95% CI 1.29–1.51; P b 0.001).	-	Relative difference of postpartum blood loss (ml) (95% CI), 7.2 (-9.4 to 23.8) P value: 0.391

Okonofua et al.	Nigeria	800 ug sublingual	Misoprostol used as the primary treatment for PPH in 3 Nigerian cities (Kano, Jos, Lagos) Blood transfusions, Oxytocin and ergometrine if needed available	Multicenter trial	Kano (n = 37) Median age (year): 28 (19 – 40) Parity: 0: 2, 5.4% 1: 5, 13.5% 2-4: 14, 38% +5: 4, 10.8% Add. Treatments*: 4, 10.8% Jos (n = 38) Median age (year): 30 (19 – 40) Parity: 0: 11, 28.9% 1: 2, 5.3% 2-4: 11, 28.9% +5: 14, 36.9% Add. Treatments*: 2, 5.3% Lagos (n = 56) Median age (year): 30 (18 – 36) Parity: 0: 16, 28.6% 1: 16, 28.6% 2-4: 21, 37.5% +5: 3, 5.3% Add. Treatments*: 14, 25% Add. Treatments*: IV ergometrine and oxytocin, continuous high-dose oxytocin infusion, blood transfusion and plasma expanders as needed.	EBL (ml): Kano Mean: 685 (550 – 1000) Jos Mean: 616 (500 – 2500) Lagos Mean: 650 (550 – 1500) The results show that 15.3% of the women treated with misoprostol required additional treatment with either oxytocin, ergometrine or both, while 32.8% of the women required blood transfusion.	-	-

N. Prata et al.	Tanzania	1000 ug rectal	454 with misoprostol and 395 Non-intervention		**Intervention** (Misoprostol) group (n= 454): Mean age (year): 24.6 (SD 4.8) Mean parity: 2 (SD 1.7) **Non-Intervention** (only referral) group (n= 395): Mean age (year): 26.7 (SD 6.5) Mean parity: 2.4 (SD 2.0)	PPH (blood loss > +500 ml) Intervention: 111/454 (24.5%) Non-intervention: 73/395 (18.5%) Additional interventions among PPH cases: Other medical interventions for the referrals group (n=73): 7, 9.6%		Odds Ratio for PPH: 1.3 with 95% CI (1.0 – 1.7) Odds Ratio for referrals: 0.1 with 95% CI (0.0 – 0.2)
Walley et al.	Ghana	400 ug (powder in water orally)	Misoprostol, n=203 Oxytocin, n= 198	Double-blind placebo controlled randomized trial	**Misoprostol** (n=203): Mean maternal age (year) (n =202): 25.7 (SD 5.0) Mean gestational age (weeks) (n= 200): 38.0 (SD 2.0) Mean gravidity (n= 203): 2.0 [1.0, 3.0] Mean Parity (n= 202): 1.0 [0.0, 2.0] Birthweight (g) (n= 195): 3118 (SD 442) **Oxytocin** (n=198): Mean maternal age (year) (n =196): 26.1 (SD 5.5) Mean gestational age (weeks) (n= 196): 38.0 (SD 1.9) Mean gravidity (n= 198): 2.0 [1.0, 3.0] Mean Parity (n= 198): 1.0 [0.0, 2.0] Birthweight (g) (n= 192): 3139 (SD 518)	**Misoprostol** (n=203) Estimated Blood Loss (ml) (n=202): 190 (SD 78) Estimated Blood Loss > 500 (ml): 0/202 Additional oxytocics: Oxytocin: 4/168 Ergometrine: 2/168 Syntrometrine: 0/168 **Oxytocin** (n=198) Estimated Blood Loss (ml) (n=196): 187 (SD 78) Estimated Blood Loss > 500 (ml): 2/196 Additional oxytocics: Oxytocin: 5/172 Ergometrine: 1/172 Syntrometrine: 2/172		RR for estimated blood loss (EBL) in ml: 1.8% with 95% CI (-7.3 to 10.8%) P: 0.61

Innocent A. Ugwu et al.	Nigeria	200 ug vs. 400 ug Misoprostol alongside with IV oxytocin	200 ug Misoprostol (n = 62) 400 ug Misoprostol (n = 62)	Randomized Control trial	**200 ug Misoprostol (n = 62)** Mean age (year): 30.52 (SD 5.3) Mean Parity: Primiparous: 28 (SD 45.2) Multiparous: 34 (SD 54.8) Mean gestational age at delivery (weeks): 39.0 (SD 1.4) Mean birthweight (kg): 3.1 (SD 0.5) **400 ug Misoprostol (n = 62)** Mean age (year): 30.45 (SD 4.0) Mean Parity: Primiparous: 27 (SD 43.5) Multiparous: 35 (SD 56.5) Mean gestational age at delivery (weeks): 38.8 (SD 1.5) Mean birthweight (kg): 3.1 (SD 0.4)	**200 ug Misoprostol (n = 62)** Postpartum blood loss, ml: 307 (SD 145) Postpartum hemorrhage: Yes: 5/62 (8.1%) No: 57/62 (91.9%) Need for increase in oxytocin dose: Yes: 27/62 (43.5%) No: 35/62 (56.5%) Additional uterotonics: Yes: 10/62 (16.1%) No: 52/62 (83.9%) **400 ug Misoprostol (n = 62)** Postpartum blood loss, ml: 296 (SD 151) Postpartum hemorrhage: Yes: 6/62 (9.7%) No: 56/62 (90.3%) Need for increase in oxytocin dose: Yes: 26/62 (41.9%) No: 32/62 (51.6%) Additional uterotonics: Yes: 9/62 (14.5%) No: 53/62 (85.5%) T test/Chi square value for blood loss: 0.415 P value: 0.679	-

Figure 2 is a meta-analysis using a Cohen's D (95% CI) scale. The studies conducted by Atukunda et al., Musa et al., Walley et al, and Ugwu et al. were specifically selected for this analysis because their results all included estimated mean blood loss as well as relative risk values. The first three articles have negative values, showing that oxytocin is favored over misoprostol (Figure 2). The last article by Ugwu et al. shows that this study favors the use of misoprostol over oxytocin. The overall result of this meta-analysis favors the use of oxytocin over misoprostol [-0.13 (95% CI -0.26, 0.01)]. Two main conclusions can be drawn from this meta-analysis, (1) there is a tendency for oxytocin to have a positive effect on blood loss but (2) since the overall result is not statistically significant, misoprostol also have a positive effect on blood loss.

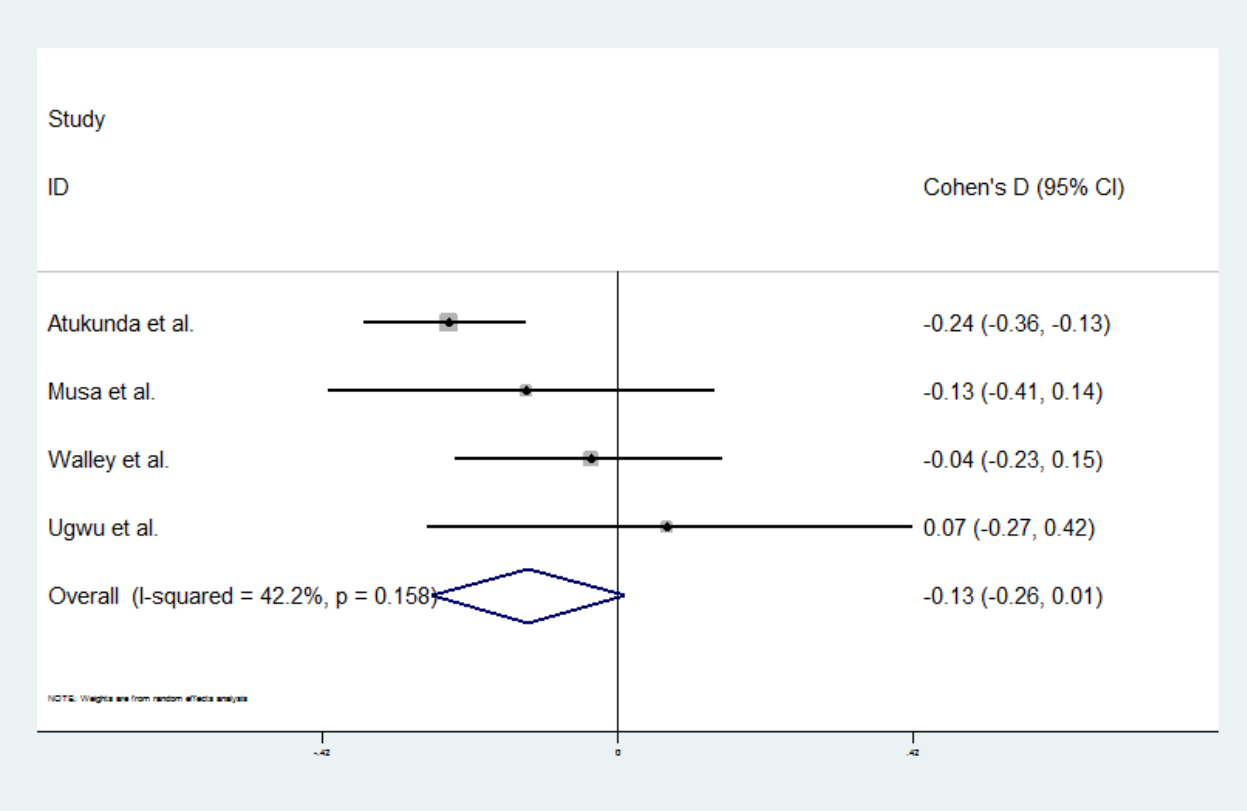


Figure 2. Meta-Analysis 1: The overall effect of misoprostol on blood loss based on collected data from key selected articles

Figure 3 is also a meta-analysis using a Cohen's D (95% CI) scale. The effect of two different doses of misoprostol (400 and 600 mcg) on blood loss are compared in this meta-analysis. Figure 3 shows that at 600 mcg, oxytocin have a more positive and statistically significant effect on EBL than misoprostol even though the effect is small [-0.22 (95% CI -0.33, -0.12)]. At 400 mcg, oxytocin has an even smaller positive effect on EBL compared to misoprostol but this effect is not statistically significant [-0.01 (95% CI -0.18, 0.15)]. Overall, the main conclusion drawn from this meta-analysis is that there is an effect modification on the overall population and dosage was found to be a confounder in blood loss [-0.13 (95% CI -0.26, 0.01)].

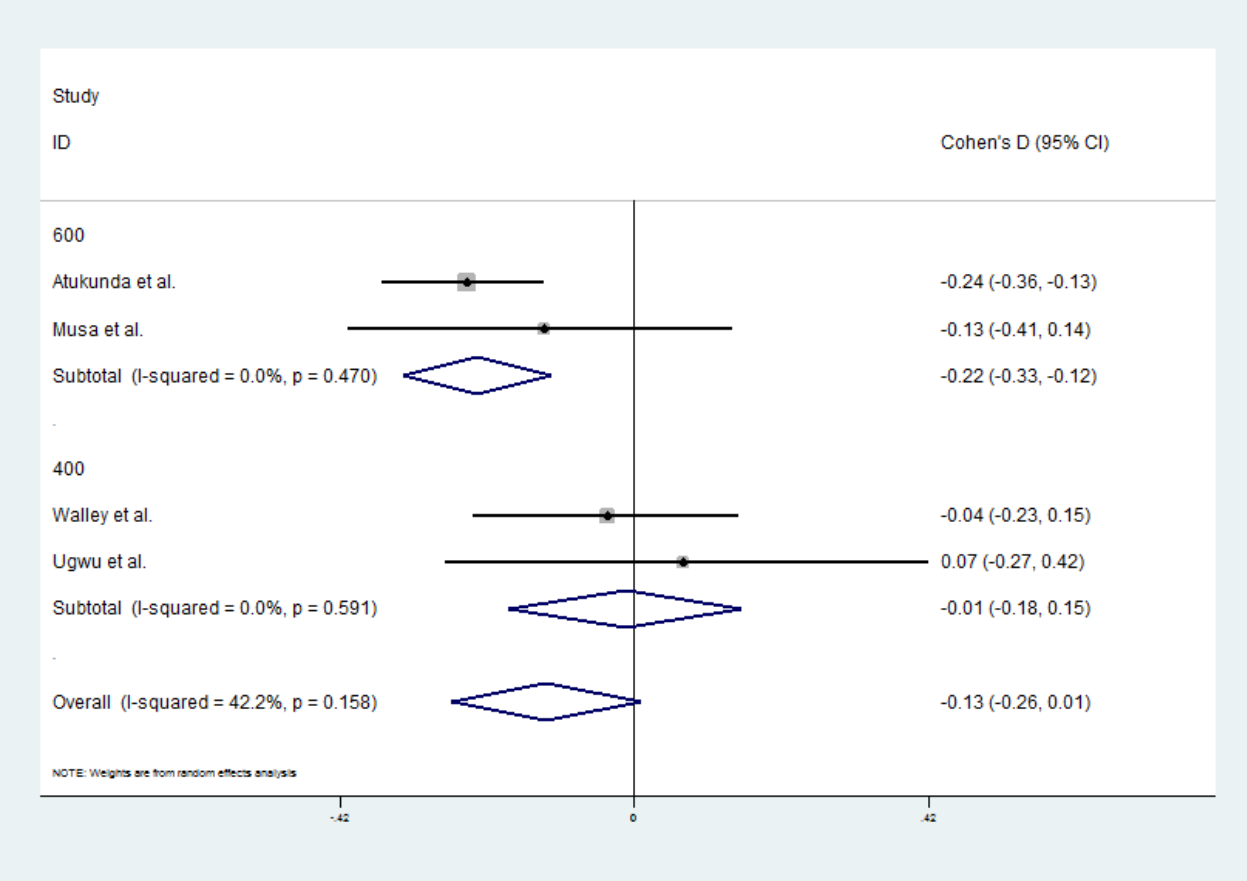


Figure 3. Meta-Analysis 2: The effect of different doses of misoprostol (600 and 400 mcg) on EBL (mL)

Figure 4 is also a meta-analysis using a Cohen's D (95% CI) scale. This meta-analysis compares the effect that adding oxytocin to misoprostol to control postpartum blood loss has on EBL. When oxytocin is added, the result shows that there is a small positive effect on blood loss compared to misoprostol alone [-0.13 (95% CI -0.42, 0.16)]. When oxytocin is not added to misoprostol, there is an even smaller positive effect on blood loss compared to misoprostol [-0.07 (95% CI -0.22, 0.09)]. Both results from this meta-analysis are not statistically significant. Overall, the main conclusion drawn from this meta-analysis is that there is no statistical significant in adding oxytocin to a misoprostol regimen and in this case, the addition of oxytocin does not have a confounding effect on misoprostol [-0.13 (95% CI -0.26, 0.01)].

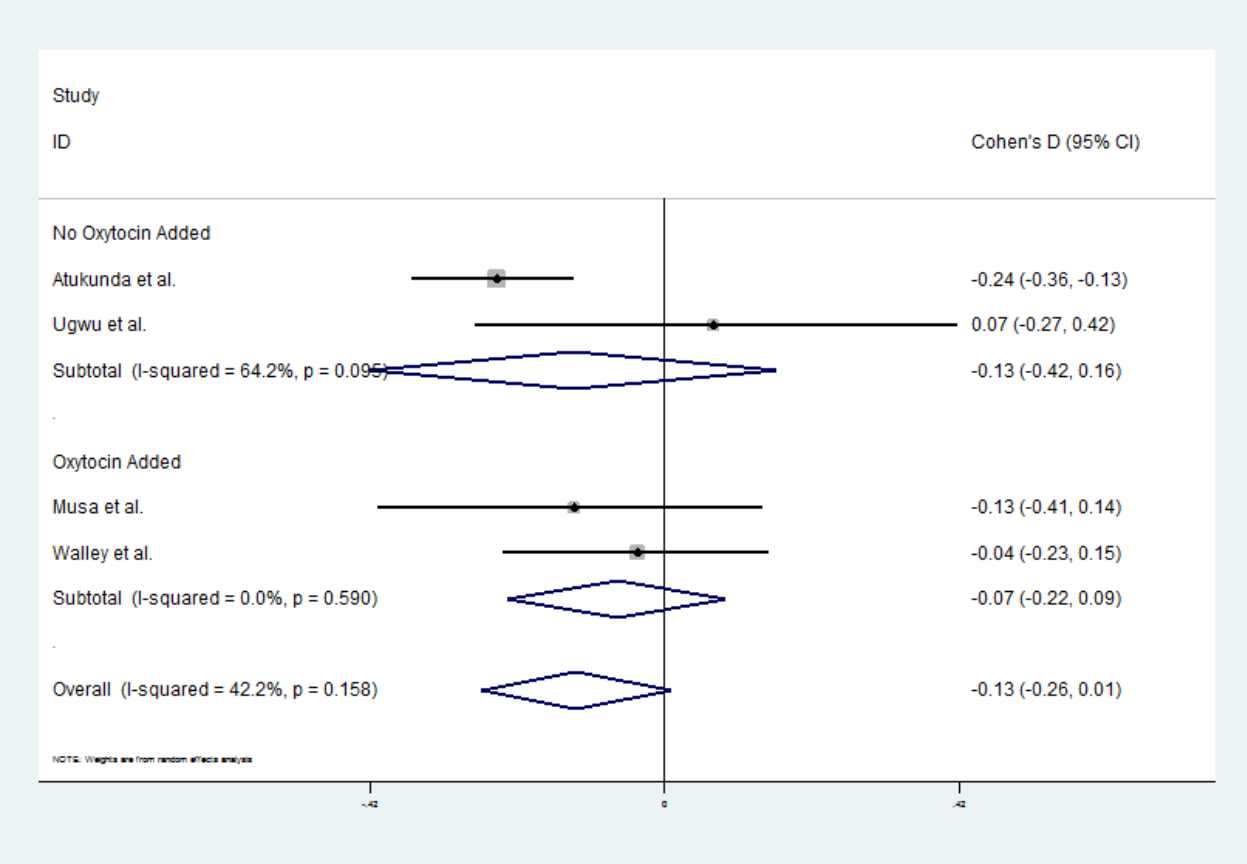


Figure 4. Meta-Analysis 3: The effect of adding oxytocin to misoprostol on EBL (mL)

DISCUSSION

In Atunkunda et al article[7], a double-blind randomized controlled trial was performed. This study was interested in comparing the administration of sublingual misoprostol (dose: 600 μg) versus the use of intramuscular oxytocin (dose: 10 IU) to 38 – 41 weeks pregnant women in early active labor, at the Mbarara Regional Referral Hospital in Uganda. Results have shown that in settings where oxytocin is available, it should remain the preferred agent and gold standard for the prevention of PPH. However, sublingual misoprostol still maintains an important role for the prevention of severe PPH and subsequent complications in area where oxytocin is unavailable.

Another interesting example is an article written by Diadhiou et al[9], where they evaluated the benefits of misoprostol in a difference approach. The objective of this study was to demonstrate that PPH could be prevented among women giving birth if proper oral misoprostol distribution and administration was ensured by auxiliary midwives in rural Senegal. The method consisted of a 6-days training with auxiliary midwives, with one day dedicated to the use, administration and prevention of misoprostol and PPH, followed by a practicum (conducting deliveries during the training period). Results showed that "all study participants, whose deliveries were assisted by auxiliary midwives that were trained in the study, received correct and safe administration of misoprostol for PPH prevention". This study also recognized in the discussion section that "although the study was not designed to and did not measure postpartum blood loss, there is substantial evidence that misoprostol effectively prevents PPH and severe PPH".

As demonstrated in the previous literatures and throughout this study, oxytocin is the gold standard for preventing PPH. recommended by the WHO, misoprostol has been approved to be the alternative drug in settings where oxytocin is not available. Multiple studies, including the ones selected for this review all supported these current recommendations (Figure 2). A study conducted by Ugwu et al. as well as results from Figure 3 demonstrated that the current dose of misoprostol (600 mcg) can be as low as 200 mcg and still be efficient in reducing EBL. Misoprostol is a prostaglandin E1 analog and its side effects have been proven to be dose

dependent[16]. The idea of changing the current recommendation and eventually using a lower dose (200 mcg) is not only favorable for the prevention of PPH, but also for the reduction in the incidence of common side effects (e.g. shivering and fever). In addition, on a global health standpoint, since each tablet of misoprostol has a concentration of 200 mcg, a lower dose will be more cost effective and practical, as a single current dose (600 mcg or three tablets) will be able to protect three mothers instead of one.

Despite these WHO guidelines and the evidence that misoprostol is a convenient alternative in settings where oxytocin is not available, implementing the use of uterotonic drugs is still a challenge. Perhaps this could be due to difficulty in facilitating the distribution of misoprostol or the proper use of the medication and studies like the one conducted by Diadhiou et al[9] are trying to address such issues.

Another challenge that a lot of countries in Sub-Saharan Africa might be facing is with the distribution of misoprostol. With very strict abortion laws, the abortive properties of misoprostol might be a threat in countries where abortion is restricted and viewed as a crime. The multi-functions of misoprostol can might be the reason why there have not been a significant decrease in MMR in countries of Sub-Saharan Africa despite all the global health efforts and WHO recommendations.

CONCLUSION AND FUTURE DIRECTIONS

There have been previous individual studies evaluating the benefits of misoprostol as a reliable alternative to oxytocin in different countries of Sub Saharan Africa (e.g. Uganda, Nigeria, Kenya, Tanzania). However, a systematic approach that focuses on Sub Saharan African women of reproductive age has not yet been published. The World Health Organization recommends the use of Misoprostol in remote areas where women do not necessarily have access to a skilled birth attendant during childbirth.

Based on such evidences and on the pharmaceutical benefits of Misoprostol, future directions of this study could include a bigger sample size with more articles, for more reliable and statistically significant data.

Lastly, I believe this research project is very important because with reducing maternal death a 2030 Millennium Developmental Goal and PPH being among the leading causes of maternal death worldwide, supporting the use of Misoprostol could, in a futuristic approach, improve its regulation, distribution and reduce maternal death.

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