www.jmscr.igmpublication.org

Impact Factor 3.79
ISSN (e)-2347-176x

IGM Publication

Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Effectiveness of Misoprostol for the Prevention of Postpartum Haemorrhage: A Review

Authors
Joy Chidinma Agom[1], David A. Agom[2], Chidiebere V. Ekuma[3], Jude N. Ominyi[4], Simon N.Onwe[5]
[1]RN, RM., BNSc, MSc Midwifery
[2,3,4,5]RN, BNSc, MSN
Corresponding Author
Joy Chidinma Agom
RN, RM., BNSc, MSc Midwifery
Contact No: +447435362175
Email: *joycharis12@yahoo.com*

Abstract

Postpartum haemorrhage (PPH) is the major cause of maternal morbidity and mortality globally. Prevention of PPH will reduce the number of maternal deaths in rural communities of developing countries. This study aim to access evidence on the effectiveness of misoprostol compared to oxytocin or placebo, and to explore the optimal dose and the best route of administration for the prevention of PPH. The MEDLINE, CINAHL, Science Direct, Intermid and the Cochrane Library were systematically searched. Studies that compared misoprostol and oxytocin or placebo for the prevention of PPH were selected following inclusion and exclusion criteria. Also, hand-searches of 7 Journals and citations tracking were employed. A total of 16 articles that met the inclusion criteria were selected and used for this review. Among the 16 studies included in the review, misoprostol was found to be as effective as oxytocin in the prevention of PPH in developing countries. Misoprostol at the dose of 600 µg to 1000 µg was associated with higher percentages of side-effects, while sublingual route at the dose of 400 µg seems to be better in minimizing the adverse side-effects.

Introduction

Postpartum haemorrhage (PPH) is defined as estimated blood loss (EBL) of ≥500ml and massive PPH of≥1000ml within 24 hours of delivery (Leduc *et al.*, 2009). Obstetric bleeding after delivery has been recognized to be the leading cause of maternal mortality in both developing and developed countries (World Health Organisation (WHO), 2006). In pregnancy and childbirth, all women, including those with no

pre-existing health issues are exposed to significant health risks. A number of authors have noted the high numbers of women who die from complications of pregnancy. For example, Mairiga and Saleh (2009) reported that about 600,000 women die globally due to complications of pregnancy. Despite the initiation of active management of third stage of labour (AMTSL) using uterotonics (oxytocin), maternal death still remains high especially in developing countries (WHO, 2009). A greater percentage of these deaths occur in developing countries, because women don't receive any preventive measures during childbirth in rural areas (Ronsmans and Grahams, 2006). In Nigeria the maternal mortality rate is estimated to be 545 per 100,000 live deliveries with the major percentage being due to PPH (NPC and ICF Macro, 2009).

Oxytocin, ergometrine or a combination of both have been the common oxytocic drugs used globally for the prevention of PPH during the third stage of labour. Unfortunately these drugs cannot survive in high ambient temperatures (Uthman *et al.*, 2011). Therefore, there is a need for an effective uterotonic drug that will be easy to administer and which does not need special storage conditions. It is therefore essential to investigate the evidence to identify an alternative drug with similar effects which does not require these storage conditions and is low-cost to prevent PPH in order to improve the maternal and neonatal survival rates in developing countries. Misoprostol, a synthetic prostaglandin E1 analogue, which is used for the management of gastric ulcers, induction of abortion and induction of labour acts upon the uterine myometrium causing the uterus to contract and thus can be used for the prevention of PPH in developing countries (Derman *et al.*, 2006).

Methodology

A literature review was undertaken to explore the effectiveness of misoprostol compared to oxytocin, and to ascertain the optimal dosage and best route of administration of misoprostol for the prevention of PPH. In order to gather relevant published literatures for this study, various subject-specific databases were explored extensively. The databases searched include INTERMID, MEDLINE, CINAHL, Cochrane Library, Science Direct and Google Scholar. Furthermore, "hand searching" of seven (7) journals was applied to supplement the electronic database search, which assisted in locating additional literatures that was not found in other search processes. The references of each article for inclusion were scrutinized and any that appeared good were further checked with against the original articles. Keywords such as misoprostol, oxytocin, third stage of labour, postpartum haemorrhage, prevention etc. were combined in different databases using 'Boolean Operators, Truncations' and wildcards symbols. The Boolean operator used are 'AND' 'OR' and Truncation symbol used is '&', wildcards symbols used are #, $, and *. These assisted in expanding the search when it is combined with relevant keywords which yielded better and broader results (Thompson *et al.*, 2005).

A total of 1174 articles were retrieved during the search from the five databases. After scanning through the title and abstract, the articles that did

not meet the inclusion criteria were excluded leaving total of 40 articles. A further step was taken to read through the full text of the 40 articles to ensure that they were suitable for this review. This step led to the inclusion of only 12 research papers, plus 4 articles found during reference list searching, making a total of 16 relevant studies used for the review.

Inclusion criteria

The primary research articles published in English language from the year 2009 till 2013 were selected. Studies that involved women with both high and low-risk of PPH, compared misoprostol with oxytocin or placebo with any route of administration and dosage were included so as to determine how effective misoprostol can be in both situations.

Article appraisal and key data extraction

The selected articles were analysed to elicit their relevance in answering the research questions by adopting a structured process known as critical appraisal. Polit and Beck (2005) highlighted that the critical appraisal skills program (CASP) tool is suitable for researcher as it helps to ensure that all literature is reviewed systematically in the same format, hence an evaluation tool for quantitative research studies and systematic reviews were used (Long *et al.*, 2002), because this provides a check list for evaluation of quantitative research studies used for this review.

Findings/Results

The effectiveness, the optimal dose, best route of administration was explored. The 16 selected articles were systematically reviewed and discussed based on the above themes. The primary outcomes of mean blood loss (MBL), incidence of PPH and secondary outcomes of drop in haematocrit and haemoglobin levels, duration of third stage of labour, adverse side-effects, and need for additional uterotonics of misoprostol and oxytocin were assessed in order to draw conclusion on the effectiveness of misoprostol.

Effectiveness of misoprostol compared to oxytocin or placebo for the prevention of PPH

Badejoko *et al.,* (2012) study aimed at evaluating the effectiveness of adjunctive rectal misoprostol compared to oxytocin infusion in the prevention of primary PPH after routine AMTSL in women with identifiable risk factors. Double-blinded RCT of 264 pregnant women with known risk factors such as fetal-macrosomia, twin gestation, and induction of labour was used. 600 µg of misoprostol or 20 IU in 500 ml oxytocin infusion was given to participants. Intra-partum blood loss was measured using a combination of the BRASS-V calibrated drapes and differential pad weighing. There was no significant difference in the MBL between the two groups (387.28±203.09mls versus 386.73 ±298.51mls, p=0.07), no difference in the requirement for additional uterotonics (p=0.74), and postpartum haematocrit drop and blood transfusion were significantly less in the misoprostol group. These outcomes were measured fairly in both groups as the participants and researchers were blinded to the intervention. Their result suggests misoprostol to be as effective as oxytocin infusion for the prevention of PPH in women with risk factors for uterine atony.

Although, shivering, pyrexia and vomiting were more frequent with misoprostol, which was usually self-limited. The inclusion of high risk pregnant women in this study strengthens the reliability of the findings unlike other studies that used low risk pregnant women *(Widmer et al., 2010*). Also, the employment of an objective method of the BRASS-V calibrated drapes, rather than visual estimation as done by some previous PPH studies with the result that, the MBL for each group could be more accurately and reliably determined.

Shrestha *et al.,* (2011) compared the effectiveness of 1000 µg of misoprostol with 10 IU of intramuscular oxytocin in the prevention of PPH. The participants were randomly selected from Department of Obstetrics and Gynaecology in four different hospitals across Nepal. PPH was 4% in the misoprostol subjects and 6% in the oxytocin subjects; there were no significant difference between the groups in the drop in haematocrit. The side effects of fever and shivering between misoprostol and oxytocin group within 6 hours after delivery were statistically significant (fever at 6 hours, misoprostol=25% versus oxytocin=10%, shivering at 6 hours, misoprostol= 16% versus oxytocin=4%). Their result proved misoprostol to be effective as oxytocin in prevention of PPH.

The studies of Badejoko *et al.,* (2012) and Shrestha *et al.,* (2011) were similar in that misoprostol was as effective as oxytocin in reduction of blood loss and incidence of PPH was minimal. However, Shrestha *et al.,* (2011) found that, the side effects between the misoprostol group and oxytocin group within 6 hours was statistically significant whereas the side effect within 24 hours was statistically not significant. On the other hand, Badejoko and colleagues had higher incidence of shivering and fever in misoprostol compared to oxytocin within 24 hours of childbirth (shivering=27.0% versus 13.2%, fever= 22.2% versus 5.4 %,), vomiting was also found to be higher in misoprostol group 23.0% compared to 5.4% in oxytocin group.

Accordingly, Wangwe *et al.,* (2009) compared the efficacy, safety and cost-effectiveness of misoprostol and intramuscular oxytocin in the management of the third stage of labour. The estimated blood loss (EBL) in both misoprostol and oxytocin group were comparable (161mls versus 169mls), more women in the misoprostol group (18.1%) had a drop in haematocrit of >10% (which is particularly sensitive to detect adverse effects of PPH) as compared to oxytocin (14.2%), and the need for extra uterotonics was not statistically different between the two groups (7.4% in the oxytocin group and 4.3% in misoprostol group, p=0.19). Shivering was higher in the misoprostol group compared to oxytocin (misoprostol=3.3% versus oxytocin=1%) though not statistically significant. The study demonstrated a comparable efficacy of misoprostol versus oxytocin for the prevention of PPH; however, the researchers did not specify the method by which the EBL was measured and determined, they simply stated that, it was done according to the 'hospital protocol'. Better understanding of the measures taken to measure the blood loss would have increased the credibility of the findings.

The study by Gohil and Tripathi (2009) compared the efficacy of misoprostol, oxytocin, methyl-ergometrine and oxytocin-ergometrine on reducing blood loss during the third stage of labour. The non-randomized uncontrolled trial method used in this study increased the risk of selection bias and therefore has reduced the credibility of the findings. *Gibson and Glenny (2007)* states that randomisation of study participants gives the best evidence of effectiveness of the intervention. AMTSL was done using one of the four uterotonics as per the group of the patient. There was no significant difference in the pre-delivery and the post-delivery haemoglobin concentration amongst the four groups with p=0.061. The incidence of PPH and a drop in haemoglobin concentration from delivery to 24 hours after delivery were evaluated. Their study showed that methyl-ergomerine was superior to the rest of other drugs used in the study with shorter duration of the third stage of labour, lowest amount of blood loss, lowest incidence of PPH, while misoprostol had the highest amount of blood loss and incidence of PPH. The need for extra oxytocic and blood transfusion was highest with misoprostol as compared to other drugs used in the study with p=0.037 and p=0.009, respectively. These findings were contrary to Bellad *et al.,* (2012) study where the incidence of PPH was 3.1% in misoprostol versus oxytocin 9.1%; haemoglobin decline was 9.7% in misoprostol compared to 45.6% in oxytocin. Methyl-ergometrine was suggested to be the best uterotonic drug amongst the drugs used (Gohil and Tripathi 2009). However, the methodology for this study was not explicit couple with use of small sample size (200), and non-randomization.

The Nasreen *et al.,* (2011) quasi-experimental trial compared the effectiveness of a single dose of 400 µg of misoprostol on women that received this intervention to women without this intervention. The primary PPH was measured by women's self-reported subjective measures of the normality of blood loss using the cultural 'consensus model' which was monitored by the Community health workers (CHWs). The findings suggest that the incidence of primary PPH was lower in the intervention group (1.6%) than the control group (6.2%). More women in the control group were referred to a higher level of care for expert management. These findings could be trusted because it is similar with the findings of Mobeen *et al.,* (2010), although these studies were not methodological sound.

Ghaleh *et al.,* (2011) researched on the effectiveness of misoprostol as an uterotonic drug in comparison with oxytocin in patients with a low risk of PPH. This was done in Iran using 269 pregnant women. There was no statistical difference in drop in haematocrit level between the two groups. The need for additional oxytocic was more in oxytocin group compared to misoprostol group (34.8% versus 20.5%, p=0.013). Fever and shivering was also found to be higher in misoprostol group. Misoprostol was concluded to be no less effective as oxytocin in prevention of PPH.

Another study by Firouzbakht *et al.,* (2013) also compared the effectiveness of misoprostol and oxytocin in the prevention of PPH in Iran. There was no significant difference in the haemoglobin

concentration and duration of third stage of labour. The EBL was decreased significantly in misoprostol group compared to oxytocin (p =0.003) and the incidence of PPH was statistically not significant between the two groups (p >0.05). Shivering was also noted to be higher in misoprostol group though, the figures were conflicting in the results and table (14%, 20% versus 4%, 10%), while other side-effects were comparable.

Ghaleh *et al.,* (2011) and Firouzbakht *et al.,* (2013) studies have similar findings which suggested misoprostol to be as effective as oxytocin in the control of bleeding after childbirth. The samples were randomly selected in the both studies which reduces the risk of selection bias. However, it wasn't stated whether it was the researchers, participants or the clinicians that was single-blinded in the study of Ghaleh and colleagues. Firouzbakht and colleagues' study was not blinded from the researchers, participants and the clinicians, a double-blinded method would have provided a more reliable result that could give room for comparison and credibility. There was no accurate report in the method used for the collection of blood for measurement and estimation couple with the use of small sample size.

Studies by Nasr *et al.,* (2009) and Uthman *et al.,* (2011) had similar methodology, aim including similar primary and secondary outcome measured, though Uthman and colleague did not measure the side effect of the drugs during their study. The total number of participants used was 514 and 1800 respectively. The study by Uthman *et al.,* (2011) achieved large sample size coupled with explicit methodology for their study while in Nasr and colleagues study, incidence of PPH was 6.6% in misoprostol group and 4.7% in oxytocin group, also 10% drop in haematocrit level was higher in misoprostol group, though not statistically significant. Meanwhile, in Uthman and colleagues' study, incidence of PPH, MBL and need for additional uterotonics were higher in the oxytocin group compared to misoprostol. Nasr and colleague had postpartum blood loss that was significantly greater in misoprostol group than in the oxytocin group; while Uthman and colleagues recorded a haemoglobin drop from pre- to post-delivery which was greater in the oxytocin group. The double-blinded randomized controlled trial used in the both studies was suitable for data collection and enhanced the results/findings.

The findings of Al-Sawaf *et al.,* (2013) was different from other studies reviewed. The found that oxytocin was superior to misoprostol contrary to Bellad *et al.,* (2012), Uthman *et al.,* (2011), Nasr *et al.,* (2009), Badejoko *et al.,* (2012), Wangwe *et al.,* (2009), and Mobeen *et al.,* (2010) studies. Blood loss was significantly lower in oxytocin compared to misoprostol and the control groups (oxytocin= 314.7±94.6mls, misoprostol =348.0±112.0mls and control group =438.6±130.2mls). There was no significant difference in haemoglobin and haematocrit levels between the groups. Shivering, vomiting and nausea were statistically significant in misoprostol group. However, the outcome measured in this study was not stated at the beginning of the study, coupled with the small sample size (n=104) which makes it difficult to generalize this finding to a wider population.

Conclusively, 10 out of the 12 studies reviewed on this theme concluded that misoprostol is effective in prevention of PPH. Only 2 studies (Gohil and Tripathi, 2011 and Al-Sawaf *et al.,* 2013) found misoprostol to be less effective. However, 7 out of the 10 studies were rated as excellence and good quality study. Hence, it can be deduced that use of misoprostol in AMTSL prevents PPH after childbirth.

The optimal dose of misoprostol for the prevention of PPH

Over the years, several studies have concentrated on ascertaining the effectiveness of misoprostol in the prevention of PPH. They used different dosages of misoprostol for these effects, and there has been a lot of controversy on the optimal dose that is suitable and safe for the prevention of PPH (Mansouri and Alsahly, 2010). Therefore, to explore the optimal dose of misoprostol for the prevention of PPH, the 16 selected studies were reviewed. There was no primary research found that compared the different dosages, therefore dosages were compared among studies that compared misoprostol either with oxytocin or a placebo in their studies with different routes of administration.

In Wangwe *et al.,* (2009) study, 400 µg of misoprostol was found to be effective as oxytocin in prevention of PPH. Meanwhile, shivering was higher in misoprostol group compared to oxytocin group (3.3% versus 1%); fever, vomiting and nausea were comparable between the groups. Other RCTs that used 400 µg such as Ghaleh *et al.,* (2011) and Bellad *et al.,* (2012) had similar outcome though, the figures differ as regards the side-effects but not statistically significant. Furthermore, Chaudhuri *et al.,* (2012) and Firouzbakht *et al.,* (2013) also found similar outcome in MBL and incidence of PPH using 400 µg of misoprostol, though shivering and fever was significantly higher in misoprostol group compared to oxytocin group in Chaudhuri and colleagues' study. However, the above studies used different routes of administration which can be argued to be the cause of difference in outcomes. In a quasi-experimental study by Nasreen *et al.,* (2011), incidence of PPH was reduced using 400 µg of misoprostol compared to no intervention (misoprostol=1.6% versus no intervention=6.2%). Conversely, In a non-RCT conducted by Gohil and Tripathi (2009) 400 µg misoprostol was found to be less effective in control of bleeding compared to oxytocin, methyl-ergometrine, and oxytocin-ergometrine respectively (20%, 10%, 4% and 6%, P=0.03). Shivering and pyrexia >38°C was also significantly higher in misoprostol group compared to other drugs (misoprostol=10% and 8%; oxytocin=3% and 0%; methyl-ergometrine=2% and 0%; and oxytocin-ergometrine=1% and 1% respectively). This result was similar to Al-Sawaf and colleagues' study, incidence of PPH and measured blood loss was significantly higher using 200 µg which is a lower dose of misoprostol compared to oxytocin, which concluded that 200 µg of misoprostol is less effective in prevention of PPH. Adverse side-effects was also noticed to be higher in misoprostol compared to oxytocin.

Hofmeyr *et al.,* (2009), reviewed maternal deaths, dosage, and side effects of misoprostol compared

to oxytocin or placebo. They found in their review 11 maternal deaths of which 8 were directly due to PPH from women who received ≥600 µg of misoprostol prophylactically, adverse effects of shivering was more common in misoprostol group compared to placebo group (8 in 2070 versus 5 in 2032). Fever was higher in women who received 600 µg compared to those who received 400 µg. The integrity of this review is high with the highest level of evidence as over 46 selected articles were used with over 40,000 participants; this increases the credibility of this finding.

Badejoko *et al.,* (2012) and Mobeen *et al.,* (2010) also used 600 µg of misoprostol in a double-blinded RCT; they found no significant difference in the MBL, and PPH in their studies, which affirmed that misoprostol, is as effective as oxytocin in the prevention of PPH. In Badejoko and colleagues' study shivering, fever >38°C, vomiting was significantly higher in misoprostol group compared to oxytocin group while in Mobeen *et al.,* (2010) studies which compared misoprostol against a placebo, only shivering was significantly higher between the groups (9.4% versus 3.9%), fever, vomiting, nausea was comparable between the groups. Also, Uthman *et al.,* (2011) using 600 µg of misoprostol against 10 IU of oxytocin confirmed that, misoprostol was more effective in the prevention of PPH; however, the side-effects of the two drugs were not measured in their study. Furthermore, Patted *et al.,* (2009) in RCT to investigate the side-effects of 600 µg of misoprostol compared to placebo, shivering and fever was statistically significant in misoprostol group compared to the placebo within 2 hours of intervention.

Nasr *et al.,* (2009) and Shrestha *et al.,* (2011) used higher doses of 800 and 1000 µg of misoprostol; no statistical significant difference was found in incidence of PPH and MBL between the two groups. Meanwhile, shivering, and fever was significantly higher in misoprostol group compared to oxytocin.

In conclusion, the side effects of misoprostol was found to be of higher percentage in women who received from 600 µg to 1000 µg compared to a dose of 400 µg misoprostol, but reduction in blood loss and other measured outcomes were comparable. The higher percentages of side-effects associated with high doses can be a discomfort to a woman in the immediate postpartum period as she spends time getting to know her new baby.

Best route of administration of misoprostol that is suitable for the prevention of PPH

Misoprostol can be administered through different routes such as rectal, sublingual, oral, buccal, vaginal, intrauterine and intracervical, but no research or review have established any of these routes of administration as the best for the prevention of PPH. Three most often used routes of administration were reviewed in this work.

Sublingual Route

In the studies by Bellad *et al.,* (2012) and Chaudhuri *et al.,* (2012) 400 µg of sublingual misoprostol was found to be superior and equivalent to oxytocin in the EBL and incidence of PPH. Women in the misoprostol group experienced transient fever and shivering higher than those in oxytocin group. In Bellad's study the

duration of third stage of labour was similar in both groups (4.3±2.2 versus 4.3±1.4), while it was significantly shorter in misoprostol group compared to oxytocin group (6.88±3.6 versus 8.01±4.32, p=0.001) in Chaudhuri and colleagues' study. Conversely, Al-Sawaf *et al.,* (2013) used smaller dose of 200 µg of misoprostol sublingually. They reported that sublingual misoprostol was less effective than intramuscular oxytocin in prevention of PPH, although the duration of third stage of labour was not statistically significant between the two groups.

Oral Route

Using the oral route, the studies by Uthman *et al.,* (2011), Mobeen *et al.,* (2010) and Patted *et al.,* (2009) reported that 600 µg of oral misoprostol was more effective than oxytocin in terms of MBL, incidence of PPH and drop in haematocrit level. These authors did not mention the duration of third stage of labour, which should have been the criteria to measure the bioavailability of this drug in a given period of time to determine the fastest, suitable and safest route of administration. Furthermore, Nasreen *et al.,* (2011) gave an interval between delivery of baby and placenta of >30 minutes to be higher in the control group than the intervention group (5.2% versus 3.5%). The need for additional uterotonics was higher in the oxytocin group compared to misoprostol group in three studies (Uthman *et al.,* 2011; Nasreen *et al.,* 2011; Ghaleh *et al.,* 2011).

Rectal Route

Mansouri and Alsahly (2010) compared rectal and oral misoprostol to test the effectiveness of rectal misoprostol in the management of third stage of labour. Women who received oral misoprostol had blood loss significantly higher compared to rectal administration of misoprostol (232.8mls versus 207.2mls; p=0.016; CI 4.86-46.18). None of the women in both groups had severe haemorrhage of ≥1000 ml and no significance difference in incidence of PPH, and blood transfusion. Duration of third stage of labour was similar (10.8 minutes versus 5.4 minutes, p=0.189). Furthermore, shivering and fever were significantly higher with those who received 600 µg oral compared to those who received 600 µg rectal misoprostol (shivering=52.1% versus 26.2% and fever=27.8% versus 15.2%) respectively. nausea and vomiting were also significantly higher in oral misoprostol group compared to rectal misoprostol (p=0.033). Rectal misoprostol reduced blood loss and was associated with minimal side-effects compared to oral misoprostol.

In Gohil and Tripathi's (2011) study, methyl-ergometrine was more effective compared to rectal misoprostol, oxytocin, and oxytocin-ergometirne in the prevention of PPH. The mean duration of third stage of labour was lowest in methyl-ergometrine group compared to misoprostol, oxytocin, and oxytocin-ergometrine, groups (7.18±3.10, 7.84±3.19, 8.94±4.18 and 10.92±5.92 in minutes). Also, Wangwe *et al.,* (2009); Shrestha *et al.,* (2011) and Nasr *et al.,* (2009) found no significant difference in the mean duration of third stage of labour at average of 8.7 minutes which is similar to Mansouri and Alsahly study. The need for additional uterotonics was higher in oxytocin group compared to misoprostol group in their studies, while duration of third stage

of labour was similar also in misoprostol and oxytocin groups in Firouzbakht and colleagues study (stage=5.08±3.07 versus 5.49±2.45).

In conclusion, the outcome measured of MBL, incidence of PPH, drop in haematocrit and haemoglobin level, need for additional uterotonic were similar across the studies. The adverse effects of misoprostol were higher in percentage of women who receive misoprostol rectally and orally compared to those who received misoprostol sublingually.

Discussion

In determining the effectiveness of misoprostol for the prevention of PPH, ten out of twelve studies found misoprostol to be as effective as oxytocin in the prevention of PPH. These ten studies found no significant difference between oxytocin and misoprostol in the measured outcomes. However, there was heterogeneity of findings; this could be due different routes of administration and dosages. Although Uthman *et al.,* (2011) report that blood loss and incidence of PPH was significantly higher in oxytocin compared to misoprostol group. The differences could be due to environmental factors as their study was done in the Northern part of Nigeria where there are higher temperatures, this probably degraded the efficacy of oxytocin due to lack of steady power supply to preserve the oxytocin (Ameenah *et al.*, 2011). The effectiveness of misoprostol in the AMTSL to prevent PPH found in this review was encouraging in that it can be administered by TBAs and CHWs in the rural community where there are no skilled attendants, sterile needles and syringes to administer oxytocin parenteral. Misoprostol was also found to be effective, convenient and acceptable by the women in rural communities (Nasreen *et al.,* 2011; Mobeen *et al.*, 2010), this evidence implies that, if misoprostol is distributed in rural areas across developing countries by train TBAs and CHWs, the women might be willing to accept it in view of prevention of PPH to reduce maternal death in developing countries.

The adverse side-effects of shivering and fever was commonly associated with misoprostol compared to oxytocin group, while vomiting, nausea and diarrhea was not statistically significant between the compared groups. These side-effects were found to be dose-related in other studies (Hofmeyr *et al.*, 2009; Khan and El-Rafaey *et al.*, 2003). Also, Durocher *et al.,* (2010) in their study to ascertain the efficacy, safety and acceptability of sublingual misoprostol by the Ecuadorian women, they affirmed that, the side-effects associated with misoprostol are only transient and has no obvious deterrents on the women. This further strengthens the effectiveness of misoprostol application in rural areas since the side effects are transient and does not pose any further threat to the women. Furthermore, the side-effects can be due to rapid absorption of misoprostol given orally and high bioavailability when administered sublingually (Patted *et al.*, 2009; Tang and Ho, 2006).

In determining the optimal dose of misoprostol for the prevention of PPH. The evidence shows that shivering and fever was found to have greater percentages with doses from 600 µg to 1000 µg of misoprostol (Nasr *et al.*, 2009; Patted *et al.,* 2009; Mobeen *et al.*, 2010; Shrestha *et al.,* 2011;

Uthman *et al.,* 2011 and Badejoko *et al.,* 2012). This is comparable with Hofmeyr *et al.,* (2009) review; the higher percentages of side-effects observed in their review was from women who received 600 µg of misoprostol and above. 400 µg of misoprostol was found effective with lower percentages of side-effects (Wangwe *et al.,* 2009; Nasreen *et al.,* 2011; Ghaleh et al., 2011; Chaudhuri *et al.,* 2012; Bellad *et al.,* 2012 and Firouzbakht *et al.,* 2013). These dosages were reviewed in the different selected studies with different routes of administration due to non-availability of primary research comparing the doses of misoprostol; this makes it difficult to determine the optimal dose of misoprostol for the prevention of PPH, hence, more randomized trials should be done to compare specifically the different doses of misoprostol with a specific route of administration for the prevention of PPH. However, the optimal dose of misoprostol for the prevention of PPH still remains undecided as no study was found that compared only the dosages with a particular route of administration. This made the findings inconclusive as there is not enough evidence to warrant a conclusion.

Furthermore, the best route of administration of misoprostol for the prevention of PPH such as sublingual, oral and rectal routes were compared across the selected studies. There was no significant different in MBL/EBL, incidence of PPH and drop in haematocrit and haemoglobin levels between the three routes. The adverse effects of misoprostol (shivering and fever) were found to be higher in percentages in women who received misoprostol rectally or orally (Nasr *et al.,* 2009; Patted *et al.,* 2009; Badejoko *et al.,* 2012; Mobeen *et al.,* 2010;). Meanwhile, the women that received sublingual misoprostol had lower percentages of side effects and the duration of third stage of labour was shorter (Bellad *et al.,* 2012 and Chaudhuri et al., 2012). However, in Mansouri and Alsahly (2010) study, rectal route was found to be superior to oral route in reduction of blood loss with minimal side-effects. This result is consistent with the findings of Hofmeyr *et al.,* (2004) that found that rectal route have slower uptake of misoprostol and longer duration of action, oral route had the fastest uptake but with a shorter duration of action, and the sublingual route has the highest peak concentration, longer duration of action and greatest bioavailability. For the prevention of PPH during the third stage of labour, rapid absorption of misoprostol and avoidance of first-pass metabolism through the liver is necessary to minimize eruption of gastrointestinal side-effects (nausea, vomiting, and diarrhea). Sublingual administration of misoprostol has been proven to achieve full systemic bioavailability with the highest serum peak concentrations when compared with other routes (Tang *et al.,* 2002). Also, oral route has been linked to dose-related side effects of shivering, fever and the rectal route is said to minimize gastrointestinal side effects of vomiting, nausea and diarrhea (Tang and Ho, 2006). However, it is difficult to draw conclusion on the best route of administration for the prevention of PPH in this review because only one study was found that compared oral and rectal route which cannot be used to draw conclusion.

Conclusion

The overall aim of this review was to ascertain the effectiveness, optimal dose and the best route of administration of misoprostol for the prevention of PPH. It can be concluded that misoprostol is as effective as oxytocin in the prevention of PPH in the developing countries. It is safe, affordable, cost-effective and easy to administer by Traditional Birth Attendants (TBAs) and Community Health Workers (CHWs) in the rural communities. The adverse effects of shivering and fever frequently associated with misoprostol group was dose-related and a transient that has no later complications on the women. Also, community-based education/training of TBAs and CHWs on administration of misoprostol was found to reduce the incidence of PPH in rural areas where maternal mortality is higher and parenteral administration of oxytocin is not feasible. Regarding the optimal dosage and the best route of administration of misoprostol for the prevention of PPH, there was inadequate published evidence from RCTs to compare the routes and dosages of misoprostol. However a manual and narrative analysis of the evidence suggests that sublingual route at the dose of 400 µg looks promising compared to other routes and dosages, though more research is needed to establish this fact. In summary, the benefits of misoprostol outweighs the associated side-effects, thus, the issue of misoprostol for the prevention of PPH should not be neglected in strive to reduce maternal mortality.

Acknowledgement

I would like to thank my academic supervisors Dr Alison Brettle, Dr Lesley Lappin and Sarah Davies in the School of Nursing, Midwifery, Social Work and Social Sciences at the University of Salford, UK for their guidance and input into the systematic review and academic studies which formed the basis for this paper

References

1. Al-Sawaf, A., Mazny, El. and Shohayeb, A. (2013). A randomized controlled trial of sublingual misoprostol and intramuscular oxytocin for prevention of postpartum haemorrhage. *Journal of Obstetrics and Gynaecology*, 33: pp.277-279.
2. Ameenah, K., Amrita, H., Poonam, P., Carissa, B., Smita, T. and Aimara, P. (2011). *Drug degradation*. Lecture delivered [Online] available from: http:/C/www.slideshare.net/ms optimistic/degradation. (Retrieved on 8th March, 2013).
3. Badejoko, O. O., Ijarotimi, A. O., Awowole, I. O., Loto, O. M., Badejoko, B. O., Olaiya, D. S., Fatusi, O. A., Kuti, O., Orji, E. O. and Ogunniyi S. O. (2012). Adjunctive rectal misoprostol versus oxytocin infusion for the prevention of postpartum haemorrhage in women at risk: a randomised controlled trial. *The Journal of Obstetrics and Gynaecology Research*, 38(11), pp. 1294-1301.
4. Bellad, M., Tara, D., Ganachari, M., Mallapur, M., Gouder, S., Kodkany, B., Sloan, N. and Derman, R. (2012).

Prevention of postpartum haemorrhage with sublingual misoprostol or oxytocin: a double-blind randomised controlled trial. *British Journal of Obstetrics and Gynaecology*, 119: pp.975-986.

5. Chaudhuri, P., Biswas, J. and Mandal, A. (2012). Sublingual misoprostol versus intramuscular oxytocin for prevention of postpartum haemorrhage in low-risk women. *International Journal of Gynecology and Obstetrics*, 116: pp.138-142.
6. Derman, R. J., Kodkany, B. S., Gouder, S. S., Geller, S. E., Naik, V. A., Bellad, M. B., Patted, S., Patel, A., Edlavitch, S. A., Hartwell, T., Chakraborty, H. and Moss, N. (2006). Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. *The Lancet*, 368: pp.1248-1253.
7. Durocher, J., Bynum, J., Leon, W., Barrera, G. and Winikoff, B. (2010). High fever following postpartum administration of sublingual misoprostol. *British Journal of Obstetrics and Gynaecology*, 117: pp. 845-852.
8. El-Refaey, H., Noor, R., O'Brien, P., Abdellah, M., Geary, M., Walder, J. (2000). The misoprostol for third stage of labour study. *British Journal of Obstetrics and Gynecology*, 107: pp. 1104-1110.
9. Firouzbakht, M., Kiapour, A. and Omidvar, S. (2013). Prevention of postpartum haemorrhage by rectal misoprostol: a randomised clinical trial. *Journal of Natural Science, Biology and Medicine*, 4(1), pp. 134-137.
10. Gibson, F. and Glenny, A. M. (2007). Critical appraisal of quantitative studies 1: Is the quality of the study good enough for you to use the findings? In J. V. Craig and R. L. Smyth (eds), *The evidence-based practice manual for nurses*, (pp.95-126). London: Churchill Livingstone, Edinburgh.
11. Ghaleh, T. D., Lalooha, F., Movahed, F., Moradi, S. and Mashrabi, O. (2011). Comparison of oxytocin and misoprostol in reduction of postpartum haemorrhage. *Research Journal of Biological Sciences*, 6(12), pp. 652-655.
12. Gohil, J. T. and Tripathi, B. (2011). A study to compare the efficacy of misoprostol, oxytocin, Methyl-ergometrine and ergometrine-oxytocin in reducing blood loss in active management of 3rd stage of labour. *The Journal of Obstetrics and Gynaecology of India*, 61(4), pp. 408-412.
13. Hofmeyr, G. J., Gulmezoglu, A. M., Novikova, N., Linder, V., Ferreira, S. and Piaggio, G. (2009). Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. *Bull World Health Organisation*, 87: pp.666-677.
14. Long, A. F., Godfrey, M., Randall, T., Brettle, A. J. and Grant, M. J. (2002). *Developing Evidence Based Social Care Policy and Practice. Part 3: Feasibility of*

Undertaking Systematic Reviews in Social Care. Leeds: Nuffield Institute for Health.

15. Mansouri, H. A. and Alsahly, N. (2011). Rectal versus misoprostol for active management of third stage of labor: a randomized controlled trial. *Archives of Gynecology and Obstetrics*, 283: pp.935-939.
16. Mobeen, N., Durocher, J., Zuberi, N. F., Jahan, N., Blum, J., Wasim, S., Walraven, G. and Hatcher, J. (2010). Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: a randomised placebo-controlled trial. *British Journal of Obstetrics and Gynaecology*, 118: pp.353-361.
17. Mairiga, A. G. and Saleh, W. (2009). Maternal mortality at the state specialist hospital, Bauchi, Northern Nigeria. *East African Medical Journal*, 86(1), pp. 25-30.
18. National Population Commission and ICF Macro (2009). *Nigeria Demographic Health Survey: key findings*. [Online] available from: www.measureddhs.com/ pubs/pdf/OF12.NC.8.Hausa.pdf. (Retrieved on 27th March, 2013).
19. Nasreen, H. E., Nahar, S., Mamum, M. Al., Afsana, K. and Byass, P. (2011). Oral misoprostol for preventing postpartum haemorrhage in home births in rural Bangladesh: how effective is it? *Global Health Action*, 4: 7017 – DOI: 10.3402/gha.V4i0.7017.
20. Nasr, A., Shahin, A. Y., Elsamman, A. M., Zakherah, M. S. and Shaaban, O. M. (2009). Rectal misoprostol versus intravenous oxytocin for prevention of postpartum haemorrhage. *International Journal of Gynecology and Obstetrics*, 105: pp.244-247.
21. Patted, S. S., Goudar, S. S., Naik, V. A., Bellad, M. B., Edlavitch, S. A., Kodkany, B. S., Patel, A., Chakraborty, H., Derman, R. J. and Geller, S. E. (2009). Side effects of oral misoprostol for the prevention of postpartum haemorrhage: results of a community-based randomised controlled trial in rural India. *The Journal of Maternal-Fetal and Neonatal Medicine*, 22(1), pp. 24-28.
22. Polit, D. F. and Beck, C. (2005). Essentials of nursing research. New York: Lippincott Williams and Wilkins.
23. Ronsmans, C. and Graham, W. J. (2006). Maternal mortality: who, when, where, and why. *The Lancet*, 368: pp.1189-200.
24. Shrestha, A., Dongol, A., Chawla, C. D. and Adhikari, R. (2011). Rectal misoprostol versus intramuscular oxytocin for the prevention of postpartum haemorrhage. *Kathmandu University Medical Journal*, 33(1), pp. 8-12.
25. Tang, O. S., Schweer, H., Seyberth, H. W., Lee, S. W. and Ho, P. C. (2002). Pharmacokinetics of different routes of administration of misoprostol. *Human Reproduction*, 17(2), pp. 332-336.
26. Tang, O. S. and Ho, P. C. (2006). The pharmacokinetics and different regimes of misoprostol in early first-trimester medical

abortion. *Journal of Contraception*, 76: pp. 26-30.

27. Thompson, C., McCaughan, D., Cullum, N., Sheldon, T. and Raynor, P. (2005). Barriers to evidence-based practice in primary nursing care: why viewing decision making as context is helpful. *Journal of Advanced Nursing*, 52(4), pp. 432-444.
28. Uthman, G. S., Kwanashie, H. O., Mairiga, A. G., Gamaniel, K. S., Isa, M. H., Abdu, I. A., Geidam, A. D. and Nwaosu, C. S. (2011). A randomised clinical trial comparing the efficacy of oxytocin injection and oral misoprostol tablet in the prevetion of postpartum haemorrhage in Maiduguri Nigeria. *International Research Journal of Pharmacy*, 2(8), pp. 76-81.
29. Wangwe, P., Kidanto, H., Muganyizi and Roosmalen, J. V. (2009). Active management of third stage of labour: misoprostol or oxytocin? *African Journal of Midwifery and Women's Health,* 3(2), pp. 57-60.
30. Widmer, M., Blum, J., Hofmeyr, G. J., Carroli, G., Abdel-Aleem, H., Lumbiganon, P., Ngoc, T. N., Wojdyla, D., Thinkhamrop, J., Singata, M., Mignini, L. E., Abdel-Aleen, M. A., Thach, T. S. and Winikoff, B. (2010). Misoprostol as an adjunct to standard uterotonics for treatment of postpartum haemorrhage: a multicentre, double-blind randomised trial. *The Lancet*, 375:1808-1813.
31. World Health Organization (2006). *Making pregnancy safer: reduction of maternal mortality*. [Online] Available from: http://www.who.int/mediacentre/factsheets/fs276/en. (Retrieved on 12th March, 2013).