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MISOPROSTOL AS PREVENTION OF POSTPARTUM HEMORRHAGE: A TEN YEARS SYSTEMATIC REVIEW

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ABSTRACT

Background: *Postpartum Haemorrhage (PPH) is commonly defined as a blood loss of 500 ml or more within 24 hours after birth. PPH is the leading cause of maternal mortality in low-income countries and the primary cause of nearly one quarter of all maternal deaths globally.*

The aim: *This study aims to show about misoprostol as prevention of postpartum hemorrhage.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 23 articles, whereas the results of our search on SagePub brought up 39 articles. The results of the search conducted for the last year of 2014 yielded a total 13 articles for PubMed and 27 articles for SagePub. The result from title screening, a total 5 articles for PubMed and 14 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *Other injectable uterotonics and misoprostol are recommended as alternatives for the prevention of PPH in settings where oxytocin is unavailable.*

Keyword: *Misoprostol, postpartum hemorrhage (PPH), uterotonic.*

INTRODUCTION

Globally, one woman dies every 7 minutes from postpartum hemorrhage (PPH), which is often attributable to uterine atony. The World Health Organization recommends that women be provided with uterotonics, ideally oxytocin, during the third stage of labor. Unless a disposable prefilled single-use syringe (eg, Uniject) is available, oxytocin requires a skilled birth attendant (SBA) for administration and cold-chain storage, which is challenging in settings with staff shortages, inadequate infrastructure, or a high number of home births. When providing oxytocin is not possible, misoprostol (Cytotec) can be administered by less skilled health personnel, including community health workers (CHWs). Randomized controlled trials have demonstrated the efficacy of misoprostol for PPH prevention, and a review of 18 programs found high rates of use when CHWs distributed misoprostol to women late in pregnancy or at the time of birth.[1]

More than 303,000 women are estimated to have died globally during, and following, pregnancy and childbirth in 2015. Most of these deaths are preventable and are a result of women in remote rural areas in particular, having limited access to basic essential obstetrical care. Globally, postpartum hemorrhage (PPH) is the single leading direct cause of maternal mortality and is also associated with severe morbidity. Due to the high prevalence of anemia among pregnant women in low-resource settings, the outcome of PPH is often worsened, resulting in detrimental health outcomes from relatively moderate loss of blood. Despite the high number of deaths due to PPH, it is largely preventable with active management of the third stage of labor (AMTSL).[2,3]

Postpartum hemorrhage (PPH) is a life-threatening obstetric emergency that occurs after caesarean section (CS) or normal vaginal delivery (NVD). It may be defined as ≥500 mL hemorrhage after vaginal or ≥1000 mL hemorrhage after CS delivery. PPH is one of the most common obstetric maternal complications and is among the three most common etiologies of maternal death worldwide. Its incidence is increasing and it affects 1–5% of all deliveries. Atony is the main cause of PPH and is responsible for about 80% of PPHs. Therefore, uterotonic agents are administered. Oxytocin infusion, single dose of methylergometrine, and then carboprost tromethamine are used in 15-to-20-minute intervals in atony. Misoprostol, which is a prostaglandin E1 analog, is an inexpensive drug and can be absorbed by the following routes of administration: vaginal, rectal, or oral (sublingual or buccal absorption). Gastrointestinal symptoms (nausea, vomiting, and diarrhea) and fever are the most common adverse effects of misoprostol, which often are mild and self-limited.[4,5]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast misoprostol as prevention of postpartum hemorrhage. It is possible to accomplish this by researching or investigating misoprostol as prevention of postpartum hemorrhage. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about misoprostol as prevention of postpartum hemorrhage. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " misoprostol as prevention of postpartum hemorrhage." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("*Misoprostol*"[MeSH Subheading] OR "*Mechanism of misoprostol*"[All Fields] OR "*Effect of misoprostol*" [All Fields]) AND ("*Postpartum hemorrhage*"[All Fields] OR "* Cause of postpartum hemorrhage *"[All Fields]) AND ("*Mechanism of postpartum hemorrhage*"[All Fields]) OR ("*Benefit of misoprostol for prevention of postpartum hemorrhage" [All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources

for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

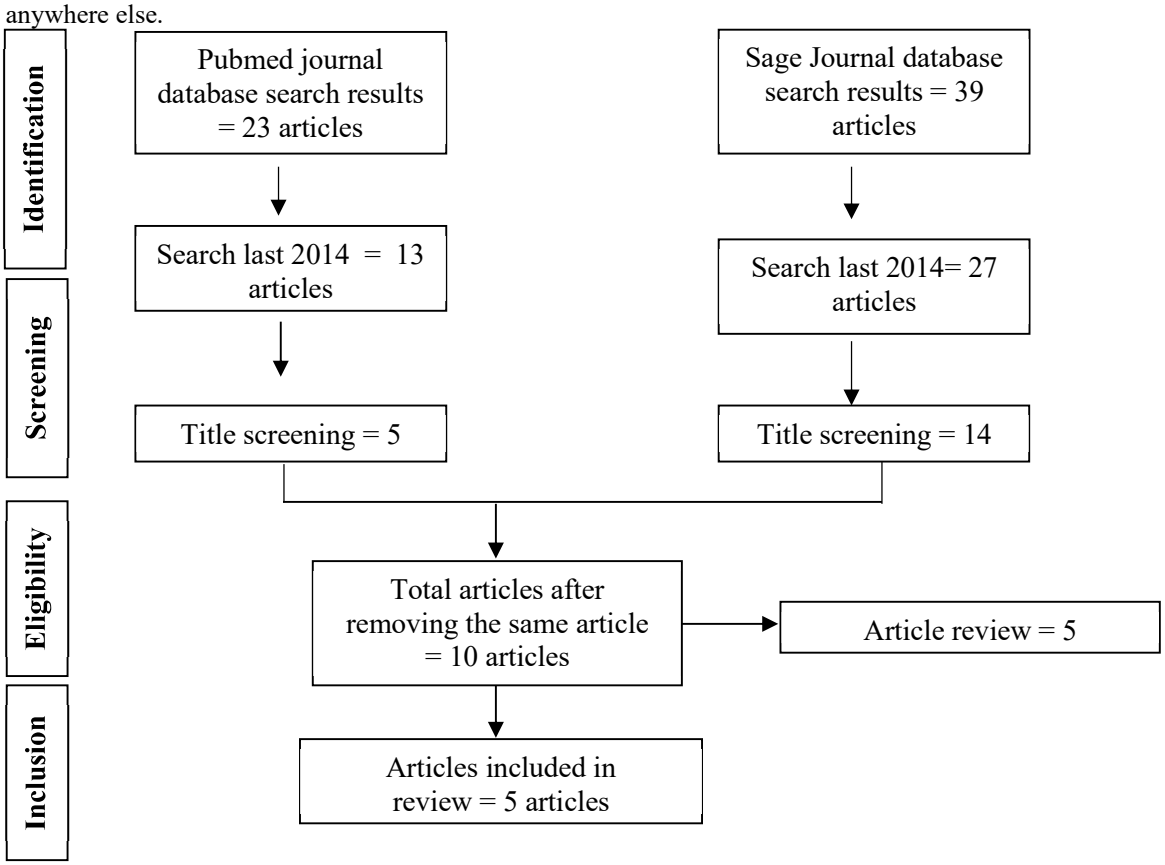

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 23 articles, whereas the results of our search on SagePub brought up 39 articles. The results of the search conducted for the last year of 2014 yielded a total 13 articles for PubMed and 27 articles for SagePub. The result from title screening, a total 5 articles for PubMed and 14 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Numfor, E *et al* (2020)[6] showed the implementation of misoprostol plus oxytocin in the prevention of PPH in this low-resource setting improved the obstetrical outcome by reducing the risk and the amount of blood loss during delivery.

Koch, DM *et al* (2020)[7] showed misoprostol in the maternity hospital has offered an accessible and effective pharmaceutical option to control postpartum hemorrhage, including the cases in which the first procedures commonly adopted failed (oxytocin and ergometrine). Despite the small number of cases investigated during the study period, the results obtained may reflect in quality of care provided to the pregnant women of the above-mentioned maternity hospital. Considering the recent provision of misoprostol in the organization, it is necessary to have uniform care actions to treat postpartum hemorrhage.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Numfor, E *et al*., 2020[6]	Africa	A retrospective cohort study	1778	We studied the obstetric records of 1778 parturients were studied; 857 in group A and 879 in group B. Their mean age was 26.3 ±5.2 years. Both groups were comparable in several baseline sociodemographic and clinical characteristics. The prevalence of PPH was 2.7% (3.4% vs 2.2%; p = 0.0744). The risk of PPH in the oxytocin only group was about 1.5 times higher than in the oxytocin plus misoprostol group. The estimated blood loss between the two groups was statistically significant (1100 ± 150 vs 800 ± 100 ml, p< 0.0001). The active management of the third stage of labor without misoprostol was the only risk factor for PPH.
Koch, DM *et al*., 2020[7]	Brazil	A descriptive observational study	717	A total of 717 prescriptions of misoprostol were identified. Of these, 10% were for treatment of postpartum hemorrhage. The majority of pregnant women were young adults, married, with complete high school education, white, residing in urban areas, multiparous (68.1%) and 25% had previous cesarean sections. The mean gestational age was 39 weeks and 51.4% had a cesarean section. There was prophylactic use of oxytocin in 47.2% of women. Treatment of postpartum hemorrhage was successful in 84.7% of women. Of these, 79.2% also used oxytocin and 54.2% methylergonovine. Only 13.5% of pregnant women had less than five prenatal visits, and the main cause of postpartum hemorrhage was uterine atony. There were 13 complications after hemorrhage, 15.3% required blood transfusion and there was one case of maternal death.
Zgaya, R *et al*.,2020[8]	Africa	A prospective randomized double blind controlled trial	211	A total of 211 patients were randomized: 111 in the Misoprostol group (Cytotec*) and 100 patients in the placebo group. The two groups were

				similar in terms of sociodemographic characteristics. Significant difference between the 400-µg of Misoprostol and placebo group were recorded in mean postpartum blood and PPH occurrence. The difference in pre- and postpartum hemoglobin loss (expressed in grams per 100 ml) was 1.21 ± 1.05 for the Misoprostol group and 1.51 ± 0.74 for the placebo group with significant difference (p = 0.02). No differences were observed in the occurrence of headache, dizziness, vomiting, diarrhea and metallic taste but the incidence of shivering was more than twice as great among women receiving Misoprostol than among those treated with placebo with a significant difference (p = 0.01). Similarly, women who received Misoprostol had a significantly higher mean temperature after delivery in comparison with those receiving placebo.
Abbas, DF *et al.*, 2020[9]	Afghanistan	A double-blind, randomized placebo-controlled trial	1884	Among the 1884 women who delivered at home, nearly all (98.7%) reported self-use of misoprostol for PPH prevention. A small fraction was diagnosed with PPH (4.4%, 82/1884) and was administered treatment. Hb outcomes, including the proportion of women with a Hb drop of 2 g/dL or greater, were similar between the study groups (misoprostol: 56.4% (22/39), placebo: 60.6% (20/33), $p = 0.45$). Significantly more women randomized to receive misoprostol experienced shivering (82.5% vs. placebo: 61.5%, $p = 0.03$). Other side effects were similar between study groups and none required treatment, including among the subset of 39 women, who received misoprostol for both of its PPH indications.
Awoleke, JO *et al.*, 2020[10]	Nigeria	A randomised controlled trial	704	Seven (6.7%) and 16 (15.7%) of the sublingual and rectal routes, respectively, had PPH. However, the odds of having PPH after rectal misoprostol were at least twice the odds after the sublingual route

				($p = 0.041$). Also, the mean blood loss after the first, fourth and 24th hour postpartum were significantly higher after rectal administration. Although significantly more patients had shivering and pyrexia after sublingual misoprostol, it was acceptable to more participants than the rectal route.

Zgaya, R *et al* (2020)[8] showed Misoprostol is a little less effective than oxytocin. This has had the effect of reducing the image of this product, despite its glory especially in disadvantaged areas. The main conclusions are to use oral misoprostol at a dose of 400 microgram for the prevention of post-hemorrhage Partum in centers where oxytocin is not available. On the other hand side effects of misoprostol persist despite a reduction in dosage. However, these side effects are not severe.

Abbas, DF *et al* (2020)[9] showed Misoprostol is currently the only pill-based uterotonic option that could be offered at the community level to treat PPH and is supported in international recommendations on PPH management as a viable alternative to oxytocin. While the study did not show a benefit of misoprostol treatment on Hb outcomes, the provision of sublingual misoprostol (800mcg) as an intermediary measure to women in remote settings has been shown to be safe, including among women given the same medicine for prophylaxis (600mcg oral misoprostol). Furthermore, it is more probable than not, that misoprostol helps control bleeding when caused by uterine atony, based on what is known about the clinical effect of misoprostol from larger hospital trials.

Awoleke, JO *et al* (2020)[10] showed when combined with other routine components of active management of the third stage of labour, sublingually administered misoprostol was associated with a reduced incidence of PPH and mean blood loss when compared with rectal administration for the prevention of PPH in low-resource settings. Although it is associated with a higher incidence of shivering and pyrexia, parturients could be reassured that these would be mild and self-limiting.

DISCUSSION

Postpartum haemorrhage (PPH) continues to be a leading cause of maternal deaths, particularly in low-income countries. Almost one-third of maternal deaths worldwide are due to haemorrhage, mostly in the postpartum period. It is therefore recommended that active management of the third stage of labour (AMTSL) be offered to all women during childbirth by a skilled attendant to prevent PPH. WHO guidelines for AMTSL include prophylactic administration of a uterotonic soon after the birth of the baby, delivery of the placenta by controlled cord traction (where skilled birth attendants are available) and late cord clamping (performed after 1 to 3 min after birth). The latter is not recommended in all guidelines. Even with these efforts to prevent PPH, some women will require treatment for excessive bleeding and timely interventions including use of additional uterotonics by skilled providers.[11,12]

Drugs that can be used for PPH prophylaxis include oxytocin (intravenous (IV) or intramuscular (IM)); syntometrine (IM); ergometrine (IV or IM) and oral misoprostol. The gold standard treatment for the prevention of PPH is 10 iU oxytocin, recommended by the World Health Organization (WHO), the International Federation of Gynecology and Obstetrics and International Confederation of Midwives. However, widespread use of oxytocin is impeded by its need for cold-chain storage and either intravenous or intramuscular administration by a skilled birth attendant. In the world's least developed countries it is estimated that only 35 % of births are attended by skilled health workers.[11]

Oxytocin (administered intravenously or intramuscularly) is recommended for the prevention of PPH, but when oxytocin is not available, misoprostol, a medication available in tablet form (600 mcg oral) can be used as an alternative. Oxytocin is rarely accessible to women giving birth outside a health care setting due to the need for refrigeration and administration via injection. Oxytocin is widely used in health facilities across Mozambique but 30% of births take place without a skilled birth attendant (SBA) and therefore many women give birth without uterotonic protection (IMASIDA).[13,14]

Misoprostol is a safe alternative for the prevention of PPH when administered immediately after the birth where oxytocin is not available. Misoprostol is available internationally in 200mcg tablets. Therapeutic or preventive doses for PPH are usually administered as 3 tablets (600mcg) or 4 tablets (800 mcg). Misoprostol can be self-administered or administered by a trained community health worker (CHW) or traditional birth attendant (TBA).[13,15]

World Health Organization recommendations for the prevention of PPH emphasize the provision of a uterotonic to all women during the third stage of labor. Oxytocin is the preferred uterotonic for prevention of PPH. Misoprostol however is a reasonable alternative, especially in home birth settings where a qualified provider or injectable oxytocin are unavailable. Misoprostol is a uterotonic used for the prevention and treatment of PPH. It is manufactured in tablet form and is taken orally for PPH prevention (three 200 mcg tablets, total dose 600 mcg). It is inexpensive, easy to store and has an excellent safety profile. Various studies have demonstrated misoprostol's effectiveness in preventing PPH, reducing

the need for additional interventions and reducing the need for referrals in a variety of community-based settings. A number of community-based programs for PPH prevention at home birth using misoprostol have been safely conducted with a variety of cadres involved in drug distribution. Advocates are calling for a scale up of this approach.[16,17]

CONCLUSION

Other injectable uterotonics and misoprostol are recommended as alternatives for the prevention of PPH in settings where oxytocin is unavailable.

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