Effect of community-based distribution of misoprostol on facility delivery: a scoping review

Gizachew Tadele Tiruneh (gizt121@gmail.com)
JSI Research and Training Institute Inc https://orcid.org/0000-0002-5842-9518
Bereket Yakob
Harvard University T H Chan School of Public Health
Wubegzier Mekonnen Ayele
Addis Ababa University School of Public Health
Muluneh Yigzaw
JHPIEGO
Meselech Assegid Roro
Addis Ababa University School of Public Health
Araya Abrha Medhanyie
Mekelle University College of Health Sciences
Etenesh Gebreyohannes Hailu
Ministry of Health
Yibeltal Tebekaw Bayou
JSI Research and Training Institute Inc

Research article

Keywords: community-based distribution, diversion of facility birth, facility delivery, misoprostol

Posted Date: September 27th, 2019

DOI: https://doi.org/10.21203/rs.2.13002/v2

Version of Record: A version of this preprint was published on November 6th, 2019. See the published version at https://doi.org/10.1186/s12884-019-2539-5.

Abstract

Introduction : Community distribution of misoprostol to pregnant women in advance of labor is one of the compelling strategies for preventing postpartum hemorrhage. Concerns have been reported that misoprostol distribution could reduce facility delivery or lead to misuse of the medication. This scoping review was conducted to synthesize the evidence on the effect of community-based misoprostol distribution on rates of facility delivery, and to assess the frequency of mothers taking distributed misoprostol before delivery, and any harmful outcomes of such misuse. Methods: We included peer-reviewed articles on misoprostol implementation from PubMed, Cochrane Review Library, Popline, and Google Scholars. Narrative synthesis was used to analyze and interpret the findings, in which quantitative and qualitative syntheses are integrated. Results: Three qualitative studies, seven observational studies, and four experimental or quasi-experimental studies were included in this study. All before-after household surveys reported increased delivery coverage after the intervention: ranging from 4 to 46 percentage points at the end of the intervention when compared to the baseline. The pooled analysis of experimental and quasi-experimental studies involving 7,564 women from four studies revealed that there was no significant difference in rates of facility delivery among the misoprostol and control groups [OR 1.011; 95% CI: 0.906-1.129]. A qualitative study among health professionals also indicated that community distribution of misoprostol for the prevention of postpartum hemorrhage is acceptable to community members and stakeholders and it is a feasible interim solution until access to facility birth increases. In the community-based distribution of misoprostol programs, self-administration of misoprostol by pregnant women before delivery was reported in less than 2% of women, among seven studies involving 11,108 mothers. Evidence also shows that most women who used misoprostol pills, used them as instructed. No adverse outcomes from misuse in either of the studies reviewed. Conclusions: The claim that community-based distribution of misoprostol would divert women who would have otherwise had institutional deliveries to have home deliveries and promote misuse of the medication are not supported with evidence. Therefore, community-based distribution of misoprostol can be an appropriate strategy for reducing maternal deaths which occur due to postpartum hemorrhages, especially in resource-limited settings.

Introduction

Maternal mortality ratios (MMR) remain high in low-and-middle-income countries (LMICs), and reduction of MMR continues to be a priority challenge in the Sustainable Development Goals (SDG) era [1]. Accordingly, to achieve the SDG of reducing the global MMR to 70 per 100,000 live births by 2030, LMICs needs to implement innovative and high impact interventions aimed at preventing and managing the main causes of maternal deaths and providing high-quality services in the continuum of maternity care [2, 3].

A wealth of evidence shows that hemorrhage is one of the major causes of maternal mortality [4-7]. More than two-thirds of maternal deaths due to hemorrhage occur during the postpartum period, which

accounts for 20 % of all maternal deaths in developing regions [5]. However, in Ethiopia, a systematic review of national evidence shows that PPH accounts for 30% of maternal deaths [8, 9].

Most maternal deaths occurring due to PPH are in poorly resourced facilities or outside of a health facility where there is no access to skilled obstetric care [10-12]. Women who deliver at home face the highest risk of PPH, as they do not benefit from the support of skilled birth attendants and are less likely to receive timely care and medications that prevent and manage PPH [12]. Evidence shows that most PPH-associated deaths could be avoided if active management of third stage of labor (AMTSL) is implemented [13], adverse outcomes and complications are prevented or managed using safe drugs in communities and facilities, and effective referral mechanisms are implemented during delivery and in the postpartum period [14].

Misoprostol distribution at community level to women during pregnancy is one of the interventions for preventing or treating PPH. Misoprostol has been studied in different setups and is endorsed by the World Health Organization (WHO) as a solution for women who give birth in facilities without oxytocin or where there is low coverage of skilled attendance [15]. Clinical trials have verified the effectiveness and safety of community distribution of misoprostol [16-19] where access to skilled birth attendance and oxytocin is limited.

Despite the existing evidence, community-based distribution of misoprostol is still the least prioritized intervention in the maternal survival strategies [20-24]. This is due to concerns of policymakers' and practitioners' [19, 18, 24, 12] that misoprostol distribution at community level might decrease facility deliveries, possibly lead to misuse of misoprostol (including taking the drug before delivery, and using the drug for the purpose of inducing abortion), and lack of technologies and expertise to diagnose multiple pregnancies before using it at community levels in resource-limited settings [17, 25]. A range of other barriers at the health system, community, and policy levels are also impeding access to misoprostol for prevention of PPH. These barriers include: 1) absence of registration of misoprostol for the management of PPH [26, 24], 2) fear and apprehensions of providers and policymakers regarding its use [26, 24], 3) lack of evidence-based guidelines and provider training [24], 4) inadequate staffing and lack of knowledge and skill of providers regarding causes of PPH, and 5) limited knowledge of the community regarding the appropriate dosage and timing of administration for PPH presentation and management [26, 17].

This scoping review was, therefore, conducted to synthesize the evidence on the effect of community-based misoprostol distribution in advance of delivery on rates of facility delivery, and to assess the frequency of mothers taking distributed misoprostol before delivery, and any harmful outcomes of such misuse.

Methods

Criteria for inclusion

In this study, researchers used a scoping review methodology to get a wide range of information from both qualitative and quantitative studies. All types of literature on community-distribution of misoprostol for the prevention of PPH reported in English language were included, with no specification on timing of publication.

Search strategy

We identified peer-reviewed articles on implementation of community distribution of misoprostol from PubMed, Cochrane Review Library, Popline, and Google Scholars which were made available from February 1-15, 2019. We also applied a snowball approach of searching from the references of papers of the initial search.

The following search strategy was used to search literature from PubMed and CENTRAL databases;

"((((((((((Africa OR Asia OR Caribbean OR West Indies OR South America OR Latin America OR Central America OR Middle East))) OR ((developing countr OR less developed country * OR under developed country * OR underdeveloped country * OR middle income country * OR low income countr*)))))) AND ((((postpartum hemorrhage) OR post partum hemorrhage) OR postpartum haemorrhage) OR post partum haemorrhage)) AND misoprostol)) AND ((((community distribution) OR community)) OR community based))) AND (((((adverse effects) OR adverse outcomes)) OR ((misuse) OR ("Drug Misuse"[Mesh] OR "Prescription Drug Misuse"[Mesh])))) OR ((((skilled delivery) OR institutional delivery) OR "Delivery, Obstetric"[Mesh]) OR delivery))"*

Moreover, a combination of terms, including 'misoprostol'; 'misuse '; 'adverse outcomes'; ' fear of diversion of facility birth'; 'misconceptions'; 'misperceptions'; 'post-partum hemorrhage' (and variations i.e. 'post-partum hemorrhage', 'postpartum hemorrhage'); 'community-based maternal'; 'maternal health interventions'; 'maternal mortality'; and 'low-income setting', 'developing country', 'resource-poor setting' have been used to identify the required literature from Popline and Google Scholar.

First, any research output with the above-mentioned terms in either the title or abstract of the article was downloaded, and then a combination of these terms was also used to download more resources.

Critical appraisal

The methodological quality of each study was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklists for different study designs as appropriate [27-29]—to assess the methodological quality of studies and to determine the extent to which included studies have addressed the possibility of bias in its design, conduct, and analysis. Two review authors (GT and MY) independently did appraising the quality of each study included and discrepancies between scores were resolved through discussions.

The quality of the studies was assessed based on the core items recommended for the assessment of methodological quality. To obtain an overall quality score, publications scored "1" point for each item fully met and "0" for none or very little information reported. Items were given equal weights and a

percentage score was generated. Studies that scored 75% or more were categorized as high quality, scores in the range of 50-74% were ranked as medium, and scores less than 50% were rated as poor.

Data extraction and analysis

The form for abstracting data from reviewed literature was designed and review team members agreed on the contents of the form. Two reviewers (GT and YT) read each identified literature and populated the sheet designed for the purpose. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Figure 1) was used for the selection of articles to be used in this scoping review.

Facility delivery rate, misuse, adverse effects from misuse of the drug, and misconceptions on the use of misoprostol and fear of diversion of facility delivery to home delivery because of misoprostol's access to mothers were the main points considered in this scoping systematic review.

A narrative synthesis was used to analyze and interpret the findings in which quantitative and qualitative syntheses are integrated. Descriptive information about the eligible studies was summarized using text and tables. Findings from the quantitative resources were narrated thematically followed by findings of qualitative resources. For intervention studies, a random-effects meta-analysis model [30, 31] was used to pool the estimates of prevalence of facility birth, accounting for the variability among studies using Stata v15 [32]. The results were presented as average treatment effects (odds ratio) with 95% confidence intervals.

Results

Description of studies

Table 1 presents the characteristics of the studies included in this review. Fourteen studies were included in the review. Seven of the studies were from Africa and the remaining seven were from Asia. Three qualitative studies [33, 25, 12], seven observational studies [34-40], and four experimental or quasi-experimental studies [41-44] were included in this review. All studies were published from 2006 to 2018.

Methodological quality of included studies

According to the JBI quality appraisal tool, two of the Randomized Controlled Trials (RCTs) scored high quality (88%) and a quasi-experimental study scored medium (61%). On the other hand, the cluster RCT study included scored low (46%) where it had baseline imbalances as well as lacked masking of study of participants, personnel, and assessors [43]. All experimental and quasi-experimental studies provided adequate information about random sequence generation as well as thorough description of the interventions.

Overall, the seven cross-sectional studies scored medium quality (70%) in which most lacked strategies to deal with confounding as well as some lacked appropriate use of statistical methods of analysis.

Likewise, all qualitative studies scored medium (65%) in which they are subjected to reporting bias in which philosophical perspectives as well as researchers' experiences, beliefs, wishes, attitudes, culture, views, and personality not stated which might bias analysis and reporting.

Table 1: Characteristics of included studies

Study ID	Country	Study design	Objectives	Description of the intervention	Outcome
Geller 2014	Ghana	Before-after intervention and comparison facility-based study	Assess the safety, feasibility, and acceptability of community-based distribution of misoprostol to prevent PPH during home deliveries in rural areas	Misoprostol distributed to midwives at seven primary health centers for provision to pregnant women	· No evidence of misuse; · Misoprostol distribution did not encourage home deliveries; · Regional household surveys showed that deliveries with skilled providers increased from 30 to 69%.
Haver 2016	Afghanistan	before-and-after cross-sectional household surveys	To determine the effectiveness of advance distribution of misoprostol for self-administration across 20 districts and identify any adverse events that occurred during expansion	Community health workers (CHWs) did advance distribution of misoprostol Interventions: 1) CHWs visited households; 2) community health councils were engaged to raise awareness of misoprostol for prevention of postpartum hemorrhage, and 3) health facility intrapartum services	· 1 out of 7,399 women in the study reported taking misoprostol before the birth of her newborn · No maternal deaths attributable to misoprostol · Increased proportion of women who gave birth in a facility after the intervention (from 50.2% to 60.8%); the intervention did not discourage women from receiving skilled birth attendance
Rajbhandari 2010	Nepal	Before-after household survey	To determine feasibility of community-based distribution of misoprostol (for preventing PPH) to pregnant woman, through community volunteers	Support and training to peripheral health workers and female community volunteers to enable them to: identify pregnant women in their area, provide prenatal health education, dispense misoprostol late in pregnancy, and make early postnatal home visits	The institutional delivery rate among live births increased from 10.9% at baseline to 14.8% at end line
Sanghvi 2010	Afghanistan	Non-randomized experimental control design	To test the safety, acceptability, feasibility, and effectiveness of community-based education and distribution of misoprostol for prevention of postpartum hemorrhage during home birth	In both the intervention and comparison areas, CHWs made 3 home visits to pregnant women and their families: CHWs used pictorial flipcharts to provide education on birth preparedness and complication readiness, and recognition of danger signs	Significant number of women delivered in facilities ($p< 0.001$): 21% and 18% of births took place at health facilities in the intervention and comparison areas respectively.

Study ID	Country	Study design	Objectives	Description of the intervention	Outcome
Weeks 2015	Uganda	Community-based placebo-randomized controlled trial (RCT)	Examine safety and effectiveness of self-administration of misoprostol by women	Women were randomized into misoprostol or placebo group during their third trimester ANC visit and they were instructed to take immediately after childbirth before the delivery of the placenta, and after confirming the absence of a twin, if they delivered at home.	Facility delivery: 56.5% in the misoprostol group vs 58.2% in the placebo group
Smith 2014	Liberia	Longitudinal observational study	Evaluate the feasibility, acceptability, effectiveness of advance distribution of misoprostol during ANC and home visits	Trained traditional midwives as CHWs provided education to pregnant women, and district reproductive health supervisors distributed misoprostol during home visits	Misoprostol taken before delivery of baby; 3 (1.1%) Based on Health Management Information System data, ANC1 and ANC4 appears to be unchanged, while, the average monthly number of facility deliveries increased from the 82 during the comparison period (same period in the previous year) to 108 during the intervention period
Ononge 2015	Uganda	Cluster RCT	To determine if antenatal distribution of misoprostol to pregnant women to self-administer at home birth, reduces PPH	Women at 28+ weeks of gestation attending antenatal care were offered misoprostol to swallow immediately after birth of baby when oxytocin was not available	· No woman took misoprostol before their baby's birth. · No difference in postpartum anemia, uterotonic use, and facility births (85.4% I vs 87.5 % C group)
Durham 2018	Lao People's Democratic Republic	Qualitative study IDI, n=25 & FGDs, n=5	Identify acceptability of misoprostol and healthcare system needs to effectively distribute misoprostol to women with limited access to facility-based birthing	NA	All healthcare professionals interviewed recognized that community distribution of misoprostol is an acceptable and feasible interim preventative solution to reduce PPH until access to facility-based birthing is improved

Study ID	Country	Study design	Objectives	Description of the intervention	Outcome
Spangler et al 2014	Ethiopia	Qualitative in-depth interviews	The purpose of this study was to examine the understanding of national policy for community-based use of misoprostol to prevent PPH	NA	Among all officials, understandings of national policy for community-based PPH prevention using misoprostol were unclear.
Wells et al 2016	Ethiopia, Ghana,	Desk review and qualitative methods	Evaluated the models and approaches used to access misoprostol at the community level in Ethiopia, Ghana, and Nigeria	NA	· There is pervasive lack of trust in women's capabilities to use misoprostol correctly and the widely held belief that women might "misuse" the pills (for abortion) persist · Fears that providers will inappropriately use misoprostol for labor induction and/or abortion
Sibley 2014	Ethiopia	Before-and-after household design; facility records	Describes regional trends in women's use of misoprostol; their awareness, receipt, and use of misoprostol at project's end line; and factors associated with its use	Community health development agents and TBAs conducted community maternal and newborn health family meetings with pregnant women and their family caregivers. Distributed misoprostol tablets to the project area woreda health offices, to distribute either through HEWs (in Amhara) or TBAs (Oromia)	· Controlling for age, parity, and education, region, any ANC, and any CMNH family meeting attendance, a woman's receipt of misoprostol during pregnancy was not significantly associated with place of birth (OR= 0.64; 95% CI, 0.35-1.19). · Very few women consumed the tablets before birth (~2%)
Rajbhandari 2017	Nepal	Mixed methods program evaluation	This paper presents findings from the first large-scale assessment of the effectiveness of the advance distribution program.		· High rate of institutional delivery; · No evidence that misoprostol was used for any other purpose (including labor induction and abortion). · The majority of those who did not use their advance misoprostol returned it after the birth and most others either threw it away or kept it.

Study ID	Country	Study design	Objectives	Description of the intervention	Outcome
Parashar 2018	India	Cross-sectional program evaluation	To design and implement an operational framework to implement and scale up “Community Based Advance Distribution of Misoprostol” program in India	Community-based distribution of misoprostol to pregnant women on completion of the 8th month of their pregnancy, in identified high home delivery geographical pockets and women who are likely to deliver at home	The institutional delivery rate in the area increased from 11 to 57% within six months of implementation
Derman 2006	India	RCT	To investigate whether oral misoprostol, a potential alternative to oxytocin, could prevent PPH in a community home-birth setting	25 auxiliary nurse midwives undertook the deliveries, administered the study drug, and measured blood loss	Institutional delivery rate: 53.2% in the intervention group vs 54.8% in comparison group

The results of our review are presented under three sections: 1) diversion of facility birth, 2) misuse, for purposes of either abortion or labor induction/augmentation, and 3) adverse events from misuse.

Diversion of facility birth

Ten studies (five observational before-after studies, four experimental or quasi-experimental trials, and one qualitative study) reported on the impact on facility birth as the outcome [36, 37, 41, 35, 42, 34, 39, 33, 43, 44]. All five before-after household surveys reported increased facility delivery coverage after the intervention: four percentage points increase in Nepal [37] and Liberia [36], 11% points in Afghanistan [35], 39% points in Ghana [34], and 46% points in India [39] at the end of the intervention when compared to the baseline (Figure 2).

A quasi-experimental study in Afghanistan demonstrated an increase of 3.3 percentage points in facility birth rates comparing between the intervention and control areas ($p< 0.001$); while a RCT in India showed a decrease of 1.6 percentage points ($p>0.05$) and two cluster randomized trials in Uganda showed a decrease of 1.5 and 2.1 percentage points ($p>0.05$) in facility birth rates, comparing between the intervention and control areas [41, 43, 44]. The pooled analysis involving 7,564 women, from four of the studies, revealed that there is no significant difference in facility delivery among the advanced distribution of misoprostol and control groups [OR 1.011; 95% CI: 0.906-1.129] (Table 2).

Table 2: Comparison of facility delivery rates between the intervention and control areas

Study	*Facility delivery rate (%)*		*OR*	*[95% CI]*		*% Weight*
	Intervention	Comparison				
Sanghvi 2010	21.4	18.1	1.229	1.023	1.477	35.93
Weeks 2015	56.5	58.0	0.940	0.697	1.269	13.52
Ononge 2015	85.4	87.5	0.834	0.647	1.075	18.80
Derman 2006	53.2	54.8	0.937	0.770	1.139	31.76
I-V pooled OR			1.011	0.906	1.129	100.0

A qualitative study among health professionals in Laos also indicated that community distribution of misoprostol, for the prevention of PPH, is acceptable to community members and stakeholders and it is a feasible interim solution until access to facility birth is improved. The study recognized misconceptions as barriers that might hinder community-based distribution of misoprostol [33]. Another study in Ethiopia reported regional differences in understanding the implementation strategy of misoprostol and a concern among policymakers that distribution of misoprostol will be seen as encouraging home birth [25].

Misuse

A program evaluation report in Nepal showed that there was no evidence to suggest that misoprostol distributed for the purpose of the prevention of PPH is being misused for labor induction or pregnancy termination [40]. Moreover, as presented in Table 3, in the community-based distribution of misoprostol programs, administration of misoprostol before delivery was reported in less than 2% (n=17) among seven studies involving 11,108 mothers [34, 35, 38, 36, 43].

A cluster randomized controlled trial in Uganda [43] and an operations research in Ghana [34] reported that no woman took misoprostol before their babies' birth. Another before-after study in Afghanistan reported that only 1 out of 7,399 women in the study took misoprostol before the birth of her newborn [35]. Similarly, according to a trial in Uganda, only 2 out of 700 women took tablets before delivery [41]. In Liberia, only 3 of 265 women took misoprostol prior to giving birth [36]; while in Ethiopia, less than 2% of women took the tablets before birth [38] (Table 3).

Table 3: Percent of women who took misoprostol before delivery

Study ID	*Country*	*%*	*n*	*N*
Geller 2014	Ghana	0.00	0	102
Ononge 2015	Uganda	0.00	0	2,057
Haver 2016	Afghanistan	0.01	1	7,399
Weeks 2015	Uganda	0.29	2	700
Smith 2014	Liberia	1.10	3	265
Sibley 2014	Ethiopia	1.80	11	585
Total			**17**	**11,108**

Evidence also shows that most women used the misoprostol pills as instructed [37, 34, 44]; unused doses were returned after birth to the point of distribution; and most others either threw it away or kept it [34, 40]. However, qualitative studies in Ethiopia identified, lack of trust in women's capabilities to use misoprostol correctly [12] and fear of misuse [12, 25], as a problem limiting the expansion of the program.

Adverse effects of misuse

No adverse outcomes of misuse were reported in either of the studies reviewed.

Discussion

This review shows that community-based distribution of misoprostol programs have demonstrated increase of facility delivery coverage after the intervention in observational studies and no significant difference of facility delivery coverage in experimental and quasi-experimental studies among the misoprostol and control groups. The studies reviewed also found very few instances of administration of misoprostol before delivery, and no adverse outcomes because of misuse. While some studies have illustrated a concern held by policymakers and provider about misoprostol misuse, diversion of facility birth, and adverse effects of its misuse [12, 25, 20]; this scoping review showed that, so far, community-based distribution of misoprostol has not negatively impacted facility birth rates (in fact some studies show an increase in facility delivery) and has not resulted in misuse of the medication for uses other than PPH prevention. Accordingly, there is no evidence that substantiates the fear of misoprostol misuse, diversion of facility birth, and other adverse effects of its misuse. As is evident from a qualitative study in Ethiopia [25], these misconceptions arise from the health providers' perceptions rather than the actual behavior of women using community-distributed misoprostol.

In addition, evidence shows that misoprostol is safe and effective for preventing and treating PPH in remote settings where both oxytocin and timely transfer to higher-level care are not available [45, 19, 24]. Previous studies also report that community health workers or other lower-level workers are able to safely administer misoprostol [15, 33]. Women were found to have no major problem of misusing the drug and it was found to be acceptable by them [15]. Another rapid review of the literature showed that distribution of misoprostol in advance of delivery by lay health workers for self-administration was feasible and acceptable at all levels—end-user, health system, community, and policy [17, 24].

Concerns by policymakers about misoprostol distribution at community level, often unsupported by available evidence [24], impedes the strategy being translated into effective policies, programs, and practice. Concerns primarily include fear of women using misoprostol for inducing abortion or labor, and diversion of facility birth to home deliveries [41, 46, 24]. In addition to policymaker resistance, there is a range of other barriers that impede access to a uterotonic for prevention of PPH for every woman. Barriers include service delivery challenges, supply and procurement, financial, national and global policy environments, and factors more closely connected to the end-user [47]. These implementation barriers represent important threats to any community-based misoprostol distribution program, and most of these barriers are common health system weaknesses in many LMICs [17].

Community-based distribution of misoprostol is a compelling strategy to be implemented parallel to strengthening healthcare facilities to increase safe institutional deliveries [20, 24] and ensuring universal access to uterotonics for every woman. A review by Hobday et al. recommends simultaneously promoting facility delivery and strengthening health systems to avail misoprostol at the community level [15]. Community distribution of misoprostol is thus a complementary strategy for increasing the availability of misoprostol and actively promoting facility births through increasing contact with pregnant women. Increasing interaction with pregnant women also offers the opportunity to promote early care-seeking and referral during pregnancy [17]. As such, community-based distribution of misoprostol programs should include the promotion of facility-based birth [4, 34, 33] as a critical intervention. Successful implementation of misoprostol distribution can be facilitated by creating an enabling environment through supportive policies, designing a formal plan for supplies, task shifting strategies, and appropriate use of guidelines and protocols [26]. Moreover, strong leadership and political commitment, training, and community mobilization were identified as critical success factors [17].

This study provides critical documentation of evidence to support policymakers and program managers to develop national policies and strategies for the implementation of community-based distribution of misoprostol to prevent PPH and reduce maternal mortality. It also highlights that rates of administration of misoprostol before delivery and adverse outcomes of such misuse are very low, especially when compared to the grave risks women can encounter without access to uterotonics. As such, community-based distribution of misoprostol is an appropriate strategy to be implemented while working towards achieving facility delivery as the norm.

National guidance and evidence-based policies on misoprostol distribution initiated by higher levels of the health system can facilitate reassuring reluctant policymakers and providers who hold persistent, but unfounded, fears of misuse and negative consequences. Creating opportunities for reflective discussions or policy dialogue is thus important for virtuous public health practice.

This review has some limitations. First, there may be possibility of missing some relevant studies due to the inclusion of only published studies and exclusion of studies published in a language other than English. Second, we found a small number of articles meeting the inclusion criteria and few rigorous studies directly investigated the negative effect of community availability of misoprostol on institutional delivery, misuse and adverse effects from misuse as a primary outcome. Accordingly, we could not be able combine all the results in a meta-analysis and show pooled estimates.

Conclusions

Community-based distribution of misoprostol programs have been associated with an increase in coverage of facility-based births. This review found very few instances of administration of misoprostol before delivery, and no adverse outcomes of misuse in any of the studies reviewed.

Fears of misuse of misoprostol and increased adverse pregnancy outcomes if distributed at community level are not supported by evidence. Therefore, community-based distribution of misoprostol can be an

appropriate strategy for reducing maternal deaths caused by postpartum hemorrhages, especially in resource-limited settings where many deliveries take place outside of health facilities.

Abbreviations

AMTSL	Active Management of the Third Stage of Labor
CHW	Community Health Workers
JBI	Joanna Briggs Institute
MoH	Ministry of Health
PPH	Postpartum Hemorrhage
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAC	Research Advisory Council
RCT	Randomized Controlled Trial
RMNCAH-N	Reproductive, Maternal, Newborn, Child, Adolescent Health, and Nutrition
WHO	World Health Organization

Declarations

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

Not applicable

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

The authors declare that they did not receive funding for this research from any source.

Authors' Contributions

GT, BT, WM, YT, and AM conceptualized the paper. GT, MY, EG, and YT performed article search, data extraction, and data analysis. GT, BY, AM, WM, YT did interpretation and critical review. All authors contributed to the interpretation, commented on multiple versions, and approved the final manuscript.

Acknowledgments

We conducted this study in response to the national Reproductive, Maternal, Newborn, Child, Adolescent Health, and Nutrition (RMNCAH-N) Research Advisory Council (RAC) of the Ministry of Health (MoH) of Ethiopia's request to produce evidence to inform the maternal health program. We would like to acknowledge the MoH for giving us this opportunity. The authors are grateful to Harvard University/Fenot Project for sponsoring the Report Writing Workshop. Researchers would also like to acknowledge Adey Abebe, Communication Specialist at JSI Research and Training Institute Inc., and Sarah Hurlburt, Deputy Director of Implementation for the Fenot project, for editing this manuscript.

References

1. WHO. Trends in Maternal Mortality: 1990 to 2015 Estimates by WHO, UNICEF, UNFPA. World Bank Group and the United Nations Population Division. Geneva, Switzerland: World health Organization; 2015.
2. WHO. Strategies toward ending preventable maternal mortality (EPMM). Geneva, Switzerland: World Health Organization; 2015.
3. Chou D, Daelmans B, Jolivet R, Kinney M, Say L. Ending preventable maternal and newborn mortality and stillbirths. British Medical Journal. 2015;351. doi:10.1136/bmj.h4255.
4. Robinson N, Kapungu C, Carnahan L, Geller S. Recommendations for scale-up of community-based misoprostol distribution programs. International Journal of Gynecology & Obstetrics. 2014;125(3):285-8.
5. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J et al. Global causes of maternal death: a WHO systematic analysis. The Lancet Global Health. 2014;2(6):e323-e33. doi:https://doi.org/10.1016/S2214-109X(14)70227-X.
6. Haeri S, Dildy GA. Maternal Mortality From Hemorrhage. Seminars in Perinatology. 2012;36(1):48-55. doi:https://doi.org/10.1053/j.semperi.2011.09.010.
7. WHO. Trends in maternal mortality: 1990 to 2008. Estimates developed by WHO, UNICEF, UNFPA and The World Bank. Geneva, Switzerland: World Health Organization 2010.
8. Mekonnen W, Gebremariam A. Causes of maternal death in Ethiopia between 1990 and 2016: systematic review with meta-analysis. Ethiopian Journal of Health Development. 2018;32(4).
9. EPHI. National MDSR annual report: 2008 EFY. Addis Ababa, Ethiopia: Ethiopian Public Health Institute; 2017.
10. Lancet. WOMAN: reducing maternal deaths with tranexamic acid. Lancet. 2017;389(10084):2081. doi:10.1016/s0140-6736(17)31111-x.

11. Ronsmans C, Graham WJ. Maternal mortality: who, when, where, and why. Lancet. 2006;368(9542):1189-200. doi:10.1016/s0140-6736(06)69380-x.
12. Wells E, Coeytaux F, Azasi E, Danmusa S, Geressu T, McNally T et al. Evaluation of different models of access to misoprostol at the community level to improve maternal health outcomes in Ethiopia, Ghana, and Nigeria. International Journal of Gynaecology & Obstetetrics. 2016;133(3):261-5. doi:10.1016/j.ijgo.2016.04.002.
13. Begley CM, Gyte GML, Devane D, McGuire W, Weeks A. Active versus expectant management for women in the third stage of labour. Cochrane Database of Systematic Reviews. 2015(3). doi:10.1002/14651858.CD007412.pub4.
14. WHO. WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva, Switzerland: World Health Organization; 2012.
15. Hobday K, Hulme J, Belton S, Homer CS, Prata N. Community-based misoprostol for the prevention of post-partum haemorrhage: A narrative review of the evidence base, challenges and scale-up. Global public health. 2018;13(8):1081-97.
16. WHO. WHO recommendations for the prevention and treatment of postpartum haemorrhage. World Health Organization, Geneva, Switzerland. 2012.
17. Smith HJ, Colvin CJ, Richards E, Roberson J, Sharma G, Thapa K et al. Programmes for advance distribution of misoprostol to prevent post-partum haemorrhage: a rapid literature review of factors affecting implementation. Health policy and planning. 2015;31(1):102-13.
18. Oladapo OT. Misoprostol for preventing and treating postpartum hemorrhage in the community: a closer look at the evidence. International Journal of Gynecology & Obstetrics. 2012;119(2):105-10. doi:10.1016/j.ijgo.2012.08.004.
19. Hofmeyr GJ, Gulmezoglu AM, Novikova N, Lawrie TA. Postpartum misoprostol for preventing maternal mortality and morbidity. Cochrane Database of Systematic Reviews. 2013(7):CD008982. doi:10.1002/14651858.CD008982.pub2.
20. Smith JM, Gubin R, Holston MM, Fullerton J, Prata N. Misoprostol for postpartum hemorrhage prevention at home birth: an integrative review of global implementation experience to date. BMC pregnancy and childbirth. 2013;13(1):44.
21. Chu CS, Brhlikova P, Pollock AM. Rethinking WHO guidance: review of evidence for misoprostol use in the prevention of postpartum haemorrhage. Journal of the Royal Society of Medicine. 2012;105(8):336-47.
22. Prata N, Mbaruku G, Grossman AA, Holston M, Hsieh K. Community-based availability of misoprostol: is it safe? African Journal of Reproductive Health. 2009;13(2).
23. Prata N, Passano P, Bell S, Rowen T, Potts M. New hope: community-based misoprostol use to prevent postpartum haemorrhage. Health Policy and Planning. 2012;28(4):339-46.
24. Starrs A, Winikoff B. Misoprostol for postpartum hemorrhage: moving from evidence to practice. International Journal of Gynaecology & Obstetetrics. 2012;116(1):1-3. doi:10.1016/j.ijgo.2011.10.005.

25. Spangler SA, Gobezayehu AG, Hailemariam TG, Sibley LM. Interpretation of national policy regarding community-based use of misoprostol for postpartum hemorrhage prevention in Ethiopia: a tale of two regions. Journal of Midwifery & Women's Health. 2014;59 Suppl 1:S83-90. doi:10.1111/jmwh.12154.
26. Samnani AABA, Rizvi N, Ali TS, Abrejo F. Barriers or gaps in implementation of misoprostol use for post-abortion care and post-partum hemorrhage prevention in developing countries: a systematic review. Reproductive health. 2017;14(1):139.
27. Lockwood C, Munn Z, Porritt K. Qualitative research synthesis: methodological guidance for systematic reviewers utilizing meta-aggregation. International journal of evidence-based healthcare. 2015;13(3):179-87.
28. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute; 2017.
29. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R et al. Chapter 7: Systematic reviews of etiology and risk. Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute; 2017.
30. Sterne JA, Palmer TM. Meta-analysis in Stata: an updated collection from the Stata Journal. 2 ed. StataCorp LP; 2016.
31. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2011.
32. StataCorp. Stata: Release 15. Statistical Software. College Station, Texas: Stata Press; 2017.
33. Durham J, Phengsavanh A, Sychareun V, Hose I, Vongxay V, Xaysomphou D et al. Misoprostol for the prevention of postpartum hemorrhage during home births in rural Lao PDR: establishing a pilot program for community distribution. International Journal of Womens Health. 2018;10:215-27. doi:10.2147/IJWH.S150695.
34. Geller S, Carnahan L, Akosah E, Asare G, Agyemang R, Dickson R et al. Community-based distribution of misoprostol to prevent postpartum haemorrhage at home births: results from operations research in rural Ghana. International Journal of Obstetrics & Gynaecology. 2014;121(3):319-26.
35. Haver J, Ansari N, Zainullah P, Kim YM, Tappis H. Misoprostol for prevention of postpartum hemorrhage at home birth in Afghanistan: program expansion experience. Journal of midwifery & women's health. 2016;61(2):196-202.
36. Smith JM, Baawo SD, Subah M, Sirtor-Gbassie V, Howe CJ, Ishola G et al. Advance distribution of misoprostol for prevention of postpartum hemorrhage (PPH) at home births in two districts of Liberia. BMC pregnancy and childbirth. 2014;14(1):189.
37. Rajbhandari S, Hodgins S, Sanghvi H, McPherson R, Pradhan YV, Baqui AH. Expanding uterotonic protection following childbirth through community-based distribution of misoprostol: Operations research study in Nepal. International Journal of Gynecology & Obstetrics. 2010;108(3):282-8.
38. Sibley LM, Spangler SA, Barry D, Tesfaye S, Desta BF, Gobezayehu AG. A Regional Comparison of Distribution Strategies and Women's Awareness, Receipt, and Use of Misoprostol to Prevent

Postpartum Hemorrhage in Rural Amhara and Oromiya Regions of Ethiopia. Journal of Midwifery & Women's Health. 2014;59(s1):S73-S82. doi:doi:10.1111/jmwh.12136.

39. Parashar R, Gupt A, Bajpayee D, Gupta A, Thakur R, Sangwan A et al. Implementation of community based advance distribution of misoprostol in Himachal Pradesh (India): lessons and way forward. BMC Pregnancy Childbirth. 2018;18(1):428. doi:10.1186/s12884-018-2036-2.
40. Rajbhandari SP, Aryal K, Sheldon WR, Ban B, Upreti SR, Regmi K et al. Postpartum hemorrhage prevention in Nepal: a program assessment. BMC Pregnancy Childbirth. 2017;17(1):169. doi:10.1186/s12884-017-1347-z.
41. Weeks AD, Ditai J, Ononge S, Faragher B, Frye LJ, Durocher J et al. The MamaMiso study of self-administered misoprostol to prevent bleeding after childbirth in rural Uganda: a community-based, placebo-controlled randomised trial. BMC pregnancy and childbirth. 2015;15(1):219.
42. Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet. 2006;368(9543):1248-53. doi:10.1016/s0140-6736(06)69522-6.
43. Ononge S, Campbell OM, Kaharuza F, Lewis JJ, Fielding K, Mirembe F. Effectiveness and safety of misoprostol distributed to antenatal women to prevent postpartum haemorrhage after child-births: a stepped-wedge cluster-randomized trial. BMC Pregnancy Childbirth. 2015;15:315. doi:10.1186/s12884-015-0750-6.
44. Sanghvi H, Ansari N, Prata NJ, Gibson H, Ehsan AT, Smith JM. Prevention of postpartum hemorrhage at home birth in Afghanistan. International Journal of Gynecology & Obstetrics. 2010;108(3):276-81. doi:10.1016/j.ijgo.2009.12.003.
45. Oladapo OT, Fawole B, Blum J, Abalos E. Advance misoprostol distribution for preventing and treating postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2012(2). doi:10.1002/14651858.CD009336.pub2.
46. Collins L, Mmari K, Mullany LC, Gruber CW, Favero R. An exploration of village-level uterotonic practices in Fenerive-Est, Madagascar. BMC Pregnancy and Childbirth. 2016;16(1):69. doi:10.1186/s12884-016-0858-3.
47. Smith HJ, Colvin CJ, Richards E, Roberson J, Sharma G, Thapa K et al. Programmes for advance distribution of misoprostol to prevent post-partum haemorrhage: a rapid literature review of factors affecting implementation. Health Policy Plan. 2016;31(1):102-13. doi:10.1093/heapol/czv012.

Figures

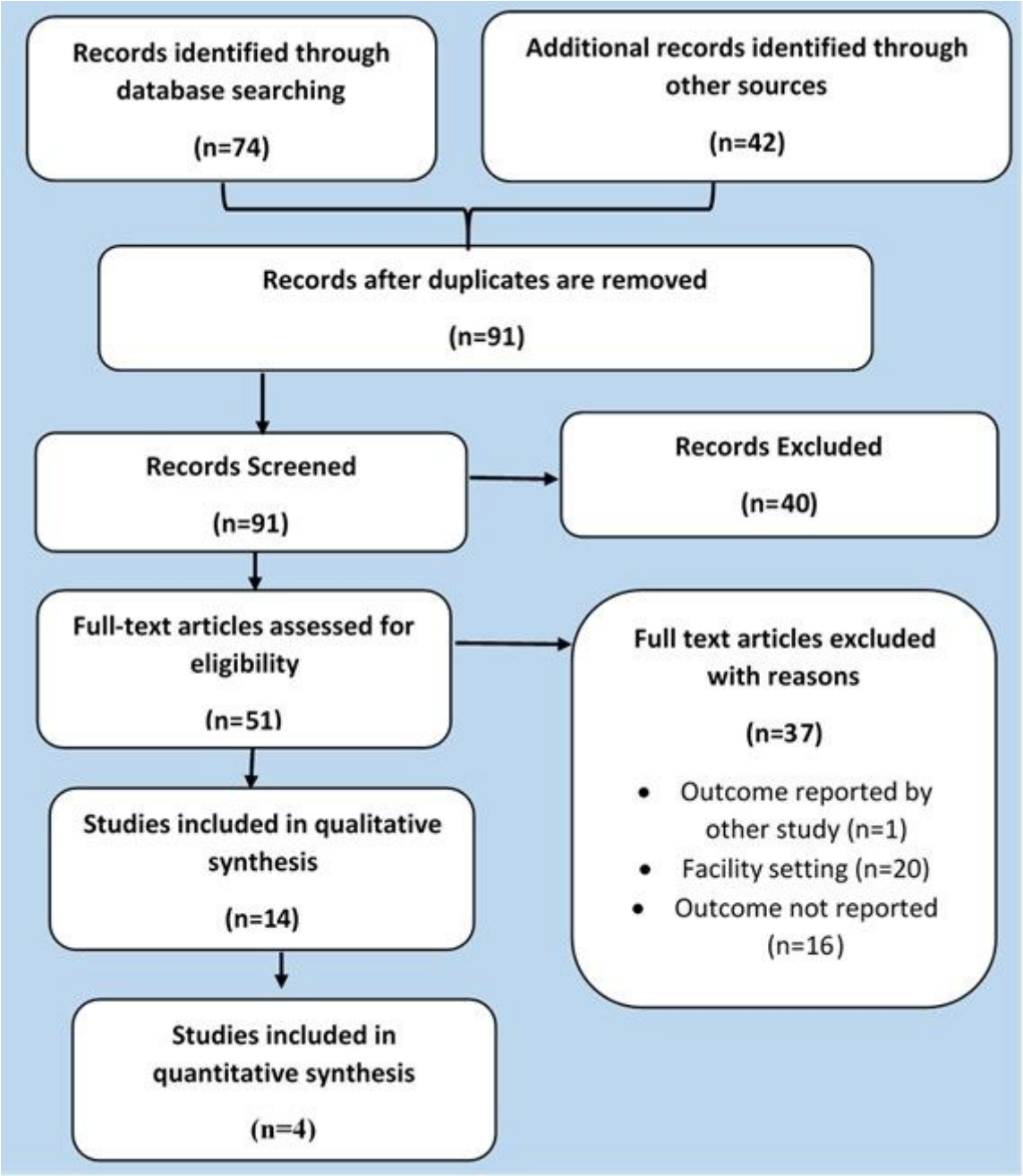

Figure 1

Study flow diagram

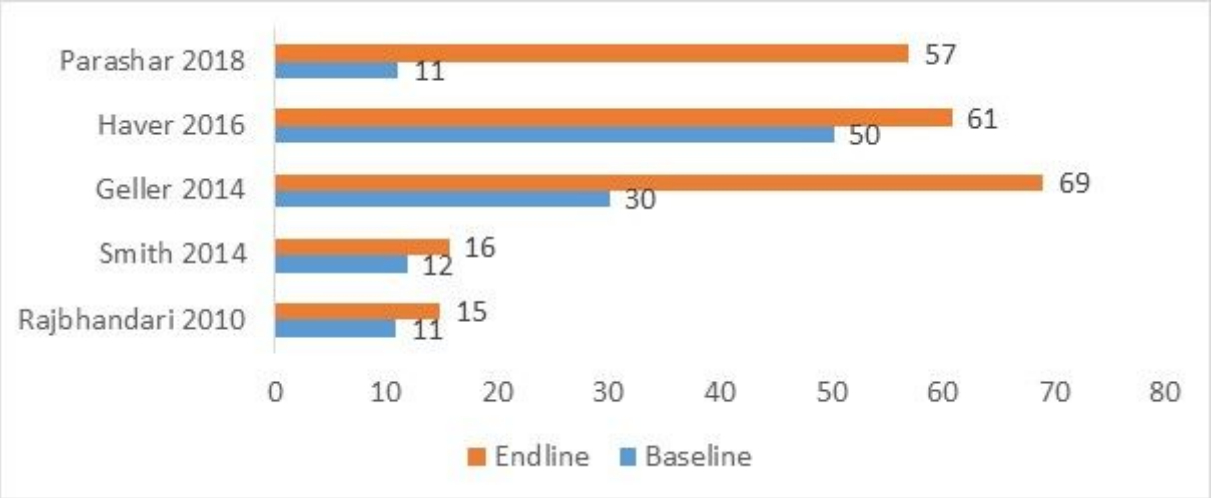

Figure 2

Changes in facility delivery rate before and after the intervention