



WHO recommendation on
**Advance misoprostol
distribution to pregnant
women for prevention of
postpartum haemorrhage**



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ISBN 978-92-4-001390-2 (electronic version)

ISBN 978-92-4-001391-9 (print version)

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Suggested citation. WHO recommendation on advance misoprostol distribution to pregnant women for prevention of postpartum haemorrhage. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

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Acknowledgements

The World Health Organization (WHO) Department of Sexual and Reproductive Health and Research and Department of Maternal, Newborn, Child and Adolescent Health and Ageing gratefully acknowledge the contributions of many individuals and organizations to the updating of this recommendation. Work on this update was coordinated by Fernando Althabe, Tina Lavin, Olufemi Oladapo, Joshua Vogel and Mariana Widmer of the Department of Sexual and Reproductive Health and Research.

WHO extends its sincere thanks to Oluwarotimi Ireti Akinola, Brendan Carvalho, Melania Amorim, Catherine Deneux-Tharoux, Tippawan Liabsuetrakul, Martin Meremikwu, Suellen Miller, Mari Nagai, Hayfaa Wahabi, Dilys Walker and Andrew Weeks who served as members of the Guideline Development Group (GDG), and to Ashraf Nabhan (Chair) for leading the meeting. We also thank Christine East, Gill Gyte, Justus Hofmeyr, Syeda Batool Mazhar, Enrique Oyarzun and Qian Xu, who were members of the External Review Group (ERG). WHO also gratefully acknowledges the contribution of the members of the Executive Guideline Steering Group (GSG).

Edgardo Abalos, Anna Cuthbert, Virginia Diaz, Kenneth Finlayson, Leanne Jones, Frances Kellie and Myfanwy Williams reviewed the scientific evidence, prepared the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables and drafted the narrative summary of the evidence. Fernando Althabe, Olufemi Oladapo, Mariana Widmer and Joshua Vogel revised the narrative summaries and double-checked the corresponding GRADE tables and prepared the Evidence to Decision (EtD) frameworks. The ERG peer reviewed the final document prior to executive clearance by WHO and publication.

We acknowledge the various organizations that were represented by observers, including Deborah Armbruster (United States Agency for International Development [USAID]), Ingela Wiklund (International Confederation of Midwives [ICM]) and Carlos Fuchtnr (International Federation of Gynecology and Obstetrics [FIGO]). We also appreciate the contributions of staff at the WHO regional offices, including Nino Berdzuli, Bremen De Mucio, Hayfa Elamin, Chandani Anoma Jayathilaka, Ramez Khairi Mahaini, Howard Sobel and Claudio Sosa.

WHO acknowledges the financial support for this work received from USAID and the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction the Department of Sexual and Reproductive Health and Research. WHO emphasizes that donors do not participate in any decision related to the guideline development process, including the composition of research questions, membership of the guideline development groups, conducting and interpretation of systematic reviews, or formulation of the recommendations. The views of the funding bodies have not influenced the content of this recommendation.

Acronyms and abbreviations

CerQUAL	Confidence in the Evidence from Reviews of Qualitative Research
CHEC	Consensus Health Economic Criteria
DOI	declaration of interest
ERG	Evidence Review Group
ESG	Evidence Synthesis Group
EtD	Evidence to Decision
FIGO	International Federation of Gynecology and Obstetrics
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSG	Guideline Steering Group
HRP	UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction
ICM	International Confederation of Midwives
IU	international units
µg	microgram
PICO	population (P), intervention (I), comparator (C), outcome (O)
PPH	postpartum haemorrhage
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization

Executive summary

Introduction

Postpartum haemorrhage (PPH) is commonly defined as a blood loss of 500 mL or more within 24 hours after birth and affects about 5% of all women giving birth around the world. Globally, nearly one quarter of all maternal deaths are associated with PPH and, in most low-income countries, it is the main cause of maternal mortality. Improving care during childbirth to prevent PPH is a necessary step towards the achievement of the health targets of the third Sustainable Development Goal (SDG 3), particularly target 3.1: reduce the global maternal mortality ratio to less than 70 per 100 000 live births by 2030. Efforts to prevent and reduce morbidity and mortality due to PPH can help to address the profound inequities in maternal and perinatal health globally. To achieve this, skilled health personnel, health managers, policy-makers and other stakeholders need up-to-date and evidence-informed recommendations to guide clinical policies and practices.

In 2019, the Executive Guideline Steering Group (GSG) for World Health Organization (WHO) maternal and perinatal health recommendations prioritized updating of the existing WHO recommendations for advance misoprostol distribution to pregnant women for prevention of PPH in response to the availability of new evidence. The recommendation in this document thus supersedes the previous WHO recommendation for the prevention of PPH as published in the 2012 guideline, *WHO recommendations for the prevention and treatment of postpartum haemorrhage*.

Target audience

The primary audience for these recommendations includes health professionals who are responsible for developing national and local health-care guidelines and protocols (particularly those related to PPH prevention and treatment) and those involved in the provision of care to women and their newborns during labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians, as well as managers of maternal and child health programmes, and relevant staff in ministries of health and training institutions, in all settings.

Guideline development methods

The updating of these recommendations was guided by standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development*. The recommendations were initially developed and updated using this process, namely: (i) identification of priority questions and outcomes; (ii) retrieval of evidence; (iii) assessment and synthesis of evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and future updating of the recommendations.

The scientific evidence supporting the recommendation was synthesized using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. An updated systematic review was used to prepare the evidence profiles for the prioritized question. WHO convened a meeting on 11–12 March 2020 where the Guideline Development Group (GDG) members reviewed, deliberated and achieved consensus on the strength and direction of the recommendation presented herein. Through a structured process, the GDG reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity.

Recommendation

The GDG reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource

requirements and cost-effectiveness, acceptability, feasibility and equity. The GDG issued the recommendation on a strategy of advance misoprostol distribution to pregnant women for the prevention of PPH, with remarks and implementation considerations. To ensure that the recommendation is correctly understood and applied in practice, guideline users may want to refer to the remarks, as well as to the evidence summary, including the considerations on implementation.

WHO recommendation on advance misoprostol distribution to pregnant women for prevention of postpartum haemorrhage

In settings where women give birth outside of a health facility and in the absence of skilled health personnel, a strategy of antenatal distribution of misoprostol to pregnant women for self-administration is recommended for prevention of postpartum haemorrhage, only with targeted monitoring and evaluation.

(Context-specific recommendation)

Justification

- There is insufficient trial evidence to assess the benefits and possible harms of advance misoprostol distribution for postpartum haemorrhage prevention. However, misoprostol is known to be an effective uterotonic agent for postpartum haemorrhage prevention and is recommended by WHO in settings where oxytocin is unavailable, its quality cannot be guaranteed, or skilled health personnel are not present to administer it. Observational studies and evaluations of advance misoprostol distribution programmes in several countries indicate that this strategy can increase coverage of uterotonic use for postpartum haemorrhage prevention in remote and hard-to-reach areas where no skilled health personnel can attend, with very few reports of incorrect use of misoprostol or adverse events. As this strategy is specifically aimed at preventing postpartum haemorrhage in women in more remote or underserved areas who would otherwise not receive any uterotonic during birth, it is likely to increase health equity and improve health outcomes. These programmes are probably acceptable to women and providers. While the cost-effectiveness of this strategy is not known, it is likely to confer cost savings.

Remarks

- Antenatal distribution of misoprostol to pregnant women should not replace standard policies for scaling up effective uterotonic use, but it should be considered as a strategy for increasing coverage of uterotonic use in settings where a large proportion of women still give birth outside of health facilities and where it is highly likely that skilled health personnel will not be present at time of birth.
- While acknowledging that there is currently no clear evidence of harm with a strategy of antenatal misoprostol distribution, the Guideline Development Group agreed that, to address potential safety concerns, such programmes should only be implemented with appropriate monitoring and evaluation. This should consider:
 - whether women are trained appropriately in the use of misoprostol;
 - monitoring the distribution, use and potential misuse of misoprostol;
 - the effect of the programme on utilization of health services and health outcomes – this should include (but is not limited to) the rate of antenatal care attendance and facility-based childbirth, maternal and perinatal mortality, and severe maternal morbidity and potential complications from inappropriate use (such as uterine rupture); and
 - whether appropriate supervisory systems of health personnel involved in the distribution of misoprostol are in place.

- Within an antenatal distribution programme, misoprostol ideally should be provided to women during an antenatal care visit in the third trimester of pregnancy (typically as part of a safe delivery kit). It should be accompanied by clear, culturally appropriate instructions on its purpose, correct dose (400 or 600 micrograms [μg] for oral administration) and timing of use, possible side-effects and remedies for these, and prompt recognition of danger signs and how to access health services, while emphasizing the importance of giving birth in a health facility.
- In settings where a strategy of antenatal distribution of misoprostol will be initiated, prospective research that evaluates the impact of introducing these programmes on maternal health outcomes and health service utilization should be considered a priority.

1. Introduction

1.1 Background

An estimated 295 000 women and adolescent girls died as a result of pregnancy and childbirth-related complications in 2017, and around 99% of these deaths occurred in low-resource settings (1). Obstetric haemorrhage, especially postpartum haemorrhage (PPH), is responsible for more than a quarter of all maternal deaths worldwide (2). In most low-income countries, PPH is the leading cause of maternal deaths. Thus, improving access to safe and effective interventions to prevent PPH is critical to World Health Organization (WHO) strategic priorities (particularly universal health coverage) for achieving the targets of the third Sustainable Development Goal (SDG 3) (3).

International human rights law includes fundamental commitments of States to enable women and adolescent girls to survive pregnancy and childbirth, as part of their enjoyment of sexual and reproductive health and rights, and living a life of dignity (4). WHO envisions a world where “every pregnant woman and newborn receives quality care throughout pregnancy, childbirth and the postnatal period” (5). To provide good-quality care, skilled health personnel at all levels of the health system need to have access to appropriate medications and training in relevant procedures (6). Health-care providers, health managers, health policy-makers and other stakeholders also need up-to-date, evidence-informed recommendations to guide clinical policies and practices to optimize quality of care and improve health-care outcomes.

PPH is commonly defined as a blood loss of 500 mL or more within 24 hours after birth and affects about 5% of all women giving birth around the world (7,8). Severe maternal complications, such as organ dysfunction or death, generally occur following substantial blood loss that compromises maternal haemodynamic stability. Uterine atony is the most common cause of PPH and a leading cause of PPH-related maternal mortality worldwide (9). Genital tract trauma (including vaginal or cervical lacerations and uterine rupture), retained placental tissue or maternal bleeding disorders can cause PPH. Although PPH can occur in any woman, even those without risk factors, grand multiparity, prolonged labour, prior history of PPH and multiple gestation are associated with an increased risk of bleeding after birth (10). In addition, anaemia is a common aggravating factor (11). The majority of PPH-associated complications could be avoided by the use of prophylactic uterotonics during the third stage of labour (that is, the time between the delivery of the baby and complete expulsion of the placenta).

One prophylactic uterotonic is misoprostol, a prostaglandin E1 analogue, licensed for the prevention and treatment of gastric ulcers and well known for its off-label use as an uterotonic agent (12). It is water-soluble and heat stable, absorbed within 9–15 minutes and has a half-life of about 20–40 minutes (13). Oral and sublingual routes have the advantage of rapid onset of action, while the vaginal and rectal routes result in prolonged activity and greater bioavailability (13). Misoprostol is recommended by WHO as an uterotonic option for the prevention of PPH, especially in settings where oxytocin is unavailable (7).

For women who are likely to give birth outside a health facility, access to an effective uterotonic to prevent or treat PPH is a major challenge. This has led to the development and evaluation of advanced distribution strategies to ensure women have access to misoprostol after birth at home or in the community (14). An advanced distribution strategy may involve community-based distribution of misoprostol to traditional birth attendants, community health workers or lay health workers who attend home or community births and have been educated on how to administer misoprostol safely. In contexts where women give birth at home – without skilled health personnel – advance distribution of misoprostol to pregnant women themselves (during the last trimester of pregnancy) for self-administration in the third stage of labour has become a potential strategy to increase access to PPH prevention.

1.2 Rationale and objectives

WHO has established a new process for prioritizing and updating maternal and perinatal health recommendations, whereby an international group of independent experts – the Executive Guideline Steering Group (GSG) – oversees a systematic prioritization of MPH recommendations in most urgent need of updating (15,16). Recommendations are prioritized for updating on the basis of changes or important new uncertainties in the underlying evidence base on benefits, harms, values placed on outcomes, acceptability, feasibility, equity, resource use, cost-effectiveness or factors affecting implementation. The Executive GSG prioritized updating of the existing WHO recommendation on a strategy of advance misoprostol distribution to pregnant women in anticipation of the publication of new and potentially important evidence on this intervention.

This updated recommendation was developed in accordance with the standards and procedures in the *WHO handbook for guideline development*, including synthesis of available research evidence, use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)¹ and GRADE Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CerQUAL)² methodologies, and formulation of recommendations by a Guideline Development Group (GDG) composed of international experts and stakeholders (17). The recommendation published in this document thus supersedes the previous recommendation for advance misoprostol distribution to pregnant women for prevention of PPH that was published in 2012 in the *WHO recommendations for the prevention and treatment of postpartum haemorrhage* (18). The primary aim of this recommendation is to improve the quality of care and outcomes for women giving birth, as they relate to PPH and its complications. These recommendations thus provide a foundation for sustainable implementation of a strategy of advance misoprostol distribution to pregnant women for the prevention of PPH.

1.3 Target audience

The primary audience includes health professionals who are responsible for developing national and local health-care guidelines and protocols (particularly those related to PPH prevention and treatment) and those involved in the provision of care to women during labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians, as well as managers of maternal and child health programmes, and relevant staff in ministries of health and training institutions, in all settings.

This recommendation will also be of interest to women giving birth in low-resource settings, as well as members of professional societies involved in the care of pregnant women, staff of nongovernmental organizations concerned with promoting people-centred maternal care, and implementers of maternal and perinatal health programmes.

1.4 Scope of the recommendation

Framed using the Population (P), Intervention (I), Comparison (C), Outcome (O) (PICO) format, the question for this recommendation was:

- For women in the third stage of labour giving birth outside of a health facility (P), does a strategy of advance misoprostol distribution to pregnant women for PPH prevention (I) compared with no advance misoprostol distribution to pregnant women or usual care (C) improve maternal outcomes (O)?

1.5 Persons affected by the recommendation

The population affected by this recommendation includes all pregnant women in low- and middle-income settings.

¹ Further information is available at: <http://www.gradeworkinggroup.org/>.

² Further information is available at: <https://www.cerqual.org/>.

2. Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development* (17). In summary, the process included: (i) identification of the priority question and critical outcomes; (ii) retrieval of evidence; (iii) assessment and synthesis of evidence; (iv) formulation of the recommendation; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendation.

In 2019, strategies of advance misoprostol distribution to pregnant women for the prevention of PPH was identified by the Executive GSG as a high priority for development of a recommendation, in response to new, potentially important evidence on this question. Six main groups were involved in this process, with their specific roles described in the following sections.

2.1 Executive Guideline Steering Group (GSG)

The Executive GSG is an independent panel of 14 external experts and relevant stakeholders from the six WHO regions: African Region, Region of the Americas, Eastern Mediterranean Region, European Region, South-East Asia Region and Western Pacific Region. The Executive GSG advises WHO on the prioritization of new and existing PICO questions in maternal and perinatal health for development or updating of recommendations (15,16).

2.2 WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Sexual and Reproductive Health and Research and the Department of Maternal, Newborn, Child and Adolescent Health and Ageing managed the process of updating the recommendations. The WHO Steering Group drafted the key recommendation questions in PICO format, engaged the systematic review teams and guideline methodologists (that is, the Evidence Synthesis Group [ESG]), as well as the members of the GDG and the External Review Group (ERG) (see below). In addition, the WHO Steering Group supervised the retrieval and syntheses of evidence, organized the GDG meetings, drafted and finalized the guideline document, and will also manage the guideline dissemination, implementation and impact assessment. The members of the WHO Steering Group are listed in Annex 1.

2.3 Guideline Development Group (GDG)

The WHO Steering Group identified a pool of approximately 50 experts and relevant stakeholders from the six WHO regions to constitute the WHO Maternal and Perinatal Health Guideline Development Group (MPH-GDG). This pool consists of a diverse group of experts who are skilled in the critical appraisal of research evidence, implementation of evidence-informed recommendations, guideline development methods, and clinical practice, policy and programmes relating to maternal and perinatal health. Members of the MPH-GDG are identified in a way that ensures geographic representation and gender balance, and there were no perceived or real conflicts of interest. Members' expertise cuts across thematic areas within maternal and perinatal health.

From the MPH-GDG pool, 14 external experts and relevant stakeholders were invited to participate as members of the GDG for updating this recommendation. Those selected were a diverse group with expertise in research, guideline development methods, gender, equity and rights, clinical policy and programmes relating to PPH prevention and treatment.

The 14 GDG members for this recommendation were also selected in a way that ensured geographic representation and gender balance and there were no important conflicts of interest. The GDG appraised the evidence that was used to inform the recommendation, advised on the interpretation of this evidence, formulated the final recommendation based on the draft prepared by the WHO Steering Group and reviewed and reached unanimous

consensus for the recommendation in the final document. The members of the GDG are listed in Annex 1.

2.4 Evidence Synthesis Group (ESG)

WHO convened an ESG composed of guideline methodologists and systematic review teams to conduct or update systematic reviews, appraise the evidence and develop the Evidence to Decision (EtD) frameworks. A systematic review on this question was updated, supported by the Cochrane Pregnancy and Childbirth Group. The WHO Steering Group reviewed and provided input into the updated protocol and worked closely with the Cochrane Pregnancy and Childbirth Group to appraise the evidence using the GRADE methodology. Representatives of the Cochrane Pregnancy and Childbirth Group and a methodologist attended the GDG meeting to provide an overview of the available evidence and GRADE tables and to respond to technical queries from the GDG.

Evidence for the other domains of the GRADE EtD frameworks were obtained from two existing systematic qualitative reviews exploring what matters to women during childbirth and what matters to women and health-care providers in relation to interventions for the prevention of PPH, including views on advance misoprostol distribution programmes for the prevention of PPH (19,20). A systematic review on the cost-effectiveness of misoprostol updated until March 2020 was used for evidence in the cost-effectiveness domain in the EtD framework (21). All members of the ESG attended the GDG meetings to provide an overview of the synthesized evidence and to respond to technical queries from the GDG. The members of the ESG are listed in Annex 1.

2.5 External partners and observers

Representatives of the United States Agency for International Development (USAID), the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO) participated in the GDG meetings as observers. These organizations, with their long history of collaboration with WHO in maternal and perinatal health guideline dissemination and implementation, were identified as potential implementers of the recommendations. The list of observers who participated in the GDG meetings is included in Annex 1.

2.6 External Review Group (ERG)

The ERG included six technical experts with interests and expertise in the provision of evidence-based care to prevent and treat PPH. The group was geographically diverse and gender balanced, and the members had no important conflicts of interest. The experts reviewed the final document to identify any factual errors and commented on the clarity of language, contextual issues and implications for implementation. They ensured that the decision-making processes had considered and incorporated contextual values and the preferences of persons affected by the recommendations, health-care professionals and policy-makers. It was not within the remit of this group to change the recommendations that were formulated by the GDG. Members of the ERG are listed in Annex 1.

2.7 Identification of priority questions and outcomes

The priority outcomes were aligned with those from the 2012 *WHO recommendations for the prevention and treatment of postpartum haemorrhage* (18). These outcomes were initially identified through a search of scientific databases for relevant, published systematic reviews and a prioritization of outcomes by the GDG for the 2012 guideline. After due consideration of the recently published core outcome set for prevention and treatment of PPH (22), two additional outcomes – maternal well-being and maternal satisfaction – were included for this update to ensure that evidence synthesis and recommendation decision-making by the GDG were driven by outcomes that are important to women and to ensure that the final set of recommendations would be woman-centred. All the outcomes were included in the scope

of this document for evidence searching, retrieval, synthesis, grading and formulation of the recommendation. The list of priority outcomes is provided in Annex 2.

2.8 Evidence identification and retrieval

Evidence to support this update was derived from several sources by the ESG working in collaboration with the WHO Steering Group.

2.8.1 Evidence on the effects of advance misoprostol distribution to pregnant women

An existing systematic review on advance distribution of misoprostol was updated (14). This systematic review was the primary source of evidence of effectiveness for this recommendation.

Randomized controlled trials relevant to the key question were screened by the review authors, and data on relevant outcomes and comparisons were entered into the Review Manager 5 (RevMan) software. The RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons and outcomes (those that were not relevant to the recommendation were excluded). The RevMan file was then exported to GRADE profiler software (GRADEpro), and GRADE criteria were used to critically appraise the retrieved scientific evidence (23). Finally, evidence profiles (in the form of GRADE summary of findings tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome and the estimated risks.

2.8.2 Evidence on values, resource use and cost-effectiveness, equity, acceptability and feasibility

Two reviews were the primary sources of evidence on acceptability, feasibility and equity as they relate to the EtD framework for advance misoprostol distribution (19,20). A qualitative review exploring perceptions of PPH prevention and treatment, including advance misoprostol distribution, was used for evidence for the acceptability domain (20). This review included views from populations in rural areas of low- and middle-income countries on perceived benefits and effectiveness of advance misoprostol distribution, instructions for use, perceived safety and practicality of use. The same review included views on the potential misuse of misoprostol in community contexts where it might be used to induce abortion or act as a deterrent to facility-based childbirth. A review of qualitative studies evaluating “what women want” from intrapartum care was used for the values and equity domains relating to medical interventions, feelings about labour and birth, recognition of complications and receiving information on introduced interventions (19). In addition to this evidence, two further reviews of implementation programmes provided important additional evidence for the panel’s deliberations (24,25).

Evidence on resource use and cost-effectiveness was based on a systematic review of the literature updated until March 2020, identifying six studies on the cost-effectiveness of misoprostol (21). All of these studies were conducted in settings with low access to modern birth facilities (that is, with a shortage of skilled birth attendants, inadequate transport and storage facilities for oxytocin or where oxytocin was not available). These studies were of moderate to high quality according to Consensus Health Economic Criteria checklist and most used a model-based approach to estimate the incremental costs of introducing misoprostol to prevent PPH in these settings. Evidence from this domain was supplemented by findings from a qualitative systematic review evaluating prevention and treatment of PPH from the perception of providers and women, including advance distribution of misoprostol. This review identified 35 studies in lower-resource rural communities and for women who may not ordinarily attend a health-care facility to give birth (20).

2.9 Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence for each outcome was performed using the GRADE approach (26). Using this approach, the certainty of evidence for each outcome was rated as “high”, “moderate”, “low” or “very low” based on a set of established criteria. The final rating of certainty of evidence was dependent on the factors briefly described below.

Study design limitations: The risk of bias was first examined at the level of each individual study and then across the studies contributing to the outcome. For randomized trials, certainty was first rated as “high” and then downgraded by one (“moderate”) or two (“low”) levels, depending on the minimum criteria met by the majority of the studies contributing to the outcome.

Inconsistency of the results: The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed in different studies. The certainty of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas it was downgraded when the results were in different directions and confidence limits showed minimal or no overlap.

Indirectness: The certainty of evidence was downgraded when there were serious or very serious concerns regarding the directness of the evidence, that is, whether there were important differences between the research reported and the context for which the recommendation was being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes of interest.

Imprecision: This assessed the degree of uncertainty around the estimate of effect. As this is often a function of sample size and number of events, studies with relatively few participants or events, and thus wide confidence intervals around effect estimates, were downgraded for imprecision.

Publication bias: The certainty rating could also be affected by perceived or statistical evidence of bias to underestimate or overestimate the effect of an intervention as a result of selective publication based on study results. Downgrading evidence by one level was considered where there was strong suspicion of publication bias.

Certainty of evidence assessments are defined according to the GRADE approach:

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The findings of the qualitative reviews were appraised for quality using the GRADE-CERQual tool (27). The GRADE-CERQual tool, which uses a similar conceptual approach to other GRADE tools, provides a transparent method for assessing and assigning the level of confidence that can be placed in evidence from reviews of qualitative research. The systematic review team used the GRADE-CERQual tool to assign a level of confidence (high, moderate, low and very low) to each review finding according to four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question of the individual studies contributing to a review finding. Findings from individual cost-effectiveness studies were reported narratively for each comparison of interest.

2.10 Formulation of the recommendation

The WHO Steering Group supervised and finalized the preparation of summary of findings tables and narrative evidence summaries in collaboration with the ESG using the GRADE EtD framework. EtD frameworks include explicit and systematic consideration of evidence on prioritized interventions in terms of specified domains: effects, values, resources, equity, acceptability and feasibility. For the priority questions, judgements were made on the impact of the intervention on each domain to inform and guide the decision-making process. Using the EtD framework template, the WHO Steering Group and ESG created summary documents for each priority question covering evidence on each domain:

- **Effects:** The evidence on the priority outcomes was summarized in this domain to answer the questions: “What are the desirable and undesirable effects of the intervention?” and “What is the certainty of the evidence on effects?” Where benefits clearly outweighed harms for outcomes that are highly valued by women, or vice versa, there was a greater likelihood of a clear judgement in favour of or against the intervention, respectively. Uncertainty about the net benefits or harms, or small net benefits, usually led to a judgement that did not favour the intervention or the comparator. The higher the certainty of the evidence of benefits across outcomes, the higher the likelihood of a judgement in favour of the intervention. In the absence of evidence of benefits, evidence of potential harm led to a recommendation against the intervention. Where the intervention showed evidence of potential harm and was also found to have evidence of important benefits, depending on the level of certainty and the likely impact of the harm, such evidence of potential harm was more likely to result in a context-specific recommendation, with the context explicitly stated within the recommendation.
- **Values:** This domain relates to the relative importance assigned to the outcomes associated with the intervention by those affected, how such importance varies within and across settings, and whether this importance is surrounded by any uncertainty. The question asked was: “Is there important uncertainty or variability in how much women value the main outcomes associated with the intervention?” When the intervention resulted in benefit for outcomes that most women consistently value (regardless of setting), this was more likely to lead to a judgement in favour of the intervention. This domain, together with the “effects” domain (see above), informed the “balance of effects” judgement.
- **Resources:** For this domain, the questions asked were: “What are the resources associated with the intervention?” and “Is the intervention cost-effective?” The resources required to implement a strategy of advance misoprostol distribution to pregnant women for prevention of PPH mainly include the costs of providing supplies, training, and monitoring and evaluation. A judgement in favour of or against the intervention was likely where the resource implications were clearly advantageous or disadvantageous, respectively.
- **Acceptability:** For this domain, the question was: “Is the intervention acceptable to women and health-care providers?” Qualitative evidence from systematic reviews on the views and experiences of women and providers with a strategy of advance misoprostol distribution (19,20) informed the judgements for this domain. The lower the acceptability, the lower the likelihood of a judgement in favour of the intervention.
- **Feasibility:** The feasibility of implementing this intervention depends on factors such as the resources, infrastructure and training requirements, and the perceptions of health-care providers responsible for administering it. The question addressed was: “Is it feasible for the relevant stakeholders to implement the intervention?” Qualitative evidence from the systematic reviews on women’s and providers’ views and experiences with advance misoprostol distribution was used to inform judgements for this domain (19,20), as well as two additional reviews on implementation (24,25). Where major barriers were identified, it was less likely that a judgement would be made in favour of the intervention.

- **Equity:** This domain encompasses evidence or considerations as to whether or not the intervention would reduce health inequities. Therefore, this domain addressed the question: “What is the anticipated impact of the intervention on equity?” The findings of qualitative reviews of evidence (19,20,24,25) as well as the experiences of the GDG members, were used to inform judgements for this domain. The intervention was likely to be recommended if its proven (or anticipated) effects reduce (or could reduce) health inequalities among different groups of women and their families.

For each of the above domains, additional evidence of potential harms or unintended consequences are described in the Additional considerations subsections. Such considerations were derived from studies that might not have directly addressed the priority question but provided pertinent information in the absence of direct evidence. These were extracted from single studies, systematic reviews or other relevant sources.

The WHO Steering Group provided the EtD frameworks, including evidence summaries, summary of findings tables and other documents related to each recommendation, to GDG members two weeks in advance of the GDG meeting. The GDG members were asked to review and provide comments (electronically) on the documents before the GDG meeting. During the GDG meeting (11-12 March 2020), which was conducted under the leadership of the GDG chairperson, the GDG members collectively reviewed the EtD frameworks, and any comments received through preliminary feedback, and formulated the recommendations. The purpose of the meeting was to reach consensus on the recommendation and the specific context, based on explicit consideration of the range of evidence presented in each EtD framework and the judgement of the GDG members. The GDG was asked to select one of the following categories for the recommendation:

- **Recommended:** This category indicates that the intervention should be implemented.
- **Not recommended:** This category indicates that the intervention should not be implemented.
- **Recommended only in specific contexts (“context-specific recommendation”):** This category indicates that the intervention is applicable only to the condition, setting or population specified in the recommendation and should only be implemented in these contexts.
- **Recommended only in the context of rigorous research (“research-context recommendation”):** This category indicates that there are important uncertainties about the intervention. With this category of recommendation, implementation can still be undertaken on a large scale, provided it takes the form of research that addresses unanswered questions and uncertainties related both to effectiveness of the intervention or option, and its acceptability and feasibility.

2.11 Management of declarations of interests

WHO has a robust process to protect the integrity of its normative work, as well as to protect the integrity of individual experts with whom it collaborates. WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to actual or ostensible conflict of interest. The disclosure and the appropriate management of relevant financial and non-financial conflicts of interest of GDG members and other external experts and contributors are a critical part of guideline development at WHO. According to WHO regulations, all experts must declare their interests prior to participation in WHO guideline development processes and meetings according to the guidelines for declaration of interest (DOI) for WHO experts (17). All GDG members were therefore required to complete a standard WHO DOI form before engaging in the guideline development process and before participating in the guideline-related processes. The WHO Steering Group reviewed all declarations before finalizing the experts’ invitations to participate. Where any conflict of interest was declared, the WHO Steering Group determined whether such conflicts were serious enough to affect an expert’s objective judgement in the guideline and recommendation development process. To ensure consistency, the WHO Steering Group

applied the criteria for assessing the severity of conflict of interests as outlined in the *WHO handbook for guideline development* to all participating experts. All findings from the DOI statements received were managed in accordance with the WHO procedures to assure the work of WHO and the contributions of its experts is, actually and ostensibly, objective and independent. The names and biographies of individuals were published online four weeks prior to the meeting. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, the experts were only required to openly declare such conflicts of interest at the beginning of the GDG meeting, and no further actions were taken. Annex 3 shows a summary of the DOI statements and how conflicts of interest declared by invited experts were managed by the WHO Steering Group.

2.12 Decision-making during the GDG meetings

During the meeting, the GDG reviewed and discussed the evidence summary and sought clarification. In addition to evaluating the balance between the desirable and undesirable effects of the intervention and the overall certainty of the evidence, the GDG applied additional criteria based on the GRADE EtD framework to determine the direction and strength of the recommendation. These criteria included stakeholders' values, resource implications, acceptability, feasibility and equity. Considerations were based on the experience and opinions of the GDG members and supported by evidence from a literature search where available. EtD tables were used to describe and synthesize these considerations.

Decisions were made based on consensus, defined as the agreement by three quarters or more of the participants. None of the GDG members expressed opposition to the recommendation.

2.13 Document preparation

Prior to the online meeting, the WHO Steering Group prepared a draft version of the GRADE evidence profiles, the evidence summary and other documents relevant to the GDG's deliberation. The draft documents were made available to the participants of the meeting two weeks before the meeting for their comments. During the meeting, these documents were modified in line with the participants' deliberations and remarks. Following the meeting, members of the WHO Steering Group drafted a full guideline document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to the GDG and the ERG for their final review and approval.

2.14 Peer review

Following review and approval by GDG members, the final document was sent to eight external independent experts (comprising the ERG) who were not involved in the guideline panel for peer review. The WHO Steering Group evaluated the inputs of the peer reviewers for inclusion in this document. After the meeting and external peer review, the modifications made by the WHO Steering Group to the document consisted only of the correction of factual errors and improving language to address any lack of clarity.

3. Recommendation and supporting evidence

The following section outlines the recommendation and the corresponding narrative summary of evidence for the prioritized question. The EtD table, summarizing the balance between the desirable and undesirable effects and the overall certainty of the supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity that were considered in determining the strength and direction of the recommendation, is presented in the EtD framework (Annex 4).

The following recommendation was adopted by the GDG. Evidence on the effectiveness of this intervention was derived from the updated systematic review and summarized in GRADE tables (Annex 4).

To ensure that the recommendation is correctly understood and appropriately implemented in practice, additional remarks reflecting the summary of the discussion by the GDG are included under the recommendation.

In settings where women give birth outside of a health facility and in the absence of skilled health personnel, a strategy of antenatal distribution of misoprostol to pregnant women for self-administration is recommended for prevention of postpartum haemorrhage, only with targeted monitoring and evaluation.

(Context-specific recommendation)

Justification

- There is insufficient trial evidence to assess the benefits and possible harms of a strategy of advance misoprostol distribution for postpartum haemorrhage prevention. However, misoprostol is known to be an effective uterotonic agent for postpartum haemorrhage prevention and is recommended by WHO in settings where oxytocin is unavailable, its quality cannot be guaranteed or skilled health personnel are not present to administer it (7). Observational studies and evaluations of advance misoprostol distribution programmes in several countries indicate that this strategy can increase coverage of uterotonic use for postpartum haemorrhage prevention in remote and hard-to-reach areas where no skilled health personnel can attend, with very few reports of incorrect use of misoprostol or adverse events. As this strategy is specifically aimed at preventing postpartum haemorrhage in women in more remote or underserved areas who would otherwise not receive any uterotonic during birth, it is likely to increase health equity and improve health outcomes. These programmes are probably acceptable to women and providers. While the cost-effectiveness of this strategy is not known, it is likely to confer cost savings.

Remarks

- Antenatal distribution of misoprostol to pregnant women should not replace standard policies for scaling up effective uterotonic use, but it should be considered as a strategy for increasing coverage of uterotonic use in settings where a large proportion of women still give birth outside of health facilities and where it is highly likely that skilled health personnel will not be present at time of birth.

- While acknowledging that there is currently no clear evidence of harm with a strategy of antenatal misoprostol distribution, the Guideline Development Group agreed that to address potential safety concerns, such programmes should only be implemented with appropriate monitoring and evaluation. These should consider:
 - whether women are trained appropriately in the use of misoprostol;
 - monitoring the distribution, use and potential misuse of misoprostol;
 - the effect of the programme on utilization of health services and health outcomes – this should include (but is not limited to) the rate of antenatal care attendance and facility-based childbirth, maternal and perinatal mortality, and severe maternal morbidity and potential complications from inappropriate use (such as uterine rupture); and
 - whether appropriate supervisory systems of health personnel involved in the distribution of misoprostol are in place.
- Within an antenatal distribution programme, misoprostol ideally should be provided to women during an antenatal care visit in the third trimester of pregnancy (typically as part of a safe delivery kit). It should be accompanied by clear, culturally appropriate instructions on its purpose, correct dose (400 or 600 µg for oral administration) and timing of use, possible side-effects and remedies for these, prompt recognition of danger signs and how to access health services, while emphasizing the importance of giving birth in a health facility.

In settings where a strategy of antenatal distribution of misoprostol will be initiated, prospective research that evaluates the impact of introducing these programmes on maternal health outcomes and health service utilization should be considered a priority.

4. Dissemination, adaptation and implementation of the recommendation

The dissemination and implementation of this recommendation are to be considered by all stakeholders involved in the provision of care for pregnant women at the international, national and local levels. There is a vital need to increase women's access to maternal health care at community level and to strengthen the capacity at health-care facilities of all levels to ensure they can provide high-quality services and information to all women giving birth, whether in health facilities or outside of a health facility and in the absence of skilled health personnel. It is therefore crucial that this recommendation be translated into care packages and programmes at country, health-care facility and community levels, where appropriate. Nevertheless, WHO stresses the importance of safe childbirth in health facilities, where skilled health personnel are available.

4.1 Recommendation dissemination

The recommendation will be disseminated through WHO regional and country offices, ministries of health, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. This recommendation will also be available on the WHO website and the WHO Reproductive Health Library.¹ Updated recommendations are also routinely disseminated during meetings or scientific conferences attended by WHO maternal and perinatal staff.

The recommendation document will be translated into the six United Nations languages and disseminated through the WHO regional offices. Technical assistance will be provided to any WHO regional office willing to translate the full recommendation into any of these languages.

4.2 Adaptation

National and subnational subgroups may be established to adapt and implement this recommendation based on an existing strategy. This process may include the development or revision of existing national guidelines or protocols based on the updated recommendation.

Existing global models such as those for WHO antenatal and intrapartum care guidelines can be adapted to different countries, contexts and individual needs and preferences of women. The conceptual basis of these models is to drive improvements in the quality of maternal health care, by aiming to achieve the best possible physical, emotional and psychological outcomes for the woman and her baby, irrespective of the influence of generic policies that may exist within and across health systems and countries. Both models address relevant health policy, organizational and user-level considerations. These models thus support implementation of WHO recommendations and are intended to be adapted by stakeholders and partners at regional, country and local levels into locally appropriate documents and tools.

The successful introduction of evidence-based policies (relating to updated recommendations) depends on well-planned and participatory consensus-driven processes of adaptation and implementation. These processes may include the development or revision of existing national or local guidelines and protocols, often supported by ministries of health, United Nations agencies, local professional societies and other relevant leadership groups. An enabling environment should be created for the use of this recommendation, including changes in the behaviour of health-care practitioners to enable the use of evidence-based practices.

In the context of humanitarian emergencies, the adaptation of the current recommendation

¹ Available at: www.who.int/rhl.

should consider the integration and alignment with other response strategies. Additional considerations to the unique needs of women in emergency settings, including their values and preferences, should be made. Context-specific tools and toolkits may be required in addition to standard tools to support the implementation of the recommendation in humanitarian emergencies by stakeholders.

4.3 Implementation considerations

- In settings where this strategy is being introduced, it is advised that policy-makers and health managers consider how to ensure the reliable procurement of misoprostol, access to functioning referral systems, and training and supervision of health personnel participating in antenatal misoprostol distribution programmes. Procurement agencies at all levels of supply chains should procure only quality-assured uterotonic medicines.
- Skilled health personnel, community health workers and lay health workers may (depending on the context) participate in antenatal misoprostol distribution programmes. These individuals will require training and supportive supervision on how to instruct and counsel women on the benefits and side-effects of misoprostol and its safe and appropriate use. In this strategy, misoprostol tablets are typically provided as part of a safe delivery kit, which also requires education and training to be provided to the woman by a trained health-care worker. In settings where this strategy is introduced for the first time, additional staff training and monitoring will be required.
- Special attention needs to be given in communicating to women the timing of misoprostol administration and ensuring that it is not misused for other indications (for example, through monitoring of unused tablets). Strategies for retrieving the unused tablets postnatally should also be implemented.
- WHO currently recommends 400 or 600 µg of oral misoprostol for the prevention of PPH (7). It should be provided to women late in pregnancy (ideally during an antenatal care visit in the third trimester), along with clear, culturally appropriate instructions and training on how to safely store and use this medication. To maintain the quality of misoprostol, the tablets should be taken out of the package right before its administration, as the tablets degrade with humidity.
- Antenatal misoprostol distribution programmes may benefit from community awareness campaigns or other measures to educate and raise awareness amongst pregnant women and their families.
- It is advised that programmes to implement uterotonics for PPH prevention ensure women are adequately informed in advance about the need to use a uterotonic to prevent PPH, the available uterotonic options, the possible side-effects of these options and their rights to choose what care they receive. Specifically, women should be informed about the dangers of misoprostol use during pregnancy and labour prior to birth of the baby. In settings with high rates of unexpected multiple pregnancy, provision should be made to ensure that misoprostol is not given before the birth of a second twin (that is, by only giving it after placental expulsion).
- The recommendation should be adapted into documents and tools that are appropriate for different locations and contexts to meet the specific needs of each country and health service. Modifications to the recommendation, where necessary, should be justified in an explicit and transparent manner.

5. Research implications

The GDG identified important knowledge gaps that need to be addressed through primary research, which may have an impact on this recommendation. The following questions were identified as those that demand urgent priority:

- What are the harms and benefits of advance misoprostol distribution for the prevention of PPH?
- Is one strategy of misoprostol distribution more effective than another?
- In settings where antenatal misoprostol distribution programmes are initiated for the first time, what are the effects of introducing these programmes on maternal and perinatal health outcomes and utilization of health services (particularly facility-based childbirth)?

6. Applicability issues

6.1 Anticipated impact on the organization of care and resources

A number of factors (barriers) may hinder the effective implementation and scale-up of this recommendation. These factors may be related to the behaviours of patients (women or families) or health-care professionals and to the organization of care or health service delivery. Standardization of care, by including this recommendation in existing antepartum care packages in contexts where women may not have access to skilled care personnel for birth, can encourage behaviour change in health-care providers.

As part of efforts to implement this recommendation, health system stakeholders may wish to consider the following potential barriers to their application:

- lack of understanding of the value of misoprostol in preventing PPH among women seeking maternity care, families or communities;
- lack of human resources with the necessary training and skills to implement and support the advance distribution of misoprostol;
- concerns from skilled care personnel and system managers regarding the safety of advance misoprostol distribution to pregnant women, including the misuse of misoprostol;
- lack of current systems in place to monitor the distribution and use of misoprostol as well as the return of unused misoprostol tablets; and
- lack of effective referral mechanisms and care pathways for women identified as needing additional care, including when PPH occurs outside of a health facility.

Various strategies for addressing these barriers and facilitating implementation are provided under implementation considerations in section 4.

6.2 Monitoring and evaluating guideline implementation

The implementation and impact of this recommendation will be monitored at the health service, country and regional levels, as part of broader efforts to monitor and improve the quality of maternal and newborn care. The WHO document *Standards for improving quality of maternal and newborn care in health facilities* (28) provides a list of prioritized input, output and outcome measures that can be used to define quality of care criteria and indicators and that should be aligned with locally agreed targets. In collaboration with the monitoring and evaluation teams of the WHO Department of Sexual and Reproductive Health and Research and the WHO Department of Maternal, Newborn, Child, Adolescent Health and Ageing,

data on country- and regional-level implementation of the recommendation will be collected and evaluated in the short to medium term to assess its impact on national policies of individual WHO Member States. Interrupted time series could be used to obtain the relevant data on the use of interventions contained in this guideline.

With regard to PPH prevention, WHO recommends that the coverage of prophylactic uterotonics be used as a process indicator for the monitoring and prevention of PPH (18). The suggested “prophylactic uterotonic coverage indicator” is calculated as the number of women receiving prophylactic uterotonics during the third stage of labour divided by all women giving birth. This indicator provides an overall assessment of adherence to the recommendation included in this guideline.

The use of other locally agreed and more specific indicators (such as the proportion of pregnant women given misoprostol tablets antenatally) may be necessary to obtain a more complete assessment of the quality of care related to the prevention and treatment of PPH. The proportion of unused misoprostol tablets returned to the health-care setting after birth should also be considered as an indicator to assess the success of the retrieval strategy. WHO has developed specific guidance for evaluating the quality of care for severe maternal complications (including PPH) based on the near-miss and criterion-based clinical audit concepts (29). Monitoring of the quality of uterotonic drugs available in low-resource settings may help guide skilled health personnel in selecting the most effective uterotonic option for PPH prevention in the context in which they are working.

7. Updating the recommendation

The Executive GSG convenes annually to review WHO’s current portfolio of maternal and perinatal health recommendations and to help WHO prioritize new and existing questions for recommendation development and updating. Accordingly, this recommendation will be reviewed along with other recommendations for prioritization by the Executive GSG. If new evidence that could potentially impact the current evidence base is identified, the recommendation may be updated. If no new reports or information is identified, the recommendation may be revalidated.

Following publication and dissemination of the updated recommendation, any concerns about the validity of the recommendation should be promptly communicated to the guideline implementers, in addition to any plans to update the recommendation.

WHO welcomes suggestions regarding additional questions for inclusion in the updated recommendation. Please email your suggestions to srhmph@who.int.

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Annex 1. External experts and WHO staff involved in the preparation of the recommendation

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Annex 2. Priority outcomes used in decision-making

Priority outcomes (O):¹

Critical outcomes

- Maternal death
- PPH > 1000 mL
- Blood transfusion

Important outcomes

- Severe maternal morbidity: intensive care unit (ICU) admission
- Severe maternal morbidity: shock
- PPH ≥ 500 mL
- Use of additional uterotonics
- Mean blood loss
- Postpartum anaemia
- Breastfeeding
- Less anaemia in infancy
- Side-effects²
- Maternal temperature ≥ 38 °C
- Maternal temperature ≥ 40 °C
- Maternal well-being
- Maternal satisfaction

¹ These outcomes reflect the prioritized outcomes used in the development of this recommendation, in the 2012 *WHO recommendations for the prevention and treatment of postpartum haemorrhage (18)*. The outcomes “maternal well-being” and “maternal satisfaction” have been added as part of this update.

² This includes nausea, vomiting, headache, abdominal pain, hypertension, shivering, fever, diarrhoea and placental retention.

Annex 3. Summary and management of declared interests from GDG members

Name	Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Oluwarotimi I Akinola	Content expert and end-user	None declared	Not applicable
Melania Amorim	Content expert and end-user	None declared	Not applicable
Brendan Carvalho	Content expert and end-user	Serves as technical consultant for Gauss Surgical (company that measures peripartum and operative blood loss). Receives share options from Gauss Surgical.	The conflict was not considered serious enough to affect Guideline Development Group (GDG) membership or participation
Catherine Deneux-Tharaux	Content expert and end-user	None declared	Not applicable
Tippawan Liabsuetrakul	Content expert and end-user	None declared	Not applicable
Martin Meremikwu	Content expert and end-user	None declared	Not applicable
Suellen Miller	Content expert and end-user	Serves as a technical advisor to the Blue Fuzion Group who manufactures and distributes one brand of non-pneumatic anti-shock garment, the LifeWrap. UCSF receives a royalty for the trademark.	The conflict was not considered serious enough to affect GDG membership or participation.
Ashraf Nabhan	Content expert and implementer	None declared	Not applicable
Mari Nagai	Content expert and end-user	None declared	Not applicable
Hayfaa Wahabi	Content expert and end-user	None declared	Not applicable
Dilys Walker	Content expert and end-user	Co-founder and President of the nongovernmental organization PRONTO International. PRONTO designs and implements simulation and team training for obstetric and neonatal emergencies, including postpartum haemorrhage. Professor Walker has donated funds to the organization. PRONTO International has the rights to the low-tech birth simulator, PARTO Pants and the PRONTO Pack simulation training kit.	The conflict was not considered serious enough to affect GDG membership or participation.

Name	Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Andrew Weeks	Content expert and end-user	Chief investigator of the COPE trial, and co-inventor of the Butterfly device to treat postpartum haemorrhage as well as chief investigator of the development study. Both funded by NIHR (United Kingdom) research grants to the University of Liverpool. The University is the device patent holder, but as co-inventor Professor Weeks would receive a share of the profits.	The conflict was not considered serious enough to affect GDG membership or participation.

Annex 4. Evidence to Decision framework

Question

The question of interest using the population (P), intervention (I), comparator (C), outcome (O) (PICO) format:

- For women in the third stage of labour giving birth outside of a health facility (P), does a strategy of advance misoprostol distribution to pregnant women for PPH prevention (I) compared with no advance distribution to pregnant women or usual care (C) improve maternal outcomes (O)?

Problem: PPH

Perspective: Clinical practice recommendation – population perspective

Population (P): Women in the third stage of labour giving birth outside of a health facility

Intervention (I): A strategy of advance misoprostol distribution to pregnant women

Comparator (C): No advance distribution strategy or usual care for prevention of PPH

Setting: Home or community setting.

Priority outcomes (O):¹

Critical outcomes

- Maternal death
- PPH > 1000 mL
- Blood transfusion

Important outcomes

- Severe maternal morbidity: intensive care unit (ICU) admission
- Severe maternal morbidity: shock
- PPH ≥ 500 mL
- Use of additional uterotonics
- Mean blood loss
- Postpartum anaemia
- Breastfeeding
- Less anaemia in infancy
- Side-effects²
- Maternal temperature ≥ 38 °C
- Maternal temperature ≥ 40 °C
- Maternal well-being
- Maternal satisfaction

¹ These outcomes reflect the prioritized outcomes used in the development of this recommendation, in *WHO recommendations for the prevention and treatment of postpartum haemorrhage* (2012). The outcomes “maternal well-being” and “maternal satisfaction” have been added as part of this update.

² This includes nausea, vomiting, headache, abdominal pain, hypertension, shivering, fever, diarrhoea and placental retention.

Assessment

Effects of interventions

What is the effect of a strategy of advance misoprostol distribution to pregnant women when used for PPH prevention in non-facility births on the priority outcomes?

Research evidence

Summary of evidence

Source and characteristics of studies

Evidence on the effects of advance misoprostol distribution to pregnant women for prevention of PPH in non-facility births is derived from an update of a Cochrane systematic review (1). The review includes two trials, from which 570 women having non-facility births were included.

One of the trials is a double-blind, placebo-controlled trial in which 748 women in Uganda were randomized to receive either 600 µg of misoprostol to take immediately after birth or a placebo (2). Pregnant women (without a previous caesarean section) were recruited at 28 weeks. They received instructions on how to self-administer the tablets (containing misoprostol or placebo) whether they delivered at home or in a health facility (other than a hospital). Data from the 299 non-facility births were included in the Cochrane review.

The other trial was a stepped-wedge cluster randomized trial in Uganda involving 2466 women (3). During the study period, pregnant women at 28 or more weeks of gestation were enrolled and given 600 µg of oral misoprostol to self-administer after childbirth if delivery happened outside a health facility, or when there was no oxytocin at the health facility. During the control period, women who delivered at a health facility could receive oxytocin, while women who delivered at home received no uterotonic (standard care). Data from the 271 non-facility births were considered in the systematic review.

Effects of a strategy of advance misoprostol distribution to pregnant women for PPH prevention

Advance misoprostol distribution to pregnant women for postpartum self-administration versus usual (or standard) care for PPH prevention in non-facility births

The Cochrane review included one study for this comparison (2). However, in this individually randomized pilot trial, women in the control arm received an advance provision of inert tablets for self-administration, along with pictorial and written instructions on how to take them, with the assumption that women giving birth outside of a health facility would not receive misoprostol (or any uterotonic), reflecting “no advance distribution” or usual care. Thus, the study was further downgraded for indirectness (related to the comparison arm). Results from the second study (3) were described but not included in the meta-analysis, as they were not presented in a usable format (cluster-level summaries of effect, without disaggregation by birth setting).

The included study reported on the following WHO priority outcomes: **maternal mortality, blood transfusion, severe maternal morbidity, use of additional uterotonics, postpartum anaemia** and **side-effects** such as **shivering/chills, fever, diarrhoea** and **placental retention**. The effect estimates for these priority outcomes were of very low certainty, with indirectness, no events or few events reported, and small sample sizes. This study did not report on the other priority outcomes.

Summary data were reported from the second trial (3). The study authors reported no serious **maternal morbidity** among women who had non-facility births in intervention and standard care arms. Three (out of four) **maternal deaths** reported occurred at health facility births; however, this population was not included in this Cochrane review. The other death occurred at home following alleged domestic violence while

the woman was still pregnant. Data on **PPH (at least 500 mL or as defined by authors)** were not usable as they were presented as overall rates without disaggregating by birth setting. There were no cases of **blood transfusion**. The study reported that advance misoprostol distribution may increase occurrence of **fever** in the intervention compared with standard care following non-facility birth (risk ratio [RR] 1.77, 95% confidence interval [CI] 1.06 to 2.95). **Diarrhoea** was reported in 2.3% of women in the intervention versus 2.5% in the control group (RR 0.91, 95% CI 0.19 to 4.42; 254 women). The trial did not report on the other priority outcomes.

Additional considerations

There is a growing number of observational studies evaluating the programmatic feasibility and the impact of advance misoprostol distribution to pregnant women for PPH prevention in non-facility births. Studies conducted in Afghanistan (4), Ghana (5), India (6), Liberia (7), Nepal (8) and South Sudan (9) suggest the potential benefit of this strategy to increase coverage for uterotonic use for PPH prevention, with few reports of incorrect use of misoprostol and adverse events. This strategy also appears to increase the coverage of antenatal care visits and facility births. Similarly, a quasi-randomized study conducted in Afghanistan (10) found that all women who used misoprostol in the intervention areas did so correctly and that uterotonic coverage (misoprostol and/or oxytocin) was increased in the intervention areas compared with the control areas. However, outcomes related to blood loss (such as PPH and severe PPH) and indicators of severe maternal morbidity were not reported.

Desirable effects

How substantial are the desirable anticipated effects of a strategy of advance misoprostol distribution for PPH prevention?

Judgement

✓ Don't know	— Varies	— Trivial	— Small	— Moderate	— Large
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Undesirable effects

How substantial are the undesirable anticipated effects of a strategy of advance misoprostol distribution for PPH prevention?

Judgement

✓ Don't know	— Varies	— Large	— Moderate	— Small	— Trivial
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Certainty of the evidence

What is the overall certainty of the evidence on effects of a strategy of advance misoprostol distribution for PPH prevention?

— No included studies	✓ Very low	— Low	— Moderate	— High
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Additional considerations

None.

Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with a strategy of advance misoprostol distribution for PPH prevention?

Research evidence

In a review of qualitative studies evaluating “what women want” from intrapartum care, findings indicate that most women want a normal birth (with good outcomes for mother and baby) but acknowledge that medical intervention may sometimes be necessary (*high confidence*) (11). Most women, especially those giving birth for the first time, are apprehensive about labour and birth (*high confidence*) and wary of medical interventions, although, in certain contexts and/or situations, women welcome interventions to address recognized complications (*low confidence*). Where interventions are introduced, women would like to receive relevant information from technically competent health-care providers who are sensitive to their needs (*high confidence*).

Findings from another qualitative systematic review exploring perceptions of PPH prevention and treatment among women and providers found that women’s understanding of the implications of PPH were generally good (*moderate confidence*). However, they did not always recognize the clinical definitions of blood loss or what might be considered “normal” blood loss (*moderate confidence*) (12). Furthermore, in some low- and middle-income countries (LMICs), women place a greater value on the expulsion of so-called “dirty blood”, which they perceive as a normal cleansing process and something that should not be prevented (*moderate confidence*).

The same review also highlighted women’s need for information about PPH, ideally given during antenatal care (*moderate confidence*), as well as the need for specific information about misoprostol, preferably given by a health-care provider during the third trimester (*low confidence*). Women also highlighted the importance of kind, clinically competent staff with a willingness to engage in shared decision-making around PPH management (*moderate confidence*). In addition, it was found that women are concerned about feelings of exhaustion and anxiety (at being separated from their babies) following PPH, as well as the long-term psychological effects of experiencing PPH and the negative impact this may have on their ability to breastfeed (*moderate/low confidence*).

Additional considerations

None.

Judgement

— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ Probably no important uncertainty or variability	— No important uncertainty or variability
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Balance of effects

Does the balance between desirable and undesirable effects favour a strategy of advance misoprostol distribution for PPH prevention or the comparator?

Judgement

✓ Don't know	— Varies	— Favours comparator	— Probably favours comparator	— Does not favour either	— Probably favours intervention	— Favours intervention
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Resources

How large are the resource requirements (costs) of a strategy of advance misoprostol distribution for PPH prevention?

Research evidence

A systematic review of the literature updated until 2020 identified six studies of the cost-effectiveness of misoprostol (13). All of these studies were conducted in settings with low access to modern birth facilities (that is, with a shortage of skilled birth attendants, inadequate transport and storage facilities for oxytocin and where oxytocin was not available). These studies were of moderate to high quality according to Consensus Health Economic Criteria (CHEC) checklist and most used a model-based approach to estimate the incremental costs of introducing misoprostol to prevent PPH in these settings.

Four studies evaluated misoprostol as a 600 µg dose (oral or sublingual), a 200 µg dose and a 1000 µg dose rectally administered. In most studies, administration of misoprostol was undertaken by lay health workers; in one study from Uganda, it was distributed antenatally to pregnant women for self-administration following birth (14). Although cost-effectiveness measures and reporting differed (such as incremental cost-effectiveness ratio [ICER] per case of PPH avoided, per disability-adjusted life year [DALY] gained, per life saved, cost savings per 1000 births, etc.), findings were consistent across studies and showed that misoprostol was highly cost-effective or led to cost savings compared with no use of uterotonic agents in these settings. The cost of treating side-effects of misoprostol was reported to be negligible in two studies of misoprostol use in India (15,16).

One study from Senegal that compared the cost-effectiveness of misoprostol with oxytocin (10 IU provided via Uniject device) found misoprostol (600 µg orally) to be more cost-effective than oxytocin (17), partly because the Uniject devices were reported to be associated with high wastage costs (18).

Additional considerations

The Guideline Development Group (GDG) noted that the studies of cost-effectiveness of this intervention used estimates of effect that were different from the estimates of effect from the Cochrane review, which shows very-low-certainty evidence. In light of this, the GDG considered that it is not possible to assess the cost-effectiveness of this intervention.

Main resource requirements

Resource	Description
Provider	Lay health workers can administer misoprostol in community-based settings. In some settings, it has also been distributed to women antenatally for self-administration in the event of a home birth (14). When self-administration strategies are used, trained health workers need to provide education on using misoprostol safely to the woman.
Training	Introduction of a strategy of advance misoprostol distribution would require additional training for health-care providers who distribute them to women to provide appropriate instructions to women, particularly in settings where uterotonics have not previously been available.
Supplies	Misoprostol indicative costs: <ul style="list-style-type: none"> ■ Cost per 200 µg tablet: US\$ 0.09–0.52 (13) ■ Containers (such as foil or purse) for protecting misoprostol are also required ■ In some settings, misoprostol has been distributed in advance within clean delivery kits.
Equipment and infrastructure	Minimal
Time	Minimal
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

— Don't know	— Varies	— Large costs	— Moderate costs	— Negligible costs or savings	✓ Moderate savings	— Large savings
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Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

— No included studies	— Very low	— Low	✓ Moderate	— High
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Cost-effectiveness

Judgement

✓ Don't know	— Varies	— Favours comparator	— Probably favours comparator	— Does not favour either	— Probably favours intervention	— Favours intervention
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Equity

What would be the impact of a strategy of advance misoprostol distribution for PPH prevention on health equity?

Research evidence

Misoprostol is relatively inexpensive and widely available in a range of resource settings (low to high). Findings from a qualitative systematic review evaluating prevention and treatment of PPH indicate that providers and women perceive advance distribution of misoprostol to be a useful approach for reducing maternal mortality (as a consequence of PPH) in lower-resource rural communities, especially for women who may not ordinarily attend a health-care facility to give birth (*moderate confidence*) (12).

Additional considerations

The 2015 WHO *State of inequality* report indicates that women who are poor, least educated and who reside in rural areas have lower coverage of health interventions and worse health outcomes than more advantaged women (19). Therefore, reducing maternal morbidity and mortality due to PPH could have a positive impact on health equity and improve outcomes among disadvantaged women. Advance misoprostol distribution is a strategy particularly aimed at preventing PPH in women in more remote or underserved areas.

Reducing the need for additional interventions to treat PPH (such as transfer to hospital, additional uterotonics and blood transfusion) would probably reduce inequities, especially in contexts where health services are covered through out-of-pocket means.

Judgement

—	—	—	—	—	✓	—
Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased

Acceptability

Is a strategy of advance misoprostol distribution for PPH prevention acceptable to key stakeholders?

Research evidence

Findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment (5) (updated in 2020) indicate that both women and providers believe that advance distribution programmes for misoprostol are an effective intervention for preventing PPH (*high confidence*). This finding was particularly apparent among populations in rural areas of LMICs, providing that information on the benefits of misoprostol and instructions for use were clearly explained to childbearing women (*high confidence*) and, in certain contexts, to husbands, mothers-in-law and the wider community (*moderate confidence*). Findings also suggest that misoprostol was perceived to be safe and more practical to use compared to oxytocin (*low confidence*).

The same review also showed that, in some LMICs, providers (including government officials, health-care managers and health professionals) had concerns about the potential misuse of misoprostol in community contexts where it might be used to induce abortion or act as a deterrent to facility-based deliveries (*moderate confidence*).

In addition, a number of providers, largely based in LMICs, felt they needed more information on the effectiveness of misoprostol (*low confidence*) and further guidance on successful implementation strategies for community distribution in LMICs (*moderate confidence*).

Findings from this review also indicate that government officials and regional health-care managers in some LMICs had concerns about the influence of civil society organizations, nongovernmental organizations and private providers in “pushing” misoprostol for other conditions (treatment of PPH) contrary to national guidelines (*low confidence*).

Additional considerations

A number of survey-based studies were identified looking at the potential benefits of advance misoprostol distribution in rural settings of LMICs where the maternal mortality ratio was relatively high (4,5,7,9,20–31). The studies were conducted in Afghanistan, Bangladesh, Ethiopia (two studies), Ghana, Liberia, Madagascar, Mozambique, Nepal, Nigeria (three studies), Pakistan, South Sudan and the United Republic of Tanzania (two studies). In most instances, misoprostol tablets were given to trained community health workers, community health volunteers or TBAs who then supplied the tablets (usually 3 × 200 µg tablets) to pregnant women in community settings during a home visit or antenatal appointment during the eighth month of pregnancy. During the home visit or appointment, women were also given information on PPH, the nature of the misoprostol tablets and how/when to take them, as well as details of potential side-effects. Nearly all of the studies reported high levels of usage, acceptability and coverage with very few safety concerns. One study from Liberia found that 87 of 265 (32.8%) women took the misoprostol tablets after the delivery of the placenta but experienced few or no ill effects from doing so (7).

In a systematic scoping review published in 2019 (32), the authors looked to explore the effect of advance community-based misoprostol distribution programmes on rates of facility delivery, the frequency of mothers taking distributed misoprostol before delivery and any harmful outcomes of such misuse. The review included 14 studies (largely from LMICs in Africa and Asia) consisting of three qualitative studies, seven observational studies and four experimental or quasi-experimental studies. All were graded according to Joanna Briggs Institute (JBI) criteria and were “medium” on average. All seven before-and-after household surveys reported increased facility delivery after the intervention: ranging from 4% to 46% at the end of the intervention when compared to the baseline. The pooled analysis of experimental and quasi-experimental studies involving 7564 women from four studies revealed that there was no significant difference in rates of facility delivery among the misoprostol and control groups (odds ratio [OR] 1.011; 95% CI 0.906–1.129). Self-administration of misoprostol by pregnant women before delivery occurred in four out of six studies reporting this outcome and ranged from 0.01% to 1.8% (a total of 17 women from a population of 11 108). Three studies reported minor adverse effects, but these were deemed to be insignificant and transitory.

The GDG noted the findings from the qualitative systematic review related to the concerns of some stakeholders (including government officials, health-care managers and health professionals) about the potential misuse of misoprostol in community contexts. However, evidence from available trials and advance misoprostol distribution programmes do not support these concerns.

Judgement

— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes
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Feasibility

Is a strategy of advance misoprostol distribution for PPH prevention feasible to implement?

Research evidence

Findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment by women and providers (5) (updated in 2020) suggest the intervention is feasible to implement but may be hampered by limited resources, particularly the availability of experienced, trained staff in LMICs (*high confidence*). Providers also reported that optimal distribution was affected by stock inconsistencies, poor staff morale and infrastructure problems (*low confidence*). In some LMICs, task shifting had been deployed to enhance/facilitate distribution (by TBAs, community health workers and community volunteers) and the perceived success of this strategy appeared to be dependent on close cooperation with health professionals and an environment of mutual trust (*moderate confidence*).

Additional considerations

A 2016 rapid review identified 18 advance misoprostol distribution programmes (research or implementation) in 14 countries in Africa, South Asia and South-East Asia (33). Seven programmes used provision of misoprostol to lay health workers for use at home births they attend, while 11 used advance distribution to women during pregnancy (typically as part of a clean delivery kit) for self-administration or administration by an untrained family or community member. All programmes included some form of additional health worker training, though in most cases lay health workers were already trained by and working for existing programmes. The review identified several health system factors affecting implementation of advance distribution programmes, including:

- Training and supervision of lay health workers and health facility staff to deliver misoprostol
- Service delivery challenges, particularly related to coverage in rural and remote areas
- Supply and procurement of misoprostol
- Monitoring and reporting on misoprostol use and safety
- Lay health workers platforms for distribution
- Financial resources for misoprostol distribution.

Identified community and policy factors affecting advance distribution programmes included:

- Fear that availability of misoprostol in the community will lead to misuse
- Fear that availability of misoprostol in the community will affect facility deliveries
- Policy and political environment, including the need for engaging with multiple stakeholders (such as international policy-makers, national professional organizations, government officials and departments, technical partners, district and community health workers, civil society organizations and end-users).

Identified end-user factors affecting advanced distribution programmes included:

- Acceptability of misoprostol
- Pregnant women's ability to self-administer appropriately
- Importance of information, education and communication.

A 2013 integrative review identified 18 programmes in which misoprostol was used for PPH prevention among women giving birth at home (34). Health workers and TBAs were most commonly the distributors of misoprostol, and self-administration or administration by a TBA were the most commonly used approaches. The review found higher coverage rates among programmes where misoprostol was distributed by TBAs. Incorrect use of misoprostol (that is, consumption before birth) occurred in seven cases across 12 615 users.

A number of survey-based studies were identified looking at the potential benefits of advance misoprostol distribution in rural settings of LMICs where the maternal mortality ratio was relatively high (4,5,7,9,20–31). The studies were conducted in Afghanistan, Bangladesh, Ethiopia (two studies), Ghana, Liberia, Madagascar, Mozambique, Nepal, Nigeria (three studies), Pakistan, South Sudan and the United Republic of Tanzania (two studies). In most instances, misoprostol tablets were given to trained community health workers, community health volunteers or TBAs who then supplied the tablets (usually 3 × 200 µg tablets) to pregnant women in community settings during a home visit or antenatal appointment during the eighth month of pregnancy. During the home visit or appointment, women were also given information on PPH, the nature of the misoprostol tablets and how/when to take them, as well as details of potential side-effects. In most of the studies, the authors concluded that the programmes were effective and feasible, although inconsistent stocks of supplies and the delivery of inadequate information by community health volunteers were highlighted as concerns in Nepal (27).

Judgement

— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes
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Summary of judgements table

Desirable effects	✓ Don't know	— Varies		— Trivial	— Small	— Moderate	— Large
Undesirable effects	✓ Don't know	— Varies		— Large	— Moderate	— Small	— Trivial
Certainty of the evidence	— No included studies			✓ Very low	— Low	— Moderate	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ Probably no important uncertainty or variability	— No important uncertainty or variability
Balance of effects	✓ Don't know	— Varies	— Favours no intervention	— Probably favours no intervention	— Does not favour either	— Probably favours intervention	— Favours oxytocin
Resources required	— Don't know	— Varies	— Large costs	— Moderate costs	— Negligible costs or savings	✓ Moderate savings	— Large savings
Certainty of the evidence on required resources	— No included studies			— Very low	— Low	✓ Moderate	— High
Cost-effectiveness	✓ Don't know	— Varies	— Favours no intervention	— Probably favours no intervention	— Does not favour either	— Probably favours intervention	— Favours intervention
Equity	— Don't know	— Varies	— Reduced	— Probably reduced	— Probably no impact	✓ Probably increased	— Increased
Acceptability	— Don't know	— Varies		— No	— Probably No	✓ Probably Yes	— Yes
Feasibility	— Don't know	— Varies		— No	— Probably No	✓ Probably Yes	— Yes

Summary of findings table

Question: Advance misoprostol distribution/provision to pregnant women for postpartum self-administration compared with usual (or standard) care for PPH prevention for preventing and treating PPH
Setting: Uganda

Reference: Oladapo OT, Blum J, Abalos E, Okusanya BO. Advance misoprostol distribution to pregnant women for preventing and treating postpartum haemorrhage. Cochrane Database Syst Rev. 2020;6:CD009336.

No. of studies	Certainty assessment						No. of patients			Effect		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Advance misoprostol provision to pregnant women for postpartum self-administration	Usual (or standard) care for PPH prevention	Relative (95% CI)	Absolute (95% CI)			
MATERNAL DEATH													
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^c	none	0/150 (0.0%)	0/149 (0.0%)	not estimable		⊕⊖⊖⊖ VERY LOW	CRITICAL	
BLOOD TRANSFUSION													
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^c	none	0/150 (0.0%)	0/149 (0.0%)	not estimable		⊕⊖⊖⊖ VERY LOW	CRITICAL	
SEVERE MATERNAL MORBIDITY (ORGAN FAILURE, HYSTERECTOMY, INTENSIVE CARE UNIT ADMISSION, OR AS DEFINED BY AUTHORS)													
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^c	none	0/150 (0.0%)	0/149 (0.0%)	not estimable		⊕⊖⊖⊖ VERY LOW	CRITICAL	
SEVERE MATERNAL MORBIDITY – PROXY: MATERNAL TRANSFER OR REFERRAL TO A HEALTH FACILITY													
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^{d,e}	none	2/150 (1.3%)	3/149 (2.0%)	RR 0.66 (0.11 to 3.91)	7 fewer per 1000 (from 18 fewer to 59 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL	

No. of studies	Certainty assessment							Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients	Relative (95% CI)	Absolute (95% CI)			
SEVERE MATERNAL MORBIDITY – PROXY: HOSPITAL ADMISSION > 24 HOURS												
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^{d,e}	none	1/150 (0.7%)	RR 0.99 (0.06 to 15.73)	0 fewer per 1000 (from 6 fewer to 99 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL	
USE OF ADDITIONAL UTEROTONICS												
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^{d,e}	none	3/150 (2.0%)	RR 0.74 (0.17 to 3.27)	7 fewer per 1000 (from 22 fewer to 61 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT	
POSTPARTUM ANAEMIA (< 9 G/DL WITHIN 5 DAYS POSTNATAL)												
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^{d,e}	none	6/149 (4.0%)	RR 1.66 (0.62 to 4.44)	27 more per 1000 (from 15 fewer to 139 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT	
SIDE-EFFECT – SHIVERING/CHILLS												
1	randomized trials	serious ^a	not serious	serious ^b	serious ^e	none	75/147 (51.0%)	RR 1.84 (1.35 to 2.50)	233 more per 1000 (from 97 more to 417 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT	
SIDE-EFFECT – FEVER (NOT DEFINED)												
1	randomized trials	serious ^a	not serious	serious ^b	serious ^e	none	40/144 (27.2%)	RR 1.87 (1.16 to 3.00)	127 more per 1000 (from 23 more to 292 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT	

		Certainty assessment						No. of patients			Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Advance misoprostol distribution/provision to pregnant women for postpartum self-administration	Usual (or standard) care for PPH prevention	Relative (95% CI)	Absolute (95% CI)				
SIDE-EFFECT - DIARRHOEA														
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^{d,e}	none	4/147 (2.7%)	1/144 (0.7%)	RR 3.92 (0.44 to 34.64)	20 more per 1000 (from 4 fewer to 234 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT		
SIDE-EFFECT - PLACENTAL RETENTION														
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^{d,e}	none	3/150 (2.0%)	2/149 (1.3%)	RR 1.49 (0.25 to 8.79)	7 more per 1000 (from 10 fewer to 105 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT		
WOMEN NOT USING/RECEIVING MISOPROSTOL AT BIRTH														
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^{d,e}	none	3/150 (2.0%)	6/149 (4.0%)	RR 0.50 (0.13 to 1.95)	20 fewer per 1000 (from 35 fewer to 38 more)	⊕⊖⊖⊖ VERY LOW	NOT PRIORITIZED		
WOMEN NOT USING/RECEIVING MISOPROSTOL CORRECTLY AT BIRTH														
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^{d,e}	none	2/147 (1.4%)	0/143 (0.0%)	RR 4.86 (0.24 to 100.46)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊖⊖⊖ VERY LOW	NOT PRIORITIZED		
INAPPROPRIATE USE (OR MISUSE) OF MISOPROSTOL (AS DEFINED BY AUTHORS)														
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^{d,e}	none	2/150 (1.3%)	0/149 (0.0%)	RR 4.97 (0.24 to 102.59)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊖⊖⊖ VERY LOW	NOT PRIORITIZED		
STILLBIRTH														
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^{d,e}	none	0/150 (0.0%)	1/149 (0.7%)	RR 0.33 (0.01 to 8.06)	4 fewer per 1000 (from 7 fewer to 47 more)	⊕⊖⊖⊖ VERY LOW	NOT PRIORITIZED		

No. of studies	Certainty assessment							No. of patients		Effect		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Advance misoprostol distribution/provision to pregnant women for postpartum self-administration	Usual (or standard) care for PPH prevention	Relative (95% CI)	Absolute (95% CI)			
EARLY NEONATAL DEATH													
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^c	none	0/150 (0.0%)	0/149 (0.0%)	not estimable		⊕⊖⊖⊖ VERY LOW	NOT PRIORITIZED	
NEONATAL DEATH (WITHIN 28 DAYS)													
1	randomized trials	serious ^a	not serious	serious ^b	very serious ^{d,e}	none	0/150 (0.0%)	2/149 (1.3%)	RR 0.20 (0.01 to 4.10)	11 fewer per 1000 (from 13 fewer to 42 more)	⊕⊖⊖⊖ VERY LOW	NOT PRIORITIZED	

CI: confidence interval; **PPH:** postpartum haemorrhage; **RR:** risk ratio

^a Most of the pooled effect provided by studies "B" or "C" but without a substantial proportion (i.e. < 50%) from studies "C".

^b Usual (or standard) care was advance distribution and postpartum self-administration of inactive study drug.

^c Not estimable. Small sample size. Less than 300 participants.

^d Wide CI crossing the line of no effect.

^e Small sample size and/or few events.

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