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REVIEW

Prevention of postpartum hemorrhage in low-resource settings: current perspectives

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Background: Postpartum hemorrhage (PPH) is the leading cause of maternal death in low-income countries and is the primary cause of approximately one-quarter of global maternal deaths. The purpose of this paper is to provide a review of PPH prevention interventions, with a particular focus on misoprostol, and the challenges and opportunities that preventing PPH in low-resource settings presents.

Methods: Using PubMed, we conducted a review of the literature on the randomized controlled trials of interventions to prevent PPH. We then searched PubMed and Google Scholar for non-randomized field trials of interventions to prevent PPH. We limited our review to interventions that are discussed in the current World Health Organization (WHO) recommendations for PPH prevention and present evidence regarding the use of these interventions. We focused our review on nondrug PPH prevention interventions compared with no intervention and uterotonics versus placebo; this review does not decipher the relative effectiveness of uterotonic drugs. We describe challenges to and opportunities for scaling up PPH prevention interventions.

Results: Active management of the third stage of labor is considered the "gold standard" strategy for reducing the incidence of PPH. It combines nondrug interventions (controlled cord traction and cord clamping) with the administration of an uterotonic drug, the preferred uterotonic being oxytocin. Unfortunately, oxytocin has limited application in resource-poor countries, due to its heat instability and required administration by a skilled provider. New heat-stable drugs and drug formulations are currently in development that may improve the prevention of PPH; however, misoprostol is a viable option for provision at home by a lay health care worker or the woman herself, in the interim.

Conclusion: As the main cause of maternal mortality worldwide, PPH prevention interventions need to be prioritized. Increased access to prophylactic uterotonics, regardless of where deliveries occur, should be the primary means of reducing the burden of this complication.

Keywords: PPH prevention, uterotonics, AMTSL, misoprostol, oxytocin

Introduction

Every year more than 14 million cases of obstetric hemorrhage occur, resulting in an estimated 127,000 deaths.[1] Postpartum hemorrhage (PPH), blood loss of 500 mL or more, accounts for the majority of these hemorrhage deaths.[2] PPH is the leading cause of maternal death in low income countries and is the primary cause of approximately one-quarter of global maternal deaths.[3] Among PPH survivors, an estimated 12% will suffer from the consequences of severe anemia.[2]

Several factors contribute to the high PPH mortality estimates. In most developing countries, 50% or more of deliveries are attended by unskilled providers at home.[4] In addition, health facilities are often not adequately staffed or lack medicines that can

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address PPH.[5] These structural barriers are further complicated by difficulties in predicting who will develop PPH. Many women who develop PPH do not present with any of the risk factors typically associated with the complication.[6] Consequently, PPH is an obstetric complication that requires effective preventive interventions, tailored to the diverse needs of women and providers in resource-poor settings.

The purpose of this paper is to present current perspectives on the prevention of PPH, particularly in resource poor-settings, where PPH is the leading cause of maternal mortality.[3] We reviewed historical events and the current evidence related to PPH prevention and highlight the progress in policy and program implementation to reduce this disease. We reviewed the current strategies being implemented to prevent PPH, ranging from active management of the third stage of labor (AMTSL) in health facilities to the use of misoprostol in home births, which was given particular attention. In addition, we looked at challenges to the implementation and scale-up of these interventions, as well as examples of ongoing efforts that could be positions as opportunities to increase access to PPH prevention interventions.

Material and methods

Using PubMed, we conducted a review of the literature on randomized controlled trials (RCTs) of interventions to prevent PPH. We then searched PubMed and Google Scholar for nonrandomized field trials of interventions to prevent PPH. We limited our review to interventions that are discussed in the current World Health Organization (WHO) recommendations for PPH prevention, which we consider to be key interventions, and present evidence on the use of these interventions from 2000 to 2013. The following search terms were used, among others, in varying combinations: "postpartum hemorrhage," "PPH," "PPH prevention interventions," "active management of the third stage of labor," "AMTSL," "controlled cord traction," "cord clamping," "uterine massage," "oxytocin," "ergometrine," "misoprostol," "systematic review," "Cochrane review," "randomized controlled trial," "RCT," "operations research," "low-resource settings," and "developing countries." We assessed the evidence from RCTs of PPH prevention interventions, as well as evidence from field trials and implementation programs. We focused our review on comparisons of nondrug PPH prevention interventions versus no intervention and of uterotonics versus placebo; this review was not intended to decipher the relative effectiveness of uterotonic drugs. The interventions and conventional uterotonic drugs reviewed are those presumed to, either alone or in combination with other drugs, prevent PPH. The nondrug interventions included were AMTSL and the specific components (ie, controlled cord traction, cord clamping, and uterine massage). The conventional uterotonics included were oxytocin, ergot-based alkaloid (ergometrine), and misoprostol. To avoid duplication, we started with systematic reviews (often Cochrane Reviews) conducted since 2000 and then added individual studies conducted after the review. We also searched for other studies not included in the most recent reviews that would meet our search criteria, including peer-reviewed articles, documents in the gray literature, manuals, reports, clinical guidelines, and relevant publications from organizations working to promote PPH prevention, such as the WHO, the International Federation of Gynecology and Obstetrics (FIGO), the International Confederation of Midwives (ICM), as well as the work of many other nongovernmental organizations.

We recognize the barriers to implementation that developing countries may face and have described the challenges to and opportunities for scaling up recommended interventions. We focused specifically on scalability in light of limited access to services and shortages in skilled health care workers and commodities.

Important events in the history of PPH prevention

Figure 1 presents a timeline of the important milestones related to PPH prevention, including discoveries, research publications, policies, and programs. To provide a historical perspective, we started in 1953 with the elucidation of the amino acid sequence of oxytocin, followed by its biochemical synthesis.[7–10] Following these discoveries, a landmark in the history of PPH prevention occurred when the three components of AMTSL were first described in 1962: the administration of a prophylactic uterotonic drug, early cord cutting and clamping, and controlled cord traction.[11] However, it was not until the 1980s that data from an RCT of AMTSL revealed a significant reduction in the incidence of PPH compared with expectant management of the third stage of labor.[12]

More than two decades later, FIGO and ICM released their first statement on AMTSL.[13] Then, recognizing that AMTSL could only be provided by skilled attendants, thus excluding women who deliver at home and limiting the coverage of this intervention, researchers were encouraged with the discovery and potential of a prostaglandin analogue in tablet form (ie, misoprostol).[14] In 2005, the first placebo-controlled trial of misoprostol use for PPH prevention at home births was carried out, with promising results.[15] The findings paved the

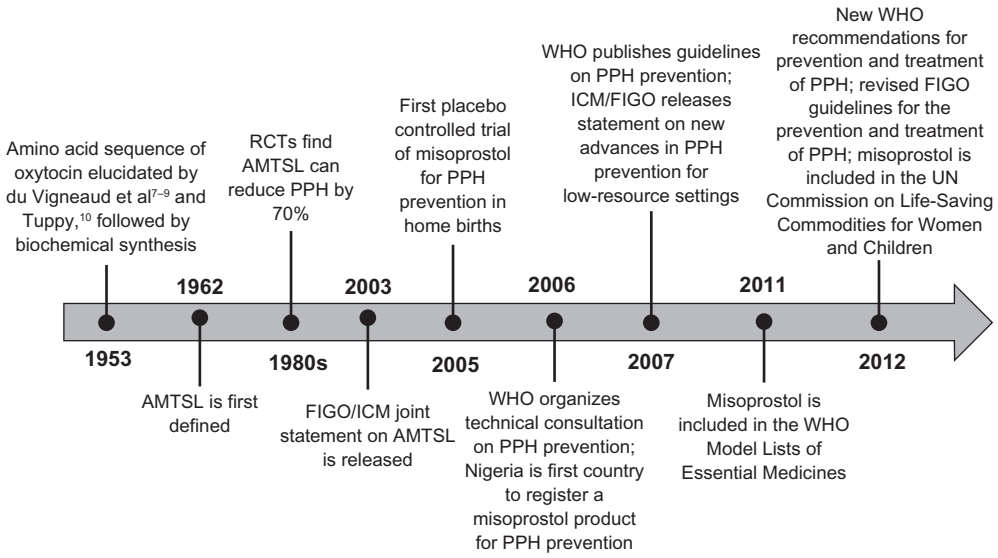

Figure 1 Important events in the prevention of PPH.
Abbreviations: AMTSL, active management of the third stage of labor; FIGO, International Federation of Gynecology and Obstetrics; ICM, International Confederation of Midwives; PPH, postpartum hemorrhage; RCT, randomized, control trials; UN, United Nations; WHO, World Health Organization.

way for women with limited or no access to health facilities to have a PPH prevention intervention delivered at home, but the use of misoprostol for this purpose also introduced policy and program-related challenges. A considerable impediment was that at the time, misoprostol was an off-patent drug that was only on the market for the treatment of gastric ulcers, and in many developing countries, a product needs to be registered for the specific indication for which it is marketed. In 2006, the WHO organized a technical consultation meeting to review the evidence for interventions to prevent and treat PPH; the following year, the WHO published recommendations based on this meeting, which included support of the use of misoprostol for PPH prevention in the absence of oxytocin but not at home births.[16] By that time, individual country efforts to take advantage of misoprostol for PPH prevention had already started. In 2006, Nigeria was the first country in the world to register the use of misoprostol for PPH prevention.[17] Five years later, another important landmark policy reform occurred, which was the inclusion of misoprostol in the WHO Model List of Essential Medicines in 2011,[18] followed by a revision of the recommendations for the prevention and treatment of PPH, in 2012.[3] Around this time, the evidence regarding the impact of misoprostol in reducing PPH became clear, and its inclusion in the United Nations Commission on Life-Saving Commodities for Women and Children in 2012 was a testament to its contribution.[19] The nonprofit organizations and professional associations with maternal health programs that attend largely to rural populations have recently issued a call for the scaling up of PPH prevention programs that include the use of misoprostol.[20,21] In addition, programs to strengthen labor and delivery practices continue to take place.[22]

Current evidence on interventions to prevent PPH

WHO recommendations

Table 1 presents a description of the key PPH prevention interventions and the WHO recommendations with respect to each. AMTSL is considered the "gold standard" strategy to reduce the incidence of PPH. It combines nondrug interventions with the administration of an uterotonic drug. The AMTSL preferred uterotonic is oxytocin,[3] and the relative importance of other components has changed over time. Even though the WHO strongly recommends AMTSL, it also provides recommendations on the relative importance of each component. For example, the practice of controlled cord traction has a weak recommendation level, only to be practiced if small reductions in blood loss or durations of the third stage of labor are perceived to be beneficial (Table 1).[3] Cord clamping is now subdivided into late and early cord clamping; the latter is no longer recommended. Similarly, sustained uterine massage is no longer recommended in women who receive prophylactic oxytocin, although it was initially a common component of AMTSL. Instead, it is recommended that abdominal tonus assessment be conducted by a skilled provider, for all women (Table 1). However, the FIGO guidelines (2012) for the prevention of PPH in low-resource settings defines AMTSL as: administration of

Table 1 Key interventions to prevent postpartum hemorrhage

Intervention	WHO recommendations
Active management of the third stage of labor	Involves a combination of interventions, including: cord clamping and cutting; controlled cord traction; and use of an uterotonic agent Specific recommendations for each component of the active management of the third stage of labor are provided below
Controlled cord traction	In settings where skilled birth attendants are available, controlled cord traction is recommended for vaginal births if the care provider and the parturient woman regard a small reduction in blood loss and a small reduction in the duration of the third stage of labor as important (weak recommendation, high-quality evidence) In settings where skilled birth attendants are unavailable, controlled cord traction is not recommended (strong recommendation, moderate-quality evidence) Only skilled provider can administer
Cord clamping	Late cord clamping (in 1 to 3 minutes) is recommended for all births while initiating simultaneous essential newborn care (strong recommendation, moderate-quality evidence) Early cord clamping (less than 1 minute) is not recommended unless the neonate is asphyxiated and needs to be moved immediately for resuscitation (strong recommendation, moderate-quality evidence) Only skilled provider can administer
Uterine massage	Sustained uterine massage is not recommended as an intervention to prevent PPH in women who have received prophylactic oxytocin (weak recommendation, low-quality evidence) Postpartum abdominal uterine tonus assessment for early identification of uterine atony is recommended for all women (strong recommendation, very low-quality evidence) Only skilled provider can conduct routine uterine tone assessment. Women can self-administer continuous uterine massage in the absence of uterotonics
Oxytocin	Oxytocin (10 IU, IV/IM) is the recommended uterotonic drug for the prevention of PPH (strong recommendation, moderate-quality evidence) Only skilled provider can administer
Ergometrine	In settings where oxytocin is unavailable, the use of other injectable uterotonics, like ergometrine/methylergometrine or fixed drug combinations of oxytocin and ergometrine) is recommended (strong recommendation, moderate-quality evidence) Only skilled provider can administer
Misoprostol	In settings where oxytocin is unavailable, oral misoprostol (600 μg) is one of the recommendations (strong recommendation, moderate-quality evidence) Skilled and unskilled providers can administer; women can self-administer as well

Note: Data from WHO.[3]
Abbreviations: IM, intramuscular; IV, intravenous; PPH, postpartum hemorrhage; WHO, World Health Organization.

oxytocin, controlled cord traction, and uterine massage after the delivery of the placenta.[23]

Uterotonic drugs, such as oxytocin, ergometrine, and misoprostol, are strongly recommended (Table 1). Some researchers feel that oxytocin, which has minimal side effects and is safe to use among women with hypertension and preeclampsia, is all that is needed.[24] Ergometrine, which has proven to be a powerful drug in reducing PPH, especially when combined with oxytocin, is known to be associated with serious side effects, such as severe vomiting and hypertension, and retained placenta when given intravenously.[25] Misoprostol is similarly associated with side effects, but none have been shown to threaten the life of the mother or newborn.[26] Its use is associated with significantly higher incidences of shivering and fever among mothers compared with placebo.[26] Misoprostol has had recent success because of its heat stability and multiple routes of administration,[27] which is critical in resource-poor countries.

It is important to note that all of these recommended interventions, with the exception of misoprostol administration, are to be provided by skilled providers; as a result, most of them are available only to women who attend facility deliveries. Large numbers of women living in countries with high maternal mortality deliver at home.[4] Thus, the recent recommendation supporting the inclusion of community health workers in the provision of misoprostol for the prevention of PPH was welcomed by the safe motherhood community.[3,28]

Randomized controlled trial data

The current recommendations with regards to PPH prevention are based largely on RCT evidence. The clinical evidence of the initial AMTSL package from the 1980s showed that PPH could be reduced by 70% compared with expectant management.[29] The most recent Cochrane review of active versus expectant management of the third stage of labor includes seven studies (Table 2), and the results indicate a significant reduction in the risk of PPH.[29]

Controlled cord traction was an initial component of AMTSL, but since 2000, three RCTs assessing AMTSL with and without cord traction were published, all of which found a nonsignificant difference in the risk of PPH (Table 2).[30–32] Regarding cord clamping, it was initially thought that early

Table 2 Randomized controlled trials testing interventions to prevent postpartum hemorrhage against placebo or no intervention

Author (year)	Study design/participants	Variable(s) of interest	Results
Active management of the third stage of labor			
Begley et al: Active versus expectant management for women in the third stage of labour (Review)[29]	Cochrane review of randomized and quasi-randomized controlled trials Included seven studies (N=8,247 women)	Active management of the third stage of labor versus expectant in hospital setting	Significant reduction in the risk of blood loss ≥1,000 mL (average RR 0.34; 95% CI 0.14–0.87), N=4,636 from three studies)
Controlled cord traction			
Althabe et al: A pilot randomized controlled trial of controlled cord traction to reduce postpartum blood loss[30]	Individually randomized superiority trial N=204 women with imminent vaginal delivery of singleton baby in two maternity hospitals in Uruguay	Active management of the third stage of labor with controlled cord traction versus hands-off method, where controlled cord traction or fundal pressure was not applied	Nonsignificant difference in median blood loss between groups (–28.2 mL; 95% CI –92.3 to 35.9; *P*=0.126) Incidence of acute PPH and severe PPH was 26% and 42% lower, respectively, in the controlled cord traction group, but the finding was not statistically significant
Gulmezoglu et al: Active management of the third stage of labour with and without controlled cord traction: a randomized, controlled, noninferiority trial[32]	Multicenter, noninferiority RCT N=23,681 women expecting to deliver singleton babies vaginally	Active management of the third stage of labor with and without controlled cord traction	Non-significant difference in risk of blood loss greater than 1,000 mL (RR 1.09; 95% CI 0.91–1.31) Omission of controlled cord traction has very little effect on risk of severe hemorrhage
Deneaux-Tharaux et al: Effect of controlled cord traction as part of the active management of the third stage of labor on postpartum hemorrhage: multicenter RCT (TRACOR)[31]	Multicenter RCT N=4,088 women aged 18 or more with a singleton fetus at 35 or more weeks of gestation and planned vaginal delivery	Active management of the third stage of labor with and without controlled cord traction	Incidence of acute PPH did not differ between the controlled cord traction arm and standard placenta expulsion arm (RR 0.95; 95% CI 0.79–1.15)
Cord clamping			
McDonald et al: Effects of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes: updated (Review)[33]	Cochrane review of RCTs comparing early and late cord clamping Included 15 RCTs (N=3,911 women and infant pairs) Included five RCTs with data on PPH (N=2,260 for acute PPH and N=2,066 for severe PPH)	Early cord clamping (30–60 seconds after birth of the baby) versus late cord clamping (2–3 minutes after birth)	There were no significant differences between early versus late cord clamping groups in terms of acute PPH (RR 1.17; 95% CI 0.94–1.44) or severe PPH (RR 1.0; 95% CI 0.65–1.65)
Uterine massage			
Chantrapitak et al: The efficacy of lower uterine segment compression for prevention of early postpartum hemorrhage after vaginal delivery[35]	RCT N=686 mothers with singleton pregnancy, gestational ages between 28 and 42 weeks in a Bangkok hospital	Lower uterine segment compression versus nothing, in addition to oxytocin, clamping and cutting of umbilical cords, and controlled cord traction	Those who receive lower uterine segment compression had statistically significantly lower incidence of PPH (RR 0.43; 95% CI 0.21–0.90)
Hofmeyr et al: Uterine massage for preventing postpartum hemorrhage (Review)[34]	Cochrane review of RCTs comparing uterine massage after birth and before or after delivery of the placenta, or both, to reduce PPH Included two RCTs (N=2,164)	Uterine massage before birth versus after versus both versus no massage	The average effect of uterine massage using a random-effects model found no statistically significant differences between groups (average RR 1.14; 95% CI 0.39–3.32)

(*Continued*)

Table 2 (*Continued*)

Author (year)	Study design/participants	Variable(s) of interest	Results
Oxytocin			
Cotter et al: Prophylactic oxytocin for the third stage of labor (Review)[36]	Cochrane review of RCTs or quasi-RCTs investigating oxytocin versus no uterotonic Seven studies N≈3,000 women (trial sample size ranged from 10 to 1,000 women with vaginal delivery) Trial carried out within context of expectant management of third stage of labor for two studies, within active management for one study, and context unclear for remaining four studies	Intramuscular oxytocin in three studies Intravenous oxytocin in four studies Dose varied from 3–10 IU of oxytocin	Oxytocin use halved the risk of acute PPH (RR 0.50; 95% CI 0.43–0.59) Oxytocin use decreased risk of severe PPH (RR 0.61; 95% CI 0.44–0.87)
Güngördük et al: Using intraumbilical vein injection of oxytocin in routine practice with active management of the third stage of labor: RCT[37]	Double-blind RCT N=412 women with vaginal delivery and no risk for PPH	Intraumbilical administration of 20 IU oxytocin diluted with 26 mL of saline or 30 mL saline alone for placebo group Active management of third stage of labor used with both groups	Compared with placebo group, mean estimated blood loss was significantly lower ($P<0.001$) in women treated with oxytocin (195.3 ± 81.0 mL) compared with placebo group (288.3 ± 134.1 mL)
Puri et al: Effects of different doses of intraumbilical oxytocin on the third stage of labor[38]	RCT N=125 primigravidas with singleton pregnancy at term and spontaneous onset of delivery	Intraumbilical administration of 50 mL of saline solution alone, 10 IU oxytocin plus 50 mL saline solution, 20 IU oxytocin plus 50 mL saline solution, or 30 IU of oxytocin plus 50 mL of saline solution compared with no saline or oxytocin (control)	Compared with control group, blood loss (mL) was greatest in group with only saline solution (193.00 ± 11.45; 95% CI 188.2–197.7) and least in group with saline plus 30 IU oxytocin (142.20 ± 32.32; 95% CI 90.35–107.25) Compared with saline solution alone, blood loss was significantly reduced in the 10 IU ($P<0.001$), 20 IU ($P<0.001$), and 30 IU ($P<0.001$) group Blood loss was not significantly different between 10 IU and 20 IU, but was significantly different between 20 IU and 30 IU
Ergometrine			
Liabsuetrakul et al: Prophylactic use of ergot alkaloids in the third stage of labour (Review)[39]	Prophylactic use of ergot alkaloids in third stage of labor versus a placebo or no treatment Six studies (RCT or quasi-RCT) N=3,941 women who delivered vaginally	Intravenous administration of ergot alkaloids in four studies with dosage varied 0.2 mg to 0.5 mg Oral administration of 0.4 mg ergot alkaloids in one study Administration in third stage of labor for all studies	Significant decrease in mean blood loss (mean difference –83.03 mL; 95% CI –99.39 to –66.66 mL) Significant reduction of PPH of at least 500 mL (RR 0.38; 95% CI 1.03–6.57)
Misoprostol			
Oladapo: Misoprostol for preventing and treating postpartum hemorrhage in the community: a closer look at the evidence[40]	Summary of the current evidence regarding the safety of misoprostol and its effectiveness in treating PPH Included three RCTs	Misoprostol (600 μg oral or sublingual) versus placebo	Meta-analysis revealed significant reduction in the reduction of acute PPH (RR 0.76; 95% CI 0.67–0.86) and severe PPH (RR 0.59; 95% CI 0.42–0.82)

Tuncalp et al: Prostaglandins for preventing postpartum hemorrhage (Review)[42]	Cochrane review to assess the effects of prophylactic prostaglandin use in the third stage of labor 72 RCTs included (N=52,678 women). Eight RCTs investigated misoprostol (600 µg oral or sublingual) specifically (N=6,886)	Prostaglandin versus placebo	Oral misoprostol findings were not totaled due to significant heterogeneity (seven trials, N=6,225 women) Sublingual misoprostol was associated with significantly lower incidence of severe PPH (RR 0.66; 95% CI 0.45–0.98) (one trial, N=661 women) Oral or sublingual misoprostol shows promising results when compared with placebo in reducing blood loss after delivery
Olefile et al: Misoprostol for prevention and treatment of postpartum hemorrhage: a systematic review[41]	Review of evidence regarding misoprostol for PPH prevention and treatment Included three RCTs (N=2,346)	Misoprostol versus placebo	Meta-analysis of three RCTs revealed nonsignificant reduction in incidence of acute PPH (RR 0.65; 95% CI 0.40–1.06)

Abbreviations: CI, confidence interval; PPH, postpartum hemorrhage; RCT, randomized controlled trial; RR, relative risk.

cord clamping was best, but recent findings indicate that the timing is not critical.[3] In 2013, the Cochrane Collaboration researchers updated a previous review on the subject, and their findings confirmed that there are no significant differences in the risk of PPH between early and late cord clamping.[33] Uterine massage, although not officially in the initial AMTSL package, was often included.[3] However, a Cochrane review of two RCTs comparing uterine massage after birth and before or after the delivery of the placenta for the prevention of PPH found the differences between groups to be insignificant.[34] In contrast, the efficacy of lower uterine segment compression versus nothing, in addition to oxytocin, cutting and clamping of the umbilical cord, and controlled cord traction, was found to be associated with a significantly lower incidence of PPH.[35]

Table 2 also presents the recent clinical evidence on the conventional uterotonics, demonstrating their importance in the prevention of PPH. A recent review of seven RCTs investigating the efficacy of oxytocin, three with intramuscular (IM) and four with intravenous (IV) preparations, showed that this uterotonic can significantly reduce the risk of PPH.[36] In addition to the IM and IV preparations, two RCTs investigating the intraumbilical administration of oxytocin also found significant reductions in blood loss when compared with a control saline solution.[37,38] Collectively, the results from these studies make it clear why oxytocin is the preferred uterotonic for PPH prevention.

In terms of the other uterotonics, a 2011 review of ergot alkaloids containing six studies (RCTs and quasi-RCTs) found a significant reduction of PPH when these were administered in the third stage of labor.[39] Regarding misoprostol, three recent reviews of RCTs comparing it to a placebo were identified, two published in 2012 and one in 2013.[40–42] Results of these reviews showed both significant reductions and nonsignificant reductions of PPH. The inconsistencies in the results could be due to the fact that misoprostol was assessed in different doses and routes and also that the individual studies' inclusion criteria varied. The Cochrane review included 72 RCTs that assessed the effects of prophylactic prostaglandin use versus a placebo, eight of which assessed 600 µg oral or sublingual misoprostol (Table 2). Based on data from one trial, the authors of the review concluded that sublingual misoprostol was associated with significant reductions in the incidence of PPH. The data from seven trials on oral misoprostol were not totaled due to heterogeneity, but the authors concluded that compared with a placebo, oral misoprostol shows promising results.[42] Another 2012 meta-analysis of three RCTs investigating

oral or sublingual misoprostol sound significant reductions in both acute and severe PPH.[40] An even more recent meta-analysis of three RCTs showed that misoprostol does not provide significant reductions in the incidence of PPH when compared with placebo.[41] Of the three RCTs included in these two latest reviews from 2012 and 2013, two of the RCTs were the same,[15, 43] while one was different.[44,45] Two seminal studies that were included showed a reduction in PPH of 24%[45] and 47%[15] in home births. Thus, factoring in the findings from the abovementioned reviews, all of which showed reductions in the risk of PPH, even if nonsignificant, it is understandable that the WHO ultimately supported the use of misoprostol in the absence of other uterotonics.

Nonrandomized data

Assessment of the nonrandomized data on the interventions to prevent PPH supports the clinical evidence from the RCTs. A quasi-experimental study of AMTSL in Vietnam (Table 3) showed similar levels of reduction in PPH to those found in the RCTs.[46] An analysis of the independent or combined effect of uterotonic agents, controlled cord traction, and uterine massage from hospital-based data in four countries also showed similar results to the RCTs.[47] No recent nonrandomized or field trials were found reporting on the individual components of AMTSL, nor for oxytocin or ergometrine use in PPH prevention. On the contrary, evidence was found on the use of misoprostol to prevent PPH in facilities and home births.

All of the nonrandomized studies with blood loss and/or acute or severe PPH as outcomes showed that misoprostol use in the third stage of labor can significantly reduce PPH (Table 3). The evidence demonstrates that misoprostol can be effective in the prevention of PPH in home births.[48-50] These findings are especially important for developing countries, which contribute the majority of PPH morbidity and mortality, where skilled attendance at delivery is limited, and where the use of the other two uterotonics is more challenging.[51]

Challenges in scaling up proven interventions

When considering scaling up PPH prevention interventions, it is important to consider where deliveries are occurring. Approximately 46% of all births worldwide take place outside of an institutional setting, attended by a traditional birth attendant, a relative, or no one.[52,53] As previously mentioned, all WHO-recommended interventions other than misoprostol administration require a skilled birth attendant, and many require a facility-based delivery.[3] One strategy for increasing access to these life-saving interventions is to encourage facility-based delivery, especially during prenatal care. However, one must keep in mind the limited number of skilled providers in settings where the most at-risk women deliver.[4]

In fact, it is in these high maternal mortality settings where the shortage of trained health providers is most acute. For example, 57 countries, many of which are among the least developed countries, have a shortage of approximately 2.4 million physicians, nurses, and midwives. In sub-Saharan Africa specifically, their health care workforce shortage is so severe that they have only 1.3% of the world's skilled providers, but 25% of the global burden of disease.[54] Most mortality from PPH would be eliminated if women had access to a skilled birth attendant, yet only 35% of births are attended by a skilled health worker in the least-developed countries.[55] It is estimated that the coverage of skilled attendance at birth is improving at a rate of less than 0.5% per year,[56] thus it will be many years until we see adequate coverage at delivery; alternative solutions are needed.

For many developing countries, poor storage conditions and deficient public sector supply chains also contribute to the limited access to and utilization of uterotonic drugs. The storage of oxytocin and ergometrine can be particularly challenging, due to their instability in high temperatures and sensitivity to light.[51,57] Additionally, because these two drugs are only available in injection form, their administration is limited to skilled providers. Finally, in some settings where oxytocin and ergometrine are accessible, procurement of unregistered drugs may be prolific and the quality of the drugs may be compromised. For example, in Ghana, researchers found 89% (N=90) of all ampoules of oxytocin and ergometrine tested did not meet the specifications for the active ingredient, which was not a result of being expired; this problem was present in both the public and private sector.[58] On the other hand, misoprostol is reportedly more stable, available in tablet form, and can be provided through multiple routes of administration.[59] However, all uterotonics can be exposed to health system failures, such as the case of oxytocin in Tanzania and Ethiopia, where the drugs were available but not properly distributed to health facilities.[60,61]

Even when available, uterotonics are not always used consistently to prevent PPH. A survey of 15 tertiary level facilities (including 452 vaginal deliveries) conducted by the Global Network for Perinatal and Reproductive Health showed that prophylactic oxytocin was used in 44% of the cases and was the least used of the three components of AMTSL assessed (use of early cord clamping was 79% and use of controlled cord traction was 70%).[62] For home births

Table 3 Nonrandomized field trials testing interventions to prevent postpartum hemorrhage against no intervention

Author (year)	Study design/participants	Variable(s) of interest	Results
Active management of the third stage of labor			
Tsu et al: Reducing postpartum hemorrhage in Vietnam: assessing the effectiveness of active management of third-stage labor[46]	Quasi-experimental design Active management of third stage of labor was introduced for all births attended by government midwives in one district Standard practice without active management of third stage labor was continued in three nearby districts N=3,607 women	Active management of third-stage labor versus standard practice without active management of third stage labor	Active management of third stage labor was associated with a 34% reduction in PPH incidence when cases with first-stage oxytocin augmentation were excluded (OR 0.66; 95% CI 0.45–0.98)
Sheldon et al: How effective are the components of active management of third stage of labor?[47]	Secondary data were analyzed from 39,202 hospital-based births in four countries Logistic regression to assess the independent and combined effectiveness of prophylactic administration of uterotonic agent, controlled cord traction, and uterine massage N=39,184 women with vaginal delivery	Oxytocin (10 IU or 5 IU) was administered intramuscularly or intravenously following delivery of baby in one clinical regimen versus no oxytocin administered for the other clinical regimen Controlled cord traction and uterine massage were provided at the discretion of each site in accordance with standard practices for both regimens	Controlled cord traction significantly reduced hemorrhage (≥700 mL) risk by nearly 50% as compared with no AMTSL components (OR 0.53; 95% CI 0.42–0.66) Uterine massage was associated with increased hemorrhage risk (≥700 mL), but the differences were only statistically significant for those receiving controlled cord traction plus massage (OR 1.66; 95% CI 1.31–2.10) Controlled cord traction reduced acute PPH by 66% when oxytocin was administered intramuscularly (OR 0.33; 95% CI 0.25–0.45), but had no benefit when oxytocin was administered intravenously (OR 1.13; 95% CI 0.43–2.96) No differences in relative risks of blood loss ≥700 mL between intravenous and intramuscular oxytocin when combined with controlled cord traction (OR 1.21; 95% CI 0.60–2.46) Route of oxytocin was only important when it was the only intervention provided; intravenous administration reduced hemorrhage risk (≥700 mL) by 76% as compared with intramuscular administration (OR 0.24; 95% CI 0.12–0.50)
Misoprostol			
Hashima et al: Oral misoprostol for preventing postpartum hemorrhage in home births in rural Bangladesh: how effective is it?[50]	Nonrandomized community trial Study purpose is to investigate whether single dose of 400 μg misoprostol orally could prevent PPH in a community home-birth setting in Bangladesh N=2,017 pregnant women who delivered at home	Administration of 400 μg misoprostol immediately after birth compared to no specific intervention	The incidence of primary PPH was found to be lower in the intervention group (1.6%) than the non-intervention group (6.2%) ($P<0.001$) After adjusting for confounding factors, risk of PPH was 81% lower among women who took misoprostol compared with women who did not (RR 0.19; 95% CI 0.08–0.48)
Mir et al: Helping rural women in Pakistan to prevent postpartum hemorrhage: a quasi experimental study[49]	Quasi-experimental design Study purpose is to assess acceptability of providing misoprostol tablets to pregnant women to prevent PPH in the rural community setting in Pakistan N=1,490 pregnant women	Administration of 600 μg misoprostol in context of TBA administered clean delivery kit versus clean delivery kit without misoprostol	Women who took misoprostol correctly were less likely to report having excessive bleeding after delivery (RR 0.43; 95% CI 0.29–0.64)

(*Continued*)

Table 3 (*Continued*)

Author (year)	Study design/participants	Variable(s) of interest	Results
Hundley et al: Should oral misoprostol be used to prevent postpartum hemorrhage in home-birth settings in low-resource countries? A systematic review of the evidence[48]	Review of evidence on oral misoprostol use compared to placebo or no treatment in a home-birth setting Included ten studies from six studies (two RCTS and four nonrandomized trials)	Oral misoprostol compared with placebo or no treatment in a home-birth setting in low-resource countries	Use of oral misoprostol associated with a significant reduction in incidence of PPH (RR 0.58; 95% CI 0.38–0.87), need for additional uterotonics (RR 0.34; 95% CI 0.16–0.73), and referral for PPH (RR 0.49; 95% CI 0.37–0.66)

Abbreviations: AMTSL, active management of the third stage of labor; CI, confidence interval; PPH, postpartum hemorrhage; RCT, randomized controlled trial; RR, relative risk; TBA, traditional birth attendant; OR, odds ratio.

without a skilled provider, misoprostol has been distributed using a variety of approaches with or without a safe delivery kit, including distribution at antenatal care visits, at household visits by community health workers during pregnancy, at home births assisted by traditional birth attendants, and in some instances, through a combination of these methods.[63] None of these approaches are without challenges related to access and utilization of the drug. For example, antenatal care distribution is only effective in increasing access to this drug in those settings where the majority of women who will deliver at home also attend antenatal care. Furthermore, if advanced distribution of misoprostol requires a specific gestational age among eligible women (eg, in Mozambique, this is 28 weeks gestation; in Bangladesh, this is 32 weeks),[64,65] only those attending antenatal care after the required gestational age would receive the drug and be able to use it in home births.

Separate from the interventions themselves is the health care system in which these interventions are being implemented. The continuum of care is an important consideration because these interventions in isolation will likely not be enough to prevent maternal morbidity and mortality. These interventions are not a replacement for a weak health care infrastructure and limited health care personnel, which must not be forgotten in this discussion of PPH prevention interventions.

The implementation of effective approaches is also dependent on the timely translation of research findings into policies and programs, which remains a considerable barrier in accelerating PPH prevention efforts. In general, the translation of research into clinical practice is often conceptualized as proceeding from awareness through acceptance to adoption.[66] However, decades may pass before research findings are integrated into guidelines and routine clinical practice (see Figure 1). There is no agreement or set of rules among policy makers regarding the amount of evidence needed (ie, number and type of studies) to prompt changes in policies and programs. As mentioned before, by 2007, there was only one RCT published on the use of misoprostol in home births, which prompted Mathai et al to express, after the 2007 release of the WHO guidelines, that there was "insufficient evidence for the safe use of misoprostol by lay providers in nonfacility settings."[67] Nonetheless, based solely on the evidence of its efficacy in clinical settings and encouraged by the potential impact that misoprostol could have in the absence of oxytocin, many countries had already begun conducting operations research to test its safety, feasibility, and acceptability for home births, even before consensus was reached and the official guidelines were in place.[68,69] Eventually, a placebo-controlled RCT with

traditional birth attendants was conducted, from 2006 to 2008, in Pakistan.[45] Similar to the history of misoprostol, but with less debate, AMTSL was first described in 1962,[11] but the first RCT comparing AMTSL with expectant management was not done until 1988,[12] and the official guidelines and policies were not adapted until later,[13] after many countries had already begun to incorporate this practice. The evidence of the relative importance of its components has only become available in the last 3 years, prompting the WHO to review its recommendations (see Table 1). Finally, the challenges in the use of evidence to recommend improvements in the quality of care are further complicated by the delays in provider uptake of practices based on new knowledge. Even when health providers recognize and accept guidelines, they may fail to adopt them,[70] and PPH prevention efforts are no exception.[62]

As noted, the translation of research into policy is often a long and inconsistent process, and the prioritization of a health intervention based solely on costs or cost-effectiveness is an equally challenging proposition. However, in resource-poor settings, the reduction of maternal mortality in the most cost-effective way possible should be a priority to policy makers.[71] In a modeling exercise, the prevention of PPH with advanced distribution of misoprostol was found to be very cost-effective in resource-poor settings, relative to other maternal-health interventions included in the WHO Mother-Baby Package, only preceded by family planning and safe abortion.[72] The cost of each intervention recommended by the WHO might differ due to the cost of each uterotonic.[67] The costs of services also depend on the level of health facility and provider involved. However, given that PPH is the main cause of maternal death, saving lives with any PPH prevention intervention is an effective way to reduce overall maternal mortality, which is the goal of every developing country, in accordance with the United Nations Millennium Development Goal (MDG) 5. An economic assessment of the reduction of PPH in developing countries estimated that the consistent use of a conventional uterotonic in every birth could avert 41 million cases of PPH, resulting in an estimated 1.4 million lives saved.[73] Specifically with regard to misoprostol, an article utilizing modeling techniques determined that misoprostol use for PPH prevention is a cost-effective intervention that could reduce maternal deaths by approximately 38%.[74]

Opportunities in PPH prevention

Evidence to action

One of the greatest opportunities in PPH prevention is the fact that the currently available evidence is sufficient to establish policies and programs that will increase access to effective interventions in low-resource settings. In order to leverage this opportunity, countries must establish a supportive national policy, which starts with the adoption of national guidelines for PPH prevention that reflect the latest research and the most recent WHO recommendations.[3,20] Early on, it is important to identify local champions who will engage policy makers and clinicians.[75] With respect to misoprostol, countries must register it for PPH prevention and ensure its inclusion on the national Essential Medicines List.[20] The next step for any of the interventions is to secure adequate funding in the national budget to ensure the consistent availability of the drugs and the training of health care providers.[20] With regards to misoprostol, correct use by community health workers and women could be increased if misoprostol is procured in indication-specific packaging, with 600 µg packets for PPH prevention,[69] and if PPH prevention information is included as part of information, education, and communication (IEC) mass media campaigns. Another crucial step is the building of community awareness and demand for services and drugs, which will help to ensure the success of any of the PPH prevention interventions, home- or facility-based. Specifically related to the community-based distribution of misoprostol, several countries have conducted successful pilot projects, and some, including Ghana, Nepal, Niger, and Bangladesh, are currently working to scale-up misoprostol access.[20,28,76,77] Country-to-county regional exchanges involving countries that have already begun to change and implement national PPH prevention policies would provide a great opportunity to share experiences and best practices.[75]

Moving from evidence to action, particularly with regard to misoprostol, is an important next step in improving PPH prevention that needs to be prioritized in low-resource countries.[75] Involving community-based and lay providers, to the extent the evidence allows, should be an integral part of this step.[28] Community health workers are being engaged more regularly in task-shifting strategies to provide basic health services, including the prevention of PPH.[63,78,79] In a recent integrative review of 18 programs using lay health care workers to provide misoprostol via advanced distribution or at-delivery distribution, Smith et al found that high coverage and use of misoprostol can be achieved via multiple routes of distribution.[63] In addition, very low rates of incorrect use were found.[63]

New PPH prevention interventions

Other opportunities are on the horizon with regard to new drug formulations/drugs and delivery mechanisms. Oxytocin is the preferred drug for preventing and managing

PPH.[3] However, in its current formulation, oxytocin is not heat stable and therefore an impractical intervention in many low-resource settings where extreme heat is coupled with limited access to refrigeration.[51] Yet it is in these low-resource settings that we see the majority of maternal deaths; therefore, research on oxytocin formulations that are heat stable is paramount. Two research teams are currently leading efforts in this field.[80] A team at Monash University, Australia is working to develop oxytocin for aerosol delivery,[81] and this formulation would allow women to inhale oxytocin immediately after childbirth, with no refrigeration of the product required. A nonprofit pharmaceutical development group in the Netherlands is attempting to stabilize oxytocin under tropical conditions.[82]

Another way to potentially increase access to oxytocin is to diversify its route of delivery. Oxytocin in the Uniject™ auto-disable injection system (Uniject; BD Biosciences, Franklin Lakes, NJ, USA) is comprised of a plastic, nonreusable, disposable syringe that is prefilled with a single dose of 10 international units (IU) of oxytocin in 1 mL. Given its simple design and safety features, Uniject can be used by lay health workers, which is the reason oxytocin in Uniject is an important innovation for resource-poor settings.[83] Oxytocin in Uniject is produced by an Argentine pharmaceutical distributor that has regulatory approval in eight countries in Latin America. Though it is not yet broadly available, access to oxytocin in Uniject would be particularly important in countries where human resources are limited and where task-shifting to lower cadres of health professionals is necessary.[84] Field studies in several countries have demonstrated the acceptability of oxytocin in Uniject among health workers with less training, due to its ease of use.[85–87] The oxytocin in Uniject is not heat stable, but the product packaging provides a straightforward time-temperature indicator to allow health workers to monitor heat exposure.[84] Given the early success of oxytocin in Uniject, the WHO has amended its Model List of Essential Medicines to include oxytocin in Uniject. However, the path to the expanded availability of oxytocin in Uniject will require a concurrent increase in demand and supply to counter the challenges of low-volume/high-price production.[84]

Another recent innovation in the prevention of PPH is carbetocin, a long-acting oxytocin agonist, which mimics the action of oxytocin and helps to reduce blood loss.[88] Carbetocin is currently indicated for the prevention of uterine atony after delivery by cesarean section in spinal or epidural anesthesia in 23 countries, but it is not approved for vaginal births. However, it has had proven success in the prevention of PPH, due to its longer duration of action and demonstrated fewer side effects in several studies.[88] Further research is necessary to determine the cost effectiveness of carbetocin as a uterotonic agent.[88] It is also important to assess the feasibility and acceptability of carbetocin in the prevention of PPH in vaginal deliveries in low-resource settings. Fortunately, in the 2012 Annual Technical Report of the WHO Special Program of Research, Development and Research Training in Human Reproduction, plans were announced for a multicenter, controlled trial in 2014 that will compare a new heat-stable formulation of carbetocin with oxytocin, for use in low- and middle-income countries.[89]

Another intervention that presents an opportunity for preventing PPH in home births but that has limited evidence of effectiveness is the home-based life-saving skills (HBLSS) package. HBLSS is "a community- and competency-based program that aims to reduce maternal and neonatal mortality by increasing access to basic life-saving measures within the home and community and by decreasing delays in reaching referral facilities where life threatening problems can be managed."[90] HBLSS is implemented by HBLSS guides who are selected by the community and who are then trained using a modular design that focuses on the prevention, recognition, and initial home management of life-threatening maternal and newborn problems and referral to a facility, where possible.[91] These guides then share their HBLSS knowledge and skills with women, family caregivers, and homebirth attendants (ie, people involved in delivery care and decision making) by way of group discussions, demonstrations, and use of pictorial learning cards.[90,91] When implemented within an existing health care infrastructure, the instruction of family and community members in techniques such as uterine fundal massage and emergency preparedness has the potential to reduce maternal morbidity and mortality due to PPH.[23] The potential effectiveness of this approach in relation to PPH relies on early identification of hemorrhage and quick initiation of treatment. The findings from an evaluation of a field test of HBLSS in Ethiopia were promising.[91] Pre- and posttraining tests of HBLSS guides' PPH knowledge demonstrated a statistically significant increase, and although lower, the knowledge remained much higher than the pretraining levels at 1 year posttraining.[91] In addition, the management of PPH (according to postpartum interviews) was significantly better among women who delivered with an HBLSS guide compared with another unskilled attendant.[91] Other similar programs implemented in low-resource settings have shown success in increasing the coverage of uterotonics and/or

reducing PPH by actively engaging women, the community, and traditional birth attendants in community-based interventions and using locally produced materials to gauge blood loss.[92–94]

Public–private partnership

Public–private partnerships need to be further developed to ensure better collaboration in the procurement, distribution, and marketing of uterotonics. For example, local pharmaceutical manufacturers, distributors, or mobile network providers can be partners in creating demand through their extensive network of product retailers, that could support the dissemination of information about misoprostol.[95] In addition, new mobile technologies are being tested to support supply chain management, provide training and diagnostic assistance for health workers, and disseminate information in hard-to-reach communities. Text messaging is being used to collect and transmit a wide range of information, from the documentation of stock levels of commodities to the circulation of information to women about where and how to access maternal health care.[96]

Conclusion

As PPH is the main cause of maternal mortality worldwide, PPH prevention interventions need to be prioritized as an essential way to improve maternal health. There is no panacea that can be universally implemented. Each country must develop its own context-dependent policies and programs, incorporating myriad approaches that combine the most recent recommendations and reflect the experiences of other countries. Though oxytocin is the recommended uterotonic, it is not readily available in settings with the highest risk for mortality and morbidity from PPH, due to its sensitivity to heat and need for provision by a skilled provider. Yet increasing access to prophylactic uterotonics, regardless of where deliveries occur, should be the primary means of reducing the burden of this complication. There is still some debate as to whether misoprostol is effective in PPH prevention,[97] and some have called for additional high-quality studies that demonstrate significant reductions in PPH.[48] But at the present time, based on the evidence available, the best way to reduce PPH deaths in low-resource settings where women continue to deliver without access to a skilled birth attendant is to make misoprostol widely available. Therefore, efforts need to be directed at increasing misoprostol supplies and supporting correct and consistent utilization by providers and by women themselves, in the case of home births.

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