Misoprostol *for*
POSTPARTUM HEMORRHAGE

PROJECT OVERVIEW

Misoprostol for Postpartum Hemorrhage: Moving from Research to Reality

Gynuity Health Projects and partners have been working since 2004 on a program of research with support from the Bill & Melinda Gates Foundation to help establish the safety, efficacy, and appropriateness of misoprostol for prevention and treatment of postpartum hemorrhage (PPH) in a variety of clinical settings. In 2009, in collaboration with partners, Gynuity embarked on a follow-up initiative to answer remaining research questions, address operational and service-delivery issues related to misoprostol's applications including at the community-level, and influence policies and clinical practice guidelines to better reflect the evidence and promote appropriate use.

BACKGROUND

PPH remains one of the major causes of maternal death worldwide, even though relatively simple remedies exist to prevent or treat it. Women in developed countries rarely die from PPH — almost all deliver in hospitals where skilled health personnel can administer appropriate clinical interventions, including drug therapy, blood transfusion, and emergency surgery. In contrast, for women in developing countries, many of whom give birth at home or in poorly equipped health facilities, these interventions are too often unavailable or of poor quality.

The most common cause of PPH is uterine atony — a failure of the uterus to contract properly after childbirth. The standard of care for preventing PPH due to uterine atony is active management of the third stage of labor (AMTSL).[1] Traditional first-line treatment includes the use of a uterotonic drug, uterine massage, and bimanual compression. Oxytocin is the most widely-used drug for prevention and treatment of PPH.

Misoprostol, a prostaglandin, offers several potential advantages over oxytocin for managing PPH due to uterine atony in resource-constrained settings. It is widely available in developing countries, is relatively inexpensive, can be transported and stored without refrigeration, and can be administered without an injection. Until recently, however, research has been insufficient to recommend a specific regimen or route of administration, or to endorse use of misoprostol in community settings and by lower-level providers.

By 2009, Gynuity Health Projects and colleagues completed five large randomized-controlled trials to evaluate the potential of misoprostol for preventing and treating PPH. The results from this body of work advanced knowledge about misoprostol's safety, efficacy, feasibility, and acceptability to women. These trials helped fill important knowledge gaps, and their results will be used to update and clarify global policies and clinical guidelines. Key findings included the following:

For preventing PPH, oral misoprostol (600 mcg) can be safely and effectively administered by lower-level health providers (Mobeen et al., 2010). This study, carried out in a community-based setting in northwestern Pakistan, supported earlier findings (Hoj et al., 2005; Derman et al., 2006; Walraven et al., 2005) that an oral dosage of 600 mcg of misoprostol is safe and effective, that it can be used for PPH prevention where oxytocin is not available or accessible, and that traditional birth attendants can be trained in its appropriate use.

[1] Active management of the third stage of labor, often abbreviated AMTSL, is a set of clinical interventions composed of: administration of a uterotonic drug (generally oxytocin), controlled cord traction, and uterine massage.

For women experiencing PPH, sublingual misoprostol (800 mcg) is a safe, effective, and acceptable treatment (Winikoff et al., 2010; Blum et al., 2010). These trials, conducted in five countries (Burkina Faso, Ecuador, Egypt, Turkey, and Vietnam), provided the largest body of evidence to-date on misoprostol's efficacy for treating PPH. The results illustrated that 800 mcg of sublingual misoprostol works well to control postpartum bleeding, both in settings where uterotonic prophylaxis is routinely administered during the third stage of labor and in those where it is not.

What We Know	Unanswered Research Questions, to be Addressed in the Next Phase
Misoprostol has been shown to be efficacious in hospital settings.	Can misoprostol be effective in community-based settings? • Can misoprostol be routinely administered as PPH prevention outside of research settings? • Is the 800 mcg sublingual dose safe for treatment of PPH at lower-level health facilities and for home births?
Misoprostol use is associated with fever.	Could a lower dose maintain efficacy but reduce side effects? • Is it worthwhile to create the evidence base for use of 600 mcg sublingual dose?
Misoprostol has been shown to work for both prevention and treatment of PPH.	Can misoprostol be used for both prevention and treatment of PPH in the same woman? • What is the effect of misoprostol used for both prevention AND treatment? • What are the elements of a successful PPH prevention AND treatment model? • Are the side effects tolerable? Are limited resources best spent on universal primary prevention or targeted secondary prevention? • What are the clinical outcomes, program feasibility, cost, and acceptability of two different community models of PPH care using misoprostol?
Misoprostol, oxytocin in Uniject®, and components of AMTSL can be effective at PPH prevention.	What is the programmatic and cost effectiveness of each of these interventions?

For women receiving oxytocin to treat PPH, adjunct use of misoprostol provides no additional benefit. A large multi-country study conducted in collaboration with the World Health Organization in five countries (Argentina, Egypt, South Africa, Thailand, and Vietnam) showed no benefit of administering 600 mcg of sublingual misoprostol at the same time as conventional uterotonics for *treating PPH* (Widmer et al., 2010). Another study (Hofmyer et al., 2011) evaluating adjunct use of misoprostol for *preventing PPH,* conducted in South Africa, Uganda, and Nigeria, also showed no beneficial effect. In both studies, misoprostol was associated with increased side effects.

THE NEXT PHASE: FROM RESEARCH TO REALITY

Gynuity's research trials provide strong evidence in support of misoprostol's potential to prevent and treat PPH. However, a number of scientific, programmatic, and policy questions still remain unanswered (see table, left). Gynuity seeks to address the critical operational and service delivery issues related to evidence-based use of misoprostol for PPH prevention and treatment, particularly at the community and lower levels of care.

Gynuity also aims to influence international and national policies, technical guidance, and clinical practice so that they accurately reflect this new body of evidence.

Key areas of activity include:

1. Community-based research

Misoprostol and Uniject®: New research will compare the program effectiveness of misoprostol and the Uniject® oxytocin device. Four large, community-based randomized trials will test the safety, efficacy, feasibility, and acceptability of misoprostol vs. oxytocin delivered via Uniject® in primary-level facilities and in home deliveries.

PPH prevention models: Existing service delivery models for misoprostol focus on PPH primary prevention. The objective of this study is to compare two community-level strategies, either universal use of 600 mcg oral misoprostol at the time of delivery for primary prevention of PPH or selective administration of 800 mcg sublingual misoprostol to women at 350 mL blood loss for secondary prevention of PPH.

Cost analysis: Little is known about the costs and benefits of large-scale programs focusing on misoprostol for PPH prevention. We will be conducting cost analyses for selected models of PPH prevention and treatment.

Self-administration: There is limited data on the effectiveness of women self-administering misoprostol for preventing PPH at home deliveries. A randomized trial will test the effectiveness of self-administration in these settings.

2. Clinical research

Misoprostol and fever: In a previous trial, unusual rates of high fever were observed among study participants in Ecuador receiving 800 mcg of sublingual misoprostol for PPH treatment. Studies will examine a reduced dose of misoprostol (600 mcg) and its relationship to elevated body temperature in Ecuador, and the 800 mcg dose in other high-altitude and/or Andean populations.

Safety of preventing and treating with misoprostol: The safety and efficacy profile of misoprostol used for prevention, and then again to treat the same woman who goes on to hemorrhage, is unknown. Further research will assess the safety and efficacy of using repeat doses for prophylactic and therapeutic purposes.

Oxytocin administered via IV and IM: Previous studies have combined data for oxytocin administered by IM and IV when given as part of AMTSL. Recent analyses suggest that the two routes do not perform equally well. Our research will compare these two methods of administration.

Develop indicators of need for PPH treatment: Data from Gynuity's previous trials show that nearly 50% of women who lose more than 500 mL of blood experience no morbidities, even if untreated, leading to questions of the value of this marker for PPH. In collaboration with the University of Liverpool and the WHO, we plan to examine the relationship between postpartum bleeding patterns and maternal health outcomes to assess the appropriateness of the 500 mL marker as the international definition of PPH. We will also evaluate other clinical indicators that may be more useful in determining when a woman requires treatment.

3. Policy and advocacy

Materials development: Development of clinical and policy materials that summarize current research findings on PPH for a range of audiences. These materials include updated clinical guidelines for PPH care for mid-level providers and developing a policy brief, among others.

Technical support and guidance: Providing governments and international agencies with tools and information to design and implement service delivery programs, monitor and evaluate activities, and understand the latest research.

Policy change: Pursuit of policy change in support of misoprostol for PPH at the country level, by identifying potential spokespersons and strategies for updating national-level essential drugs lists and country-level norms.

Advocacy messaging: Development of an evidence-based advocacy agenda and communications plan in partnership with key international and regional stakeholders to harmonize and disseminate messages on the use of misoprostol for preventing and managing PPH.

Regulatory approval/registration: Collaboration with government agencies and pharmaceutical companies that manufacture misoprostol products to encourage registration, approval, and/or introduction of misoprostol for PPH indications.

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COLLABORATING ORGANIZATIONS

Gynuity collaborates with several partner agencies, Ministries of Health, and individual researchers. Key partners include:

Aga Khan Development Network
ChildFund International
Concept Foundation
Family Care International
Guttmacher Institute
International Federation of Gynecology and Obstetrics (FIGO)
Population Services International (PSI)
University of California, San Francisco
University of Illinois, Chicago
University of Liverpool
World Health Organization

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