Misoprostol *for*
POSTPARTUM
HEMORRHAGE

PROJECT OVERVIEW
March 2006

Postpartum hemorrhage: Responding to the Challenge

Background

Postpartum hemorrhage (PPH) is a major cause of death for women during childbirth, killing more than 350 women each day. Many of these deaths could be prevented by skilled medical personnel equipped with appropriate supplies and medications. However, basic health services are out of reach for many women in the developing world, particularly those who are poor and live in rural areas.

The most common cause of PPH is uterine atony (failure of the uterus to contract properly after childbirth). Current standard practice for **preventing** PPH is a procedure called "active management of the third stage of labor." Administered immediately after the delivery of the baby, active management is a set of clinical interventions designed to speed the delivery of the placenta and prevent uterine atony. Basic components of active management include: the administration of a uterotonic (uterus-contracting) drug (generally oxytocin); controlled cord traction; and uterine massage after delivery of the placenta, as appropriate.[1]

Traditional first-line (non-surgical) **treatment** options for PPH include the use of a uterotonic drug (such as oxytocin), uterine massage, and bimanual compression. Intravenous fluid or drug therapy and blood transfusion may also be administered to stabilize the woman. If these initial measures are not able to control bleeding, advanced surgical intervention may be necessary.

In many developing country settings, primary and referral-level health facilities often do not have the necessary health personnel, supplies, or equipment to administer conventional uterotonic drugs routinely. Health facilities are generally understaffed, and skilled medical personnel may not be trained or available to administer medications even if they are on hand. In addition, oxytocin requires refrigeration, special storage, and the use of needles and syringes–all of which may not be routinely available in low-resource settings.

Misoprostol for postpartum hemorrhage

Misoprostol is a widely-marketed and available drug commonly prescribed to prevent gastric ulcers caused by long-term use of non-steroidal anti-inflammatory medications. Because of its ability to stimulate uterine contractions, misoprostol has been used off-label for a range of reproductive health indications (such as cervical ripening and induction of labor) for over a decade. Misoprostol has also demonstrated potential in preventing and treating PPH due to uterine atony. Many studies have investigated misoprostol as an alternative therapy because it offers a number of advantages over standard treatment.

Misoprostol:

- can be given via a variety of routes (oral, rectal, sublingual, vaginal);
- does not need refrigeration;
- has a long shelf life;
- is stable at high temperatures; and
- has relatively few side effects.

Because of these characteristics, misoprostol is particularly well-suited for use in developing countries. It can be used by a range of health providers in low-resource settings and delivered effectively at the community level.

Bringing misoprostol to market: Research and outreach activities

In July 2003, Gynuity Health Projects and Family Care International launched an initiative to evaluate misoprostol as an alternative therapy for PPH prevention and treatment; assist in registering the drug for these indications; and undertake a range of educational and training activities to shape policy and share information in support of misoprostol for PPH.

Specific activities include:

- Conducting large-scale clinical trials to test the effectiveness of misoprostol in preventing and treating PPH in community and clinical settings. While previous studies[2-14] have demonstrated the safety and efficacy of misoprostol as an alternative drug for prevention and treatment of PPH, standardized and monitored research is needed to document the efficacy of a specific regimen in order to register the drug for these indication(s).
- Obtaining regulatory approval for misoprostol for various PPH indications. Once a drug regimen is established, the project partners will work with pharmaceutical companies to guide misoprostol through the regulatory approval process in various countries and to facilitate the drug's marketing and distribution.
- Developing educational materials and conducting training and outreach activities to support increased availability and use of misoprostol for PPH. These activities aim to share information with policy makers, members of the media, and health workers about misoprostol's role in preventing and treating PPH.

Additional information about the clinical research component of this initiative is outlined in the next sections.

Misoprostol for prevention of postpartum hemorrhage

In many developing country settings, a large proportion of deliveries take place at home, without a skilled birth attendant present. When life-threatening complications occur, the woman must often be transported over long distances to a health facility that has the skilled providers, medications, and equipment to treat her. Since death from PPH is swift, occurring on average within 2 hours from the start of bleeding, immediate intervention is necessary to save the woman's life.

Misoprostol offers several advantages for the prevention of PPH in home birth settings where the use of injectable uterotonics is not feasible. Our research therefore tests the hypothesis that the administration of 600 mcg of oral misoprostol to women during the third stage of labor can reduce PPH in an environment where currently no drug is given for this purpose. A double-blind, randomized, placebo-controlled clinical trial is being conducted to evaluate the effectiveness and safety of misoprostol when administered by specially trained traditional birth attendants in home birth settings in rural Pakistan.

The study evaluates whether there is a clinically meaningful difference in the incidence of PPH between women given misoprostol and those given a placebo. Other outcome measures include changes in hemoglobin, rate of postpartum anemia, and mean blood loss. Side-effects of misoprostol are also assessed.

Carried out in collaboration with Agha Khan Foundation (based in France) and Agha Khan University (in Pakistan), the study will enroll consenting pregnant women in Chitral district, located in the Northwest Frontier Province.

Misoprostol for treatment of postpartum hemorrhage

While there is evidence to indicate that misoprostol is an effective treatment for PPH, further research is needed to recommend the drug as an alternative to oxytocin. A large, multi-site study is being carried out to explore the effectiveness of misoprostol for the treatment of primary PPH in tertiary care facilities. The study is a double-blind, placebo-controlled, randomized trial to compare 800 mcg of sublingual misoprostol with oxytocin, the standard first-line treatment in many hospital settings.

The study is being conducted in two circumstances: where women receive a prophylactic uterotonic drug (oxytocin) during the third stage of labor; and where they do not. One sub-study assesses the effectiveness of misoprostol vs. oxytocin for the treatment of PPH where there is no routine oxytocin prophylaxis in the third stage of labor. The study tests whether misoprostol is as effective as oxytocin in treating primary PPH in this circumstance. Another sub-study assesses the effectiveness of misoprostol vs. oxytocin for treatment of PPH among women who have received routine prophylaxis with injectible oxytocin in the third stage of labor. The study evaluates whether misoprostol is as effective as oxytocin for treatment of PPH when prophylaxis with oxytocin has failed. Sites for this study are: Burkina Faso, Ecuador, Egypt, Turkey, and Vietnam.

Outcome measures include:

- need for additional intervention after initial PPH treatment;
- mean blood loss after PPH diagnosis;
- time to bleeding cessation;
- change in hemoglobin from pre-delivery to postpartum;
- receipt of blood transfusion;
- side effects; and
- acceptability for women and providers.

Women will be randomized to receive either 800 mcg sublingual misoprostol and IV placebo resembling oxytocin (saline), or placebo pills resembling misoprostol and 40 IU oxytocin via IV. Both of these studies also assess the drugs' safety profiles, their acceptability among study participants and reported side effects, and the feasibility of integrating misoprostol into obstetric services.

Misoprostol as an adjunct treatment for postpartum hemorrhage

In collaboration with the World Health Organization, Gynuity Health Projects is conducting a study of misoprostol as an adjunct treatment to oxytocin for the treatment of PPH. This multi-site, double-blind, randomized controlled trial is being implemented in Argentina, Egypt, South Africa, Thailand, and Vietnam. All women in participating centers will undergo active management of the third stage of labor with 10 IU of oxytocin administered intramuscularly or intravenously for the prevention of PPH. Consenting women with a clinical diagnosis of PPH, or those with clinical suspicion of PPH requiring additional uterotonics, will be given routine treatment for PPH (injectable uterotonics) and, at the same time, either 600 mcg of sublingual misoprostol or a placebo. The hypothesis is that a combined regimen of 600 mcg of sublingual misoprostol in addition to standard injectable uterotonics is a more effective treatment for PPH than standard injectable uterotonics alone.

Outcome measures include: incidence of measured blood loss of 500 ml or more at 90 minutes after enrollment; side effects; blood transfusion and/or Hb level 24 hours after birth; blood loss ≥ 1000 ml at 60 and 90 minutes after enrollment; any uterotonics administered after randomization; maternal death or severe morbidity.

References:

1. FIGO ICM Joint Statement, *Management of the Third Stage of Labour to Prevent Post-Partum Haemorrhage*, 2003.
2. O'Brien P, El-Refaey H, Gordon A, Geary M, Rodeck CH. Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. *Obstetrics and Gynecology* 1998; 92: 212-214.
3. Ozan H, Bilgin T, Ozsarac N, Ozerkan RK, Cengiz C. Misoprostol in uterine atony: a report of 2 cases. *Clinical Experience in Obstetrics and Gynecology* 2000; 27: 221-222.
4. Abdel-Aleem H, El-Nashar I, Abdel-Aleem A. Management of severe postpartum hemorrhage with misoprostol. *International Journal of Gynecology and Obstetrics* 2001; 72: 75-76.
5. Shojai R, Piechon L, d'Ercole C, Boubli L, Ponties JE. Le misoprostol par voie rectale dans les hémorragies de la délivrance : Une étude préliminaire [Rectal administration of misoprostol for delivery induced hemorrhage. Preliminary study] *Journal de Gynécologie Obstétrique et Biologie de la Reproduction* 2001; 30: 572-575.
6. Adekanmi OA, Purmessur S, Edwards G, Barrington JW. Intrauterine misoprostol for the treatment of severe recurrent atonic secondary postpartum hemorrhage. *British Journal of Obstetrics and Gynaecology* 2001; 108: 541-5.
7. Oboro VO, Tabowei TO, Bosah JO. Intrauterine misoprostol for refractory postpartum hemorrhage. *International Journal of Gynecology and Obstetrics* 2003; 80:67-68.
8. Lokugamage AU, Sullivan KR, Niculescu I, Tigere P, Onyangunga F, El Refaey H, Moodley J, Rodeck CH. A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. *Acta Obstetetricia et Gynecologica Scandinavica* 2001; 80:835-839.
9. Hofmeyr GJ, Ferreira S, Nikodem VC, Mangesi L, Singata M, Jafta Z, Maholwana B, Mlokoti Z, Walraven G, Gülmezoglu AM. Misoprostol for treating postpartum haemorrhage: a randomized controlled trial. *BMC Pregnancy and Childbirth* 2004; 4: 16.
10. Walraven G, Dampha Y, Bittaye B, Sowe M, Hofmeyr J. Misoprostol in the treatment of postpartum hemorrhage in addition to routine management: a placebo randomized controlled trial. *British Journal of Obstetrics and Gynaecology* 2004; 111 (9): 1014-1017.
11. El-Refaey H, Nooh R, O'Brien P, Abdalla M, Geary M, Walder J, Rodeck C. The misoprostol third stage of labour study: a randomised controlled comparison between orally administered misoprostol and standard management. *British Journal of Obstetrics and Gynaecology* 2000; 107: 1104-1110.
12. Gulmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L, Abdel-Aleem H, Cheng L, Hofmeyr G, Lumbiganon P, Unger C, Prendiville W, Pinol A, Elbourne D, El-Refaey H, Schulz K. WHO multicentre trial of misoprostol in the management of the third stage of labour. *Lancet* 2001; 358: 689-95.
13. Walley RL, Wilson JB, Crane JM, Matthews K, Sawyer E, Hutchens D. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. *British Journal of Obstetrics and Gynaecology* 2000; 107: 1111-1115.
14. Walraven G, Blum J, Dampha Y, Sowe M, Morison L, Winikoff B, Sloan N. Misoprostol in the management of the third stage of labour in the home delivery setting in rural Gambia; a randomized controlled trial. *British Journal of Obstetrics and Gynaecology* 2005; 112(9), pp. 1277-1283.

For further information about this initiative, please contact:

Gynuity Health Projects • 15 East 26th St, Suite 1617
New York, NY 10010 USA • pubinfo@gynuity.org

Family Care International • 588 Broadway, Suite 503
New York, NY 10012 USA • pphproject@familycareintl.org