

## PREGNANCY FAILURE AND MISCARRIAGE

Of all recognized pregnancies, 15-20% are spontaneously miscarried and an additional 22% end in induced abortion<sup>1,2</sup>. Incomplete abortion occurs when products of conception are partially expelled from the uterus; and either spontaneous or induced pregnancy loss can result in incomplete abortion. Women seeking care following incomplete abortion are faced with the inadequacy of existing safe abortion and postabortion care services. In countries where access to safe abortion services is restricted, abortions may be performed by unskilled providers in poor conditions and incomplete abortion is of particular concern.

The occurrence of spontaneous fetal death after the first trimester is difficult to ascertain but one estimate is that, in the United States alone, approximately 125,000 to 190,000 2<sup>nd</sup>- and 3<sup>rd</sup>-trimester fetal deaths occur each year<sup>3</sup>. Common therapies for 2<sup>nd</sup> trimester intra-uterine fetal death (IUFD) include dilatation and evacuation surgery and non-surgical labor-induction agents; their use depends in part on gestational age and provider skills and method preference. At this stage of pregnancy, the nonviable fetus is often not spontaneously evacuated, yet timely evacuation is vital in order to avoid the possibility of serious complications for the woman.

### MISOPROSTOL ADDED TO WHO MODEL LIST OF ESSENTIAL MEDICINES FOR TREATMENT OF INCOMPLETE ABORTION AND MISCARRIAGE

In April, 2009, the World Health Organization announced the addition of misoprostol to its Model List of Essential Medicines based on its proven safety and efficacy for the treatment of incomplete abortion and miscarriage. The recommendation was made by an expert committee that evaluated available evidence, including numerous randomized comparative clinical trials and several guidelines developed by professional associations for this indication. The application was submitted by Gynuity Health Projects.

The Model Essential Medicine List is a guide for the development of national and institutional essential medicine lists. Governments often rely upon this list to inform service delivery options at different levels of the health system and drug procurement for those services. Essential medicines are selected with regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness. The Model List also forms the basis for medicines selection in emergency situations.

The recommended doses for treatment of incomplete abortion and miscarriage are:

- A single oral dose of 600 micrograms
- A single sublingual dose of 400 micrograms

This program brief describes our approach to pregnancy failure in the first and second trimesters of pregnancy.

<sup>1</sup> Griebel et al. (2005). Management of spontaneous abortion. AFP.

<sup>2</sup> Guttmacher Institute: Induced Abortion Worldwide 1999. [http://www.guttmacher.org/pubs/fb\\_0599.html](http://www.guttmacher.org/pubs/fb_0599.html) WHO Definition of unsafe abortion

<sup>3</sup> Estimate derived by Gynuity Health Projects using different modeling approaches based on data from the National Center for Health Statistics birth statistics in conjunction with the 1995 National Survey of Family Growth and a life table of spontaneous abortions by week of pregnancy generated by S. Harlap et al. (Harlap S, Shiono PH, Ramcharan S. A life table of spontaneous abortions and the effects of age, parity, and other variables. In Porter IH, Hook EB; *Human Embryonic and Fetal Death*; New York: 1980; Academic Press; pp 145-158.)

## Misoprostol for Treatment of Incomplete Abortion

Traditionally, treatment of incomplete abortion in the first trimester involves either curettage or vacuum aspiration. Though highly effective these surgical procedures require trained providers, special equipment, sterile conditions, and often anesthesia. In low resource settings with limited access to skilled providers and well-equipped facilities, use of misoprostol for medical management of incomplete abortion is an attractive alternative. Research has demonstrated that medical management of incomplete abortion is safe, effective, has a low incidence of side effects, and is highly acceptable to women.

Additionally, misoprostol is easy to administer, does not require refrigeration, is easily available in many settings, and typically low-cost. By increasing access to safe treatment of incomplete abortion, misoprostol has the potential to reduce maternal mortality associated with complications of spontaneous or induced pregnancy loss.

Compelling evidence of misoprostol's successful use in incomplete abortion has led Gynuity to further research optimal doses and routes of misoprostol administration for this indication and to conduct feasibility studies in a range of settings. Geographically, Gynuity's research has expanded to Sub-Saharan Africa, Latin America and the Caribbean, and Eastern Europe/Former Soviet Union. Next steps will involve introducing misoprostol in rural settings and documenting its use in lower levels of the health care system.

## Misoprostol for Treatment of Intra-uterine Fetal Death in the Second Trimester

Because of the scarcity of well-trained surgical providers, more and more physicians have begun turning to misoprostol as an alternative approach to surgical evacuation of the uterus after fetal death in the 2<sup>nd</sup> trimester. Misoprostol has been demonstrated to be as effective as, or more effective than, either oxytocin or other prostaglandins for this indication in a number of small trials published in the peer-reviewed literature. For many obstetricians, misoprostol has become the accepted standard of care for 2<sup>nd</sup> trimester intrauterine fetal death. In the absence of more formal study of this treatment, however, dosages are not standardized, routes of administration vary, and other issues, such as timing of doses and total dose have not been settled.

In collaboration with US-based researchers, Gynuity is conducting a study testing, in a randomized, blinded trial, two different doses of misoprostol (200 mcg vs. 100 mcg) administered buccally as a treatment for fetal death at 14 – 28 weeks' gestation. The purpose is to establish the lowest safe and effective dose of misoprostol for this indication so that providers may proceed with greater authority and confidence. The data from the study should enable a pharmaceutical entity to register misoprostol for the treatment of IUFD in the second trimester. Gynuity has been awarded orphan drug status for misoprostol for this indication and is able to undertake this research because of our receipt of a competitive award from the FDA.

### Key Outcomes of Research on Misoprostol for Incomplete Abortion

- Several clinical studies have found 600 mcg of oral misoprostol to be as safe and effective as surgical treatment for incomplete abortion.
- Recent research has found an alternative dose, 400 mcg of sublingual misoprostol, to be as safe and effective as 600 mcg of oral misoprostol for treatment of incomplete abortion.
- Satisfaction with the treatment was found to be very high (over 90%) among women in a range of research settings; side effects have been reported to be largely acceptable to women.

## COLLABORATIONS, TRAINING AND DISSEMINATION

- Partnership with public and private health care providers to introduce misoprostol for postabortion care into existing reproductive health services.
- Collaboration with pharmaceutical companies to facilitate the registration of misoprostol for pregnancy failure internationally.
- Provision of technical support to local governmental bodies to incorporate misoprostol regimens for postabortion care into technical guidelines and to improve existing protocols based on locally-generated clinical evidence.
- Development of training and educational materials for policymakers, clinicians, and users.
- Organization of seminars, educational opportunities and training courses to share information and stimulate interest in misoprostol's potential.
- Collaboration with the Postabortion Care Consortium on efforts to include misoprostol in standard PAC kits internationally.

## GEOGRAPHIC SCOPE

Gynuity Health Projects conducts research and technical assistance on pregnancy failure in several regions of the world. The following map highlights project countries. Our work on 2<sup>nd</sup> trimester IUFD is being conducted in the United States.



## GYNUITY PUBLICATIONS

### Clinical Guidelines, Meeting Reports, Newsletters

- Misoprostol for the Treatment of Incomplete Abortion: An Introductory Guidebook. Gynuity Health Projects. (forthcoming)
- Instructions for Use: Misoprostol for Treatment of Incomplete Abortion and Miscarriage. Expert Meeting on Misoprostol sponsored by Reproductive Health Technologies Project and Gynuity Health Projects. June 9, 2004. New York, NY (updated June, 2008). Available in Arabic, English, French, Portuguese, Russian, Spanish and Turkish.
- PAC in Action Newsletter: Special Issue on Misoprostol in the PAC Context, Issue 9, May 2006. Postabortion Care Consortium, Gynuity Health Projects (Guest Editor). Available in Arabic, English, French, Portuguese and Spanish.
- Misoprostol: A New Addition to Post Abortion Care. Meeting Report. Gynuity Health Projects. (October 2003)

### Peer-reviewed Articles

- Diop, A., S., Raghavan, J.P. Rakotovoao, R. Comendant, P.D. Blumenthal, B. Winikoff. "Comparison of two routes of administration for misoprostol in the treatment of incomplete abortion: A randomized clinical trial." *Contraception (in press)*
- Blum, J., B. Winikoff, K. Gemzell-Danielsson, P.C. Ho, R. Schiavon, A. Weeks. "Treatment of incomplete abortion and miscarriage with misoprostol." *IJGO (Dec 2007) Vol 99(Suppl 2);S186-S189.*
- Gemzell-Danielsson, K., P.C. Ho, R. Gómez Ponce de León, A. Weeks, B. Winikoff. "Misoprostol to treat missed abortion in the first trimester." *IJGO (Dec 2007) Vol 99(Suppl 2); S182-S185 .*
- Shwekerela, B., R. Kalumuna, R. Kipingili, N. Mashaka, E. Westheimer, W. Clark, B. Winikoff. "Misoprostol for treatment of incomplete abortion at the regional hospital level: results from Tanzania." *BJOG (Sep 2007), (OnlineEarly Articles).doi:10.1111/j.1471-0528.2007.01469.x*
- Dao, B., J. Blum, B. Thieba, S. Raghavan, M. Ouedraogo, J. Lankoande, B. Winikoff. "Is misoprostol a safe, effective and acceptable alternative to manual vacuum aspiration for postabortion care? Results from a randomised trial in Burkina Faso, West Africa." *BJOG (Sep 2007), (OnlineEarly Articles). doi:10.1111/j.1471-0528.2007.01468.x*
- Bique C., M. Ustá, B. Debora, E. Chong, E. Westheimer and B. Winikoff. "Comparison of misoprostol and manual vacuum aspiration for the treatment of incomplete abortion." *IJGO (Sep 2007), Vol 98(3), pp. 222-6.*
- Weeks, A., G. Alia, J. Blum, B. Winikoff, P. Ekwaru, J. Durocher, F. Mirembe. "A randomized trial of misoprostol compared with manual vacuum aspiration for incomplete abortion." *Obstet Gynecol 106(3), (Sep 2005), pp. 540-547.*
- Ngoc, N.T.N., J. Blum, J. Durocher, T.T.V. Quan, B. Winikoff. "A randomized controlled study comparing 600 versus 1200 mcg of misoprostol for medical management of incomplete abortion." *Contraception (Dec 2005), 72, pp.438-442.*

For more information or for copies of the publications listed above, please contact [pubinfo@gynuity.org](mailto:pubinfo@gynuity.org). For additional resources see [www.gynuity.org](http://www.gynuity.org).

Projects in this program area have been funded by multiple donors including the David and Lucile Packard Foundation, Swedish International Development Cooperation Agency (SIDA), the US Food and Drug Administration, the William and Flora Hewlett Foundation and an anonymous donor. For additional information about any of the projects described in this summary, please contact [pubinfo@gynuity.org](mailto:pubinfo@gynuity.org).

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