

Background

Emergency contraception (EC) primarily refers to the use of oral contraceptive pills (OCs/ECPs) within 72 hours of unprotected intercourse to prevent pregnancy. The regimen involves taking two doses, 12 hours apart, of certain formulations of a combination of estrogen and progestin (combined OCs/ECPs also known as the Yuzpe regimen) or progestin-only (levonorgestrel) pills.

Based on a unanimous FDA Advisory Committee recommendation in June, 1996, the FDA officially endorsed the use of ECPs. The FDA published a formal notice regarding ECPs on February 25, 1997 in the *Federal Register*. This document states that any one of six (now 12) common brands of combined oral contraceptive pills (all containing norgestrel or levonorgestrel and ethinylestradiol) are safe and effective for use as emergency contraception up to 3 days after unprotected sex. The FDA recommended that ECP treatment involves taking either 2 high dose or 4 low dose OCPs, within 72 hours after having unprotected sex, followed by a second dose 12 hours after the first dose.

Providing information about ECPs has become a medical norm. In fact, the American College of Obstetricians and Gynecologists (ACOG) recommends that women be informed of ECPs as standard good medical practice¹. Further, both ACOG and the American Medical Association (AMA) support ECPs availability over the counter (OTC) in the United States. ECPs are in the WHO Essential Drug List and the UNHCR Reproductive Health in Refugee Situations Field Manual.

Where are we on the science?

Mechanism of Action

Several studies have shown that ECPs prevent or delay ovulation; this appears to be the main mechanism of action.^{2,3} Both statistical modeling studies that examined effectiveness by cycle day of intercourse relative to ovulation and studies that have looked at chemical markers such as changes in LH levels, point to interference in ovulation as the primary mechanism of action.⁴ Another common hypothesis is that ECPs may prevent implantation of a fertilized egg, but studies show no changes in the biological markers that would demonstrate such an effect⁵. However, there are no research findings that allow us to rule out the possibility that ECPs could prevent implantation. Another hypothesis is that ECPs work by interfering with the transport of sperm or ova; however, no studies have clearly demonstrated this. While it is likely that ECPs work in different ways depending on when they are taken during a woman's menstrual cycle, the preponderance of evidence supports an effect on ovulation as the main mechanism of action.

There are no contraindications for using ECPs; however they do not work if a woman is already pregnant⁶. There is no evidence that administration of ECPs during pregnancy will have a negative effect on a fetus.

¹ Emergency Oral Contraception. ACOG Practice Bulletin. Number 25. Washington DC: The American College of Obstetricians and Gynecologists, March 2001.

² Marions L, Hultenby K, Lindell I, Sun X, Stabi B, Gemzell Danielsson K. Emergency Contraception with Mifepristone and Levonorgestrel: Mechanism of Action. *Obstet Gynecol* 2002;100(1):65-71.

³ Trussell J, Raymond EG. Statistical evidence about the mechanism of action of the Yuzpe regimen of emergency contraception. *Obstet Gynecol* 1999;93:872-876.

⁴ Croxatto HB, Fuentealba B, Brache V, Salvatierra AM, Alvarez F, Massai R, Cochon L, Faundes A. Effects of the Yuzpe regimen, given during the follicular phase, on ovarian function. *Contraception*. 2002; 65(2):121-8.

⁵ Raymond EG, Lovely LP, Chen-Mok M, Seppala M, Kurman RJ, Lessley BA. Effect of the Yuzpe regimen of emergency contraception on markers of endometrial receptivity. *Hum Reprod* 2000;15(11):2351-5.

⁶ Emergency Contraception: A Guide for Service Delivery. Geneva: World Health Organization; 1998. WHO/FRH/FPP/98.19.

Effectiveness

It is estimated that if 100 women have a single act of unprotected intercourse during the second and third weeks of their cycle, 8 would become pregnant; with combined ECP treatment the number of pregnancies reduces to 2, a reduction in the risk of pregnancy of 75%. Following treatment with progestin-only ECPs, 1 will become pregnant, a reduction in the risk of pregnancy of 88%. A WHO study showed that levonorgestrel-only ECPs are more effective (85% vs. 57% pregnancies prevented) and resulted in significantly fewer side effects than combined ECPs.⁷ With progestin-only ECPs, 23% of women experienced nausea compared to 51% of combined ECP users. In addition, 6% of progestin-only ECP users experienced vomiting compared to 19% of combined ECP users.

The WHO trial also indicated that effectiveness of both combined and progestin-only ECPs is significantly greater the earlier the first dose is given after exposure to unprotected intercourse. Effectiveness, especially with combined OCs, drops if taken more than 48 hours after unprotected sex.⁷ This speaks directly to the need for ECPs to be readily available when needed.

There are no long term or serious side effects from using ECPs. If vomiting occurs within 1 hour after taking a dose, some clinicians recommend repeating that dose. The non-prescription anti-nausea medicine meclizine reduces the risk of nausea by 27% and vomiting by 64% when two 25 mg tablets are taken 1 hour before combined ECPs, but the risk of drowsiness is doubled (to about 30%). Other side effects of ECPs include fatigue, headache, dizziness, and breast tenderness.

| Regimen | Effectiveness | Nausea | Vomiting |
|----------------|----------------------|---------------|-----------------|
| Yuzpe | 75% | 51% | 19% |
| LNG | 88% | 23% | 6% |

Biomedical Research

USAID has supported biomedical research on EC in the past, however current efforts are more focussed on operations research and issues related to program implementation. Other agencies continue to support work looking to further elucidate EC's mechanism of action, including the possible role that EC may play in reducing sperm motility and increasing the thickness of cervical mucus. Other work is looking at the time interval between doses and whether two doses are needed to make taking ECPs more convenient. Also, new hormones are being investigated to enhance effectiveness and limit side effects that can occur with the Yuzpe or levonorgestrel-only methods.

The UNDP/UNFPA/WHO/ World Bank and Special Programme of Research, Development, and Research Training in Human Reproduction (HRP) is supporting the following research:

⁷Task Force on Postovulatory Methods of Fertility Regulation. 1998. Randomized controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. *Lancet* 352 (9126): 428-433

Alternative Dosing Schedule

A large randomized, double-blind multinational study was completed during 2001, which investigates, among other things, the efficacy and side effects of a single dose of 1.5 mg (two tablets of 0.75 mg of levonorgestrel taken as one dose) compared to the regimen when the tablets are taken at 12-hour intervals. The third arm in this study is 10 mg mifepristone. The treatment was given up to 120 hours of intercourse. A total of 4136 women were enrolled in this study in 15 family planning clinics in China, Finland, Georgia, Hungary, India, Mongolia, Slovenia, Sweden, Switzerland and the U.K. The results of the study will be published in 2002. In addition, a seven-center study has started in Nigeria to investigate the efficacy and side effects of one-dose regimen of 1.5 mg of levonorgestrel compared to a two-dose regimen (0.75 mg taken at 24-hour interval). This study will include a total of 3150 women and the clinical phase is expected to be completed by the end of 2003.

The 12-hour interval between the two tablets is sometimes impractical and a double-blind, multicentre study is, therefore, investigating in China, whether this interval could be increased to 24 hours, as this would be more convenient for women. The recruitment of over 2000 women for this trial is expected to be completed by mid 2002.

Alternative Methods

The Rockefeller Foundation is funding work looking at the efficacy of the 10 mg dose of mifepristone as EC. The results indicated that the doses of 10 mg and 25 mg of mifepristone are equally effective with a very low pregnancy rate and very few side effects. Again, the efficacy appeared to be higher the sooner the treatment was taken.

Gestrinone, a registered progestin product, is used in more than 40 countries for the treatment of endometriosis, and is being compared to mifepristone for emergency contraception when administered up to 120 hours after unprotected intercourse. The study will include 1200 women and the clinical phase will be completed by the end of 2002.

Effectiveness on the 4th and 5th Day

Recent research completed by the Population Council has investigated the effectiveness of the common progestin Norethindrone and the Yuzpe method beyond 72 hours. This study, which has yet to be published, suggests at least 50% effectiveness when taken 73-120 hours after unprotected intercourse. Other studies to confirm this are under way. If this data holds, then clinical protocols will need to be revised to allow ECP provision beyond 72 hours.⁸

Experience in the Field

The Emergency Contraception Consortium, a collaboration of originally seven organizations dedicated to the integration of emergency contraception into mainstream family planning and reproductive health care, sponsored EC introductory activities in four countries: Sri Lanka, Kenya, Mexico and Indonesia. These introductory activities were evaluated and compiled into case studies, which provide programs interested in providing ECPs with valuable lessons learned. These activities were not funded by USAID. The Consortium's basic introduction framework includes the following nine steps:

1. Assess user needs and service capabilities
2. Build support for emergency contraception introduction at appropriate levels
3. Register a product
4. Develop a distribution plan

⁸ Ellertson, C, Webb A, Blanchard K, et al. Three simplifications of the Yuzpe regimen of emergency contraception: Results of a randomized, controlled trial in five centers. Unpublished manuscript.

5. Identify and meet clients' information needs
6. Train providers
7. Introduce the product
8. Monitor and evaluate emergency contraception services
9. Disseminate evaluation results

One of the Emergency Contraception success stories comes from the introduction of emergency contraception in Sri Lanka. The Sri Lanka Consortium initiated a project in 1997 to make a dedicated product available through pharmacies, youth groups, general practitioners, and community health workers. The Consortium launched a promotional plan that included an advertising campaign directed to an EC hotline, point of sale advertisements for pharmacies, a video for providers, and sent letters to all pharmacies in Sri Lanka. The Consortium also developed a brochure for clients that included multiple languages and a version for non-literate clients.

Providers and clients have been strongly supportive of the project and have appreciated the increase in EC services. The hotline is being utilized and the sales of dedicated product have steadily been increasing. The successes noted include:

- An efficient distribution system for a dedicated product was established that reached all parts of the country.
- A tiered pricing system was established that ensured ECP availability throughout the country at a low cost. The pricing system also resulted in enough revenue to support the hotline and advertising.

The challenges noted included:

- Many women still request EC after 72 hours.
- General political turmoil (unrelated to EC) in Sri Lanka has prevented some educational and training opportunities.

USAID support has funded work on emergency contraception introductory activities using ECP donated to the government by UNFPA. The Population Council has been working in Bangladesh on an operations research project to test and document how best ECPs can be introduced without adversely affecting the use of other family planning methods. The key factors for introducing ECP are increasing community awareness about the method, making it widely and easily accessible, promoting its appropriate uses, returning clients to regular contraception after using ECP, and managing side effects. The intervention phase of this study included provider training and ECP provision. Training included program managers, field supervisors and grass-roots workers. The lessons learned are as follows:

- The study indicates that grass-roots family planning workers including depot holders, can be easily trained to educate and provide ECP services in the community.
- After training, workers are able to communicate correct information about ECP to their clients.
- The training model developed for the present project - a two-day initial training and a half-day reorientation after the workers have provided the services for one month - is effective and sufficient.
- ECP training can be easily integrated in the existing training program for the FP program. In such cases, ECP training can be reduced to a half-day session.

- The trainer's manual, ECP brochures and other teaching aids developed for the project were found useful and effective. All of them could be easily adopted for introducing ECPs at the national level.
- To avoid confusion, ECP should be promoted as a dedicated product rather than cutting up standard OC pill packs.
- Prevailing misconceptions about OC and its use should be taken seriously by the program to improve the continuation of oral contraceptive pills.

The Government of Bangladesh, as of December 2001, has responded to the research results and has approved the introduction of ECPs in the national program. Further, ICDDR/B will undertake research on the impact of ECP introduction on abortion rates.

Other work on EC that USAID is supporting includes:

Cameroon - The CMS Project has developed a private/public joint activity with HRA Pharma to introduce a dedicated emergency contraceptive (Norlevo) in Cameroon. This pilot project includes the launch of ECPs in the public sector. Activities include holding a press conference with key in-country influentials, developing IEC materials, training public sector providers and providing donated product to public sector clinics. The official launch of emergency contraception in Cameroon took place in December of 2001.

Ethiopia - The Population Council is undertaking a research project to examine the impact of expanding access to coital dependant methods (physical and chemical barrier methods) of family planning to adolescents, including the introduction of ECPs.

Malawi - The Reproductive Health Unit with support from the Policy Project and input from JHPIEGO and the Deliver Project led the development of the Malawi reproductive health policy document that includes the approval of emergency contraception pills. The MOHP approved and disseminated this document in March 2002.

Pakistan - Two social marketing programs are planning to or are already offering ECPs. The Key Social Marketing Project is considering obtaining ECPs from ZAFSA, a Pakistani pharmaceutical company, which provides OCs. The Green Star Network has provided a dedicated LNG product, Postinor-2, since 2001.

Zambia - Operations research is being coordinated through the Population Council and is being implemented by CARE International, Lusaka's Contraceptive University Teaching Hospital and the Zambia Society for Family Health (PSI). The study is designed to determine where young people are comfortable and willing to obtain emergency contraception. Qualitative and quantitative data is being obtained to gauge the effectiveness of four potential sources of EC information and supplies. Sources include: peer counselors, CBD agents, pharmacists and community sales agents.

Gaps & Issues

USAID supplies information about the use of ECPs in a variety of its technical and training materials, and supports sharing information about this contraceptive option with family planning clients.

Implementation Questions

The most pertinent gaps in our knowledge revolve around how best to incorporate emergency contraception into family planning and other reproductive health programs. Questions that need to be answered include: Does introduction of ECPs into a clinic or community program reduce pregnancy rates and increase the use of other contraceptive methods? What evidence is there that the availability of ECPs reduces abortion rates? How can we introduce ECPs and make sure that it does not displace other methods but actually increases uptake of other more effective methods of contraception (bridging method)? How best do we counsel women so that they understand the "emergency" only use and the effectiveness of ECPs in relation to other methods of family planning? Who are the populations that would most benefit from having access to emergency contraception?

Educational Efforts

Emergency contraception is a contraceptive and works before pregnancy. Misperceptions and confusion between emergency contraception and medical abortion (mifepristone, RU-486, Mifeprex™) persist in many country contexts. This issue must be fully addressed when introducing emergency contraception, and implementing agencies need to explore how best to engage stakeholders, including faith-based organizations, to educate them on the issue and to identify barriers to acceptability before offering emergency contraception.

Provision of a Dedicated Product

Although USAID-supplied OCs are among the FDA-approved formulations that can be used for emergency contraception, USAID does not currently fund separate packaging of pills for this purpose nor has USAID purchased any of the two FDA-approved dedicated ECP products. If USAID Missions overseas requested USAID to provide ECPs, there would be no legislative restrictions preventing USAID from responding to these requests. However, presently USAID is working with other donors to supply ECPs in social marketing programs and for the public sector. A current issue is under what circumstances would USAID start to centrally procure a dedicated emergency contraceptive product?

Many regions, including ANE, Africa and LAC have expressed interest in emergency contraception and have requested workshops, training, and information on how to obtain a dedicated ECP product. USAID should be as responsive as possible to these requests. Emergency contraception serves a vital need for women and has become an integral part of the voluntary service delivery mix that USAID supports in a number of countries.

Should the definition of pregnancy be included in the text? According to The Code of Federal Regulations (CFR), Title 45, Public Welfare, DHHS/NIH/Office for Protection from Research Risks (1983) Part 46 - Protection of Human Subjects, Revised as of March 8, 1983, paragraph 46.203 (b), page 12, states that "pregnancy' encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.