Emergency Contraception: A Cost-Effective Approach to Preventing Unintended Pregnancy

James Trussell, PhD¹
Felicia Stewart, MD²
Elizabeth G. Raymond, MD, MPH³

August 2005

Professor of Economics and Public Affairs and Director, Office of Population Research, Princeton University, Wallace Hall, Princeton University, Princeton NJ 08544. Tel: 609-258-4946, Fax: 609-258-1039, Email: trussell@princeton.edu

Women's Health Center, UCSF Center for Reproductive Health Research & Policy, 2356 Sutter St, 2nd floor, San Francisco CA 94115

Tel: 415-502-4098; Fax 415-502-4065; Email: <u>StewartF@obgyn.ucsf.edu</u>

Associate Medical Director, Biomedical Affairs Division, Family Health International. PO Box 13950, Research Triangle Park, NC 27709.

Tel: 919-544-7040; Fax: 919-544-7261; Email: eraymond@fhi.org

The authors have no personal financial interest whatsoever in the commercial success or failure of emergency contraception.

Introduction

Half of all pregnancies in the United States are unintended: there were 3.0 million in 1994 alone, the last year for which data are available. Emergency contraception, which prevents pregnancy after unprotected sexual intercourse, has the potential to reduce significantly the incidence of unintended pregnancy and the consequent need for abortion. Emergency contraception is especially important for outreach to the 4.6 million women at risk of pregnancy but not using a regular method by providing a bridge to use of an ongoing contraceptive method. Although emergency contraceptives do not protect against sexually transmitted infection, they do offer reassurance to the 6.8 million women who rely on condoms for protection against pregnancy in case of condom slippage or breakage. Emergency contraceptives available in the United States include emergency contraceptive pills and the copper-T intrauterine device (IUD). 4,5,6

Emergency contraceptive pills

There are two types of emergency contraceptive pills (ECPs): combined ECPs containing both estrogen and progestin and progestin-only ECPs. The newer progestin-only ECPs have now largely replaced the older combined ECPs because they are more effective and cause fewer side effects. Although this therapy is commonly known as the morning-after pill, the term is misleading; ECPs may be initiated sooner than the morning after—immediately after unprotected intercourse—or later—for at least 120 hours after unprotected intercourse.

Progestin-only ECPs contain no estrogen. Only the progestin levonorgestrel has been studied for freestanding use as an emergency contraceptive. The original treatment schedule was one 0.75 mg dose within 72 hours after unprotected intercourse, and a second 0.75 mg dose 12 hours after the first dose. However, recent studies have shown that a single dose of 1.5 mg is as effective as and causes no more side effects than two 0.75 mg doses 12 hours apart. (Another study found that two 0.75 mg doses 24 hours apart were just as effective as two 0.75 mg doses 12 hours apart.) The only dedicated progestin-only product available in the United States is Plan-B, approved by the FDA as an ECP in July 1999 (Table 1). Aside from Plan-B, the only progestin-only formulation available in the United States is the birth control minipill Ovrette. Forty Ovrette tablets are needed to obtain 1.5 mg of levonorgestrel.

Combined ECPs are ordinary birth control pills containing the hormones estrogen and progestin. The hormones that have been studied extensively in clinical trials of ECPs are the estrogen ethinyl estradiol and the progestin levonorgestrel or norgestrel (which contains two isomers, only one of which—levonorgestrel—is bioactive). These are found in 19 brands of combined oral contraceptives available in the United States (Table 1).¹⁰ One specially-packaged ECP product (Preven) was approved by the FDA in 1998 but withdrawn from the market in 2004. This combination of active ingredients used in this way is also sometimes called the Yuzpe method, after the Canadian physician who first described the regimen. Newer research has demonstrated the safety and efficacy of an alternative regimen containing ethinyl estradiol and the progestin norethindrone;¹¹ this result suggests that oral contraceptive pills containing progestins other than levonorgestrel may be used for emergency contraception when the two standard regimes are not available.

Copper-bearing IUDs

Copper-IUDs can be inserted up to the time of implantation—five to seven days after ovulation—to prevent pregnancy. Thus, if a woman had unprotected intercourse three days before

ovulation occurred in that cycle, the IUD could prevent pregnancy if inserted up to ten days after intercourse. Because of the difficulty in determining the day of ovulation, however, many protocols allow insertion up to only five days after unprotected intercourse. A copper-IUD can also be left in place to provide effective ongoing contraception for up to ten years. But IUDs are not ideal for all women. Women at risk of sexually transmitted infections (STIs) may not be good candidates for IUDs; insertion of the IUD in these women can lead to pelvic infection, which can cause infertility if untreated. Women not exposed to STIs have little risk of pelvic infection following IUD insertion, 12 and use of a copper IUD is not associated with an increased risk of tubal infertility among nulligravid women (whereas infection with chlamydia is). 13

Effectiveness

The effectiveness of a preventive therapy is best measured by comparing the probability that the condition will occur if the therapy is used to the probability that it will occur without treatment. For many preventive therapies, such as vaccines, these probabilities are often determined in a randomized clinical trial comparing treatment to a placebo. In the case of emergency contraception, however, efficacy was demonstrated initially in noncomparative observational studies, and, thereafter, use of a placebo was felt to be unethical. Therefore, the chance that pregnancy would occur in the absence of emergency contraception is estimated indirectly using published data on the probability of pregnancy on each day of the menstrual cycle. This estimate is compared to the actual number of pregnancies observed after treatment in observational treatment trials. Effectiveness is calculated as 1-O/E, where O and E are the observed and expected number of pregnancies, respectively.

Calculation of effectiveness, and particularly the denominator of the fraction, involves many assumptions that are difficult to validate. Therefore, reported figures on the efficacy of emergency contraception may be underestimates or, of more concern, overestimates. Yet, precise estimates of efficacy may not be highly relevant to many women who have had unprotected intercourse, since ECPs are often the only available treatment. A more important consideration for most ECP clients may be the fact that data from both clinical trials and mechanism of action studies clearly show that at least the levonorgestrel regimen of ECPs is more effective than nothing. ¹⁶

Five studies of the levonorgestrel regimen that included a total of more than 6,000 women reported estimates of effectiveness between 60% and 93%; that is, this regimen reduced a woman's chance of pregnancy by that amount. A meta-analysis of eight studies of the combined regimen including more than 3,800 women concluded that the regimen prevents about 74% of expected pregnancies; the proportion ranged from 56% to 89% in the different studies. A more recent analysis using possibly improved methodology found an effectiveness of 53% and 47% in two of the largest trials of the combined regimen. Combined data from two randomized trials that directly compared the two regimens showed a relative risk of pregnancy of 0.51 (95% confidence limits 0.31, 0.83), indicating that the chance of pregnancy among women who received the levonorgestrel regimen was about half the chance among those who received the combined regimen.

Multiple studies have indicated that both regimens are more effective the sooner after sex the pills are taken. 7,17,18,21,22 Some studies of the combined regimen did not show this time effect. Early data showed that both regimens are effective when used up to 72 hours after intercourse. 18,24 Consequently, some product package instructions, including that for Plan B, and older guidelines advise use only within that time frame. However, more recent studies indicate

that the regimens continue to be moderately effective if started between 72 and 120 hours.^{7,9,25,26} No data are available establishing efficacy if ECPs are taken more than 120 hours after intercourse.

Emergency insertion of a copper-IUD is significantly more effective than use of ECPs, reducing the risk of pregnancy following unprotected intercourse by more than 99%.²⁷

Mechanism of action

Several clinical studies have shown that combined ECPs containing the estrogen ethinyl estradiol and the progestin levonorgestrel can inhibit or delay ovulation. 28,29,30,31 This is an important mechanism of action and may explain ECP effectiveness when used during the first half of the menstrual cycle, before ovulation has occurred. Some studies have shown histologic or biochemical alterations in the endometrium after treatment with the regimen, leading to the conclusion that combined ECPs may act by impairing endometrial receptivity to implantation of a fertilized egg. ^{29,32,33,34} However, other studies have found no such effects on the endometrium. ^{28,35,36} Additional possible mechanisms include interference with corpus luteum function; thickening of the cervical mucus resulting in trapping of sperm; alterations in the tubal transport of sperm, egg, or embryo; and direct inhibition of fertilization. 5,37,38,39 No clinical data exist regarding the last three of these possibilities. Nevertheless, statistical evidence on the effectiveness of combined ECPs suggests that there must be a mechanism of action other than delaying or preventing ovulation. ⁴⁰ Early treatment with ECPs containing only the progestin levonorgestrel has been shown to impair the ovulatory process and luteal function; ^{41,42,43,44,45} no effect on the endometrium was found in two studies, ^{42,43} but in another study levonorgestrel taken before the LH surge altered the luteal phase secretory pattern of glycodelin in serum and the endometrium. 46 Levonorgestrel also interferes with sperm migration and function at all levels of the genital tract.⁴⁷ Studies in the rat and the Cebus monkey demonstrate that levonorgestrel administered in doses that inhibit ovulation has no postfertilization effect that impairs fertility. 39,48,49 ECPs do not interrupt an established pregnancy, defined by medical authorities such as the United States Food and Drug Administration/National Institutes of Health⁵⁰ and the American College of Obstetricians and Gynecologists⁵¹ as beginning with implantation. Therefore, ECPs are not abortifacient. Its very high effectiveness implies that emergency insertion of a copper-IUD must be able to prevent pregnancy after fertilization.

To make an informed choice, women must know that ECPs—like all regular hormonal contraceptives such as the birth control pill, the implant Norplant, the vaginal ring NuvaRing, the Evra patch, and the injectables Lunelle and Depo-Provera,⁵² and even breastfeeding⁵³—may prevent pregnancy by delaying or inhibiting ovulation, inhibiting fertilization, or inhibiting implantation of a fertilized egg.

Safety

No deaths or serious complications have been causally linked to emergency contraception. According to the latest World Health Organization (WHO) medical eligibility criteria, there are no situations in which the risks of using ECPs outweigh the benefits.⁵⁴ WHO notes specifically that women with previous ectopic pregnancy, cardiovascular disease, migraines, and liver disease and women who are breastfeeding may use ECPs. Given the very short duration of exposure and low total hormone content, combined ECP treatment can be considered safe for women who would ordinarily be cautioned against use of combined oral contraceptives for ongoing contraception. Although no changes in clotting factors have been detected following combined

ECP treatment,⁵⁵ progestin-only ECPs or insertion of a copper-IUD may be preferable to use of combined ECPs for a women who has a history of stroke or blood clots in the lungs or legs and wants emergency contraception. All three of these conditions (pregnancy, migraine, or history of thromboembolism) are identified through medical history screening, so women requesting combined ECPs can be evaluated via telephone, without need for an office visit, pelvic exam or laboratory tests. Planned Parenthood Federation of America allows affiliates to prescribe ECPs via telephone.

Data are not available on the safety of current regimens of ECPs if used frequently over a long period of time. However, experience with similar regimens⁵⁶ and with high dose oral contraceptives suggests that the likelihood of serious harm from at least moderate repeat use is low. Certainly, repeated use of ECPs is safer than pregnancy, in particular when the pregnancy is unintended and women do not have access to safe early abortion services.

Side Effects

Side effects include nausea and vomiting, abdominal pain, breast tenderness, headache, dizziness, and fatigue. These usually do not occur more than a few days after treatment, and they generally resolve within 24 hours.

About 50% of women who take combined ECPs experience nausea and 20% vomit. ^{18,57} If vomiting occurs within 2 hours after taking a dose, some clinicians recommend repeating that dose. The non-prescription anti-nausea medicine meclizine has been demonstrated to reduce 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 was doubled (to about 30%). ⁵⁸ Anti-nausea medicines are not routinely offered in the United States. Many providers recommend instead that women reduce the risk of nausea by taking ECPs with food, although research suggests that doing so is ineffective. ^{11,58} The levonorgestrel regimen has a significantly lower incidence of nausea and vomiting; according to a randomized controlled trial conducted by WHO, progestin-only ECPs are associated with an incidence of nausea 50% lower and an incidence of vomiting 70% lower than that for combined ECPs. ¹⁸

Only one study has been specifically designed to assess the effects of ECPs on bleeding patterns. It found that when taken in the first three weeks of the menstrual cycle, ECPs consisting of 1.5 mg levonorgestrel in a single dose significantly shortened that cycle as compared both to the usual cycle length and to the cycle duration in a comparison group of similar women who had not taken ECPs. The magnitude of this effect was greater the earlier the pills were taken. This regimen taken later in the cycle had no effect on cycle length, but it did cause prolongation of the next menstrual period. The ECPs had no effect on the duration of the second menstrual cycle after use, but the second period was prolonged. Intermenstrual bleeding was uncommon after ECP use, although more common than among women who had not taken ECPs. ⁵⁹

Effects on pregnancy

There have been no conclusive studies of births to women who were already pregnant when they took combined ECPs or following failure of combined ECPs. However, two observations provide reassurance for any concern about birth defects. First, in the event of treatment failure, ECPs are taken long before organogenesis starts so they should not have a teratogenic effect. Second, studies that have examined births to women who inadvertently continued to take combined oral contraceptives (including high dose formulations) without knowing they were

pregnant have found no increased risk of birth defects. ^{60,61,62} The FDA removed warnings about adverse effects of combined oral contraceptives on the fetus from the package insert years ago. ⁶³

Available evidence suggests that ECPs do not increase the chance that a pregnancy following ECP use will be ectopic; moreover, like all contraceptive methods, ECPs reduce the absolute risk of ectopic pregnancy by preventing pregnancy in general.⁶⁴

Drug interactions

No specific data are available about the interactions of ECPs with other drugs, but it seems reasonable that drug interactions would be similar to those with regular oral contraceptive pills. Women taking drugs that may reduce the efficacy of oral contraceptives (including but not limited to rifampicin, certain anticonvulsant drugs, Saint John's wort, and certain antiretroviral agents) should be advised that the efficacy of ECPs may be reduced. Consideration may be given to increasing the amount of hormone administered in the ECPs, either by increasing the amount of hormone in one or both doses, or by giving an extra dose.

Barriers to more widespread use of emergency contraception

The lack of a product specifically packaged, labeled, and marketed as an emergency contraceptive was a major obstacle to more widespread use of emergency contraception in the United States until the fall of 1998, when Preven was approved (it was withdrawn from the market in 2004). A second specially-packaged emergency contraception, Plan-B, was approved a year later. While availability of these products has helped, the two pharmaceutical companies distributing them were very small and were not able to promote the products on the same scale as most contraceptives. Plan B was acquired from the tiny company Women's Capital Corporation by Barr Pharmaceuticals in February 2004 so the situation may improve.

Without commercial marketing or advertising, it is not surprising that physicians prescribe emergency contraceptives infrequently and rarely provide information about emergency contraception to women during routine visits. As a consequence, many women do not know that emergency contraception is available, effective, and safe.

One objection to making ECPs more widely available is the concern that women who know they can use ECPs may become less diligent with their ongoing contraceptive method. However, if used as an ongoing method, ECP therapy would be far less effective than most other contraceptive methods: if the typical woman used combined ECPs for a year; her risk of pregnancy would exceed 35% and if she used progestin-only ECPs, she would still have a 20% chance of pregnancy. Therefore, continued use would not be a rational choice. Reported evidence demonstrates that making ECPs more widely available does not increase risk-taking 67,68,69,70,71,72,73 and that women who are the most diligent about ongoing contraceptive use are those most likely to seek emergency treatment.⁷⁴ For example, in a recent study considering the effect of advance ECP provision on regular methods of birth control, teens receiving emergency contraception supplies in advance were more likely to use ECPs when needed but did not report higher frequencies of unprotected sex and did not use condoms or hormonal contraception less often. 70 Another study demonstrated that educating teens about ECPs does not increase their sexual activity levels or use of EC but increased their knowledge about proper administration of the drugs. 75 And finally, even if ECP availability did adversely affect regular contraceptive use, women are entitled to know about all contraceptive options.

On the other hand, no published study has yet demonstrated that increasing access to ECPs can reduce pregnancy or abortion rates in a population, although one demonstration project⁷⁶ and

two clinical trials^{72,73} were specifically designed to address this issue. The explanation for this result is that even when provided with ECPs in advance, women do not use the treatment often enough after the most risky incidents to result in a substantial population impact.

To help educate women and men about emergency contraception, the Association of Reproductive Health Professionals in Washington and the Office of Population Research at Princeton University sponsor the toll-free Emergency Contraception Hotline (1-888-NOT-2-LATE) and the Emergency Contraception Website (http://not-2-late.com). Since it was launched on February 14, 1996, the Hotline has received more than 525,000 calls. More detailed information is available on the Emergency Contraception Website, which has received approximately 2,500,000 visits since it was launched in October 1994. Both the hotline and the website are completely confidential, available 24 hours a day in English and Spanish, and offer names and telephone numbers of providers of emergency contraception located near the caller's area (in the United States and parts of Canada); the Website is available in French and Arabic as well. Public service announcements for print, radio, television, and outdoor venues advertising the hotline ran in several cities in 1997 and 1998. These were the first ads about contraception to be shown on broadcast television. A paid public education media campaign in Philadelphia and Seattle resulted in significant increases in knowledge about emergency contraception.

Improving access to emergency contraception

Several service delivery innovations involving emergency contraception would help to reduce the number of unintended pregnancies. Perhaps the greatest impact would result from making ECPs available over-the-counter (OTC) without prescription. There are no medical reasons why ECPs should remain prescription-only products in the United States. 79,80 Many medical groups, including the American Medical Association, the American College of Obstetricians and Gynecologists, the Association of Reproductive Health Professionals, the American Academy of Pediatrics, and the Society for Adolescent Medicine support making Plan B OTC. 81 An FDA advisory committee voted 23-4 in December 2003 that Plan B be switched from Rx to OTC, but the FDA rejected an OTC switch in May 2004 in an unprecedented repudiation of such an overwhelmingly positive advisory committee recommendation. Barr Laboratories submitted an amended application in July 2004 to make Plan B an Rx drug for females <16 and OTC otherwise. The FDA had until January 21, 2005 to respond. On July 15, 2005, HHS Secretary Leavitt promised that FDA would act on Barr's application by September 1 to ensure a vote on Senate confirmation of Lester Crawford as FDA Commissioner. On August 26, 2005, FDA announced that Plan B was safe for OTC use by women ≥17. But the FDA announced an indefinite delay in reaching a decision, citing three concerns: (1) can Plan B be both Rx and OTC depending on age? (2) can Rx and OTC versions of the same drug be marketed in the same package, and (3) can an age restriction be enforced? The FDA also announced a 60-day public comment period on first two concerns. The FDA failed to articulate clear criteria or explicit timetable for a final decision. Three days later, Susan Wood resigned her position as the Assistant Commissioner for Women's Health and Director of the FDA Office of Women's Health, stating that:

The recent decision announced by the Commissioner about emergency contraception, which continues to limit women's access to a product that would reduce unintended pregnancies and reduce abortions is contrary to my core commitment to improving and advancing women's health. I have spent the last 15 years working to ensure that science informs good health policy decisions. I can no longer serve as staff when scientific and

clinical evidence, fully evaluated and recommended for approval by the professional staff here, has been overruled.

ECPs are available OTC in Norway (2000) and Sweden (2001).

A second-best alternative is enabling women to obtain ECPs directly from a pharmacist without having to see a physician, as is possible in Alaska, California, Hawaii, Maine, New Hampshire, New Mexico, Washington State, 82,83,84 Australia, Belgium, Benin, Cameroon, Canada, China, Congo, Denmark, Estonia, Finland, France, French Polynesia, Gabon, Ghana, Greece, Guinea-Conakry, Iceland, India, Israel, Ivory Coast, Jamaica, Latvia, Lithuania, Madagascar, Mali, Mauritania, Mauritius, Netherlands, New Zealand, Norway, Portugal, Senegal, South Africa, Sri Lanka, Sweden, Switzerland, Togo, Tunisia, Uganda, and the United Kingdom.

A third-best alternative is screening by telephone or website, after which a prescription is called to the woman's pharmacy of choice; this service is available in several states (see the Appendix).

Another important step is changing provider practices so that women seen by primary and reproductive health care clinicians would be routinely informed about emergency contraception before the need arises; currently only 25% of gynecologists and 14% of general practice physicians routinely counsel women in advance about emergency contraception. The recent clinical practice bulletin issued by the American College of Obstetricians and Gynecologists should help clinicians achieve this goal. Additional resources include a monograph of legal issues for health care providers of ECPs produced by the Center for Reproductive Law and Policy. Information could be provided to women (and men!) in a culturally sensitive manner during counseling or by posters, brochures, audio or videocassettes, or wallet cards. Access would be enhanced if clinicians advertised emergency contraception services and if emergency contraceptive pills were prescribed by telephone without the need for an office visit. A more proactive step would be immediately accessible if the need arises.

Cost-effectiveness

Emergency contraception is nearly always cost effective. Use of combined or progestin-only ECPs reduces expenditures on medical care by preventing unintended pregnancies, which are very costly. Insertion of a copper-T IUD is not cost saving in the United States when used solely as an emergency contraceptive. Unlike the other two alternatives, however, insertion of a copper-IUD can provide continuous contraceptive protection for up to 10 years thereafter, producing savings if used as an ongoing method of contraception for as little as four months after emergency insertion. Hormonal ECs are cost-effective regardless of whether they are provided when the emergency arises or provided beforehand as a routine preventive measure. 10,89,90,91,92

Not only would making emergency contraception more widely available save medical care dollars, but also additional social cost savings would result. These include not only the monetary costs of unwanted pregnancies and births but also the considerable psychological costs of unintended pregnancy. Moreover, the average medical care cost of unintended births is likely to be greater than the average cost of all births.⁹³

Conclusion

One of every two women aged 15-44 in the United States has experienced at least one unintended pregnancy. Unintended pregnancy is a major public health problem that affects not

only the individuals directly involved but also society. Emergency contraception, whether combined estrogen-progestin, progestin-alone, or copper-IUDs, are effective, safe, simple and readily feasible in the United States. Making emergency contraceptives more widely available in the United States is one of the most important steps that can be taken to reduce the incidence of unintended pregnancy and the consequent need for abortion. As many as 51,000 abortions were averted by use of ECPs in 2000. Pregnancy following rape could potentially be reduced by 88 % if all women had access to EC after a sexual assault, a reduction of 22,000 pregnancies each year.

References

- Henshaw SK. Unintended pregnancy in the United States. Fam Plann Perspect 1998;**30**:24-9, 46.
- Trussell J, Stewart F, Guest F, Hatcher RA. Emergency contraceptive pills: a simple proposal to reduce unintended pregnancies. *Fam Plann Perspect* 1992;**24**:269-73.
- Mosher WD, Martinez GM, Chandra A, Abma JC, Wilson SJ. Use of contraception and use of family planning services in the United States: 1982-2002. Advance data from vital and health statistics, no 350. Hyattsville MD: National Center for Health Statistics, 2004.
- Stewart F, Trussell J, Van Look PFA. Emergency contraception. In Hatcher RA, Trussell J, Stewart F, Nelson A, Cates W, Guest F, Kowal D. Contraceptive Technology: Eighteenth Revised Edition. New York NY: Ardent Media, 2004.
- Glasier A. Emergency postcoital contraception. *N Engl J Med* 1997;**337**:1058-64.
- Hatcher RA, Trussell J, Stewart F, Howells S, Russell CR, Kowal D. *Emergency Contraception: The Nation's Best Kept Secret*. Decatur GA: Bridging the Gap Communications, 1995.
- von Hertzen H, Piaggio G, Ding J, Chen J, Song S, Bártfai G, Ng E, Gemzell-Danielsson K, Oyunbileg A, Wu S, Cheng W, Lüdicke F, Pretnar-Darovec A, Kirkman R, Mittal S, Khomassuridze A, Apter D, Peregoudov A. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomized trial. *Lancet* 2002;**360**:1803-10.
- Arowojolu AO, Okewole IA, Adekunle AO. Comparative evaluation of the effectiveness and safety of two regimens of levonorgestrel for emergency contraception in Nigerians. *Contraception* 2002;**66**:269-73.
- ⁹ Ngai SW, Fan S, Li S, Cheng L, Ding J, Jing X, Ng EHY, Ho PC. A randomized trial to compare 24h versus 12h double dose regimen of levonorgestrel for emergency contraception. *Hum Reprod* 2004;**20**:307-11.
- Trussell J, Koenig J, Ellertson C, Stewart F. Preventing unintended pregnancy: the cost-effectiveness of three methods of emergency contraception. *Am J Public Health* 1997;**87**:932-7.
- Ellertson C, Webb A, Blanchard K, Bigrigg A, Haskell S, Shochet T, Trussell J. Modifying the Yuzpe regimen of emergency contraception: a multicenter randomized, controlled trial. *Obstet Gynecol* 2003;**101**:1160-7.
- Farley TMM, Rosenberg MJ, Rowe PJ, Chen J-H, Meirik O. Intrauterine devices and pelvic inflammatory disease: an international perspective. *Lancet* 1992;**339**:785-8.
- Hubacher D, Lara-Ricalde R, Taylor DJ, Guerra-Infante F, Guzmán-Rodríguez R. Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women. *N Engl J Med* 2001;**345**:561-7.
- Dixon GW, Schlesselman JJ, Ory HW, Blye RP. Ethinyl estradiol and conjugated estrogens as postcoital contraceptives. *JAMA* 1980;**244**:1336-9.
- Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med* 1995;**333**:1517-21.
- Raymond E, Taylor D, Trussell J, Steiner MJ. Minimum effectiveness of the levonorgestrel regimen of emergency contraception. *Contraception* 2004;**69**:79-81.
- Ho PC, Kwan MS. A prospective randomized comparison of levonorgestrel with the Yuzpe regimen in post-coital contraception. *Hum Reprod* 1993;**8**:389-92.

- Task Force on Postovulatory Methods of Fertility Regulation. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. *Lancet* 1998;**352**:428-33.
- Trussell J, Rodríguez G, Ellertson C. Updated estimates of the effectiveness of the Yuzpe regimen of emergency contraception. *Contraception* 1999;**59**:147-51.
- Trussell J, Ellertson C, von Hertzen H, Bigrigg A, Webb A, Evans M, Ferden S. Leadbetter C. Estimating the effectiveness of emergency contraceptive pills. *Contraception* 2003;**67**:259-65.
- Kane LA, Sparrow MJ. Postcoital contraception: a family planning study. NZ Med J 1989;102:151-3.
- Piaggio G, von Hertzen H, Grimes DA, Van Look PFA. Timing of emergency contraception with levonorgestrel or the Yuzpe regimen. *Lancet* 1999;**353**:721.
- Trussell J, Ellertson C, Rodríguez G. The Yuzpe regimen of emergency contraception: how long after the morning after? *Obstet Gynecol* 1996;**88**:150-4.
- Yuzpe AA, Percival Smith R, Rademaker AW. A multicenter clinical investigation employing ethinyl estradiol combined with dl-norgestrel as a postcoital contraceptive agent. *Fertil Steril* 1982;**37**:508-13.
- ²⁵ Rodrigues I, Grou F, Joly J. Effectiveness of emergency contraception pills between 72 and 120 hours after unprotected sexual intercourse. *Am J Obstet Gynecol* 2001;**184**:531-37.
- Ellertson C, Evans M, Ferden S, Leadbetter C, Spears A, Johnstone K, Trussell J. Extending the time limit for starting the Yuzpe regimen of emergency contraception to 120 hours. *Obstet Gynecol* 2003:**101**:1168-71.
- ²⁷ Trussell J, Ellertson C. Efficacy of emergency contraception. Fert Control Rev 1995;4:8-11.
- Swahn ML, Westlund P, Johannisson E, Bygdeman M. Effect of post-coital contraceptive methods on the endometrium and the menstrual cycle. *Acta Obstet Gynecol Scand* 1996;**75**:738-44.
- Ling WY, Robichaud A, Zayid I, Wrixon W, MacLeod SC. Mode of action of dl-norgestrel and ethinylestradiol combination in postcoital contraception. *Fertil Steril* 1979;**32**:297-302.
- Rowlands S, Kubba AA, Guillebaud J, Bounds W. A possible mechanism of action of danazol and an ethinylestradiol/norgestrel combination used as postcoital contraceptive agents. *Contraception* 1986;**33**:539-45.
- Croxatto HB, Fuentalba 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;65:121-8.
- Kubba AA, White JO, Guillebaud J, Elder MG. The biochemistry of human endometrium after two regimens of postcoital contraception: a dl-norgestrel/ethinylestradiol combination or danazol. *Fertil Steril* 1986:**45**:512-6.
- Ling WY, Wrixon W, Zayid I, Acorn T, Popat R, Wilson E. Mode of action of dl-norgestrel and ethinylestradiol combination in postcoital contraception. II. Effect of postovulatory administration on ovarian function and endometrium. *Fertil Steril* 1983;**39**:292-7.
- Yuzpe AA, Thurlow HJ, Ramzy I, Leyshon JI. Post coital contraception—a pilot study. *J Reprod Med* 1974; **13**:53-8.
- Taskin O, Brown RW, Young DC, Poindexter AN, Wiehle RD. High doses of oral contraceptives do not alter endometrial α1 and ανβ3integrins in the late implantation window. *Fertil Steril* 1994;**61**:850-5.

- Raymond EG, Lovely LP, Chen-Mok M, Seppälä M, Kurman RJ, Lessey BA. Effect of the Yuzpe regimen of emergency contraception on markers of endometrial receptivity. *Hum Reprod* 2000;**15**:2351-5.
- Ling WY, Wrixon W, Acorn T, Wilson E, Collins J. Mode of action of dl-norgestrel and ethinylestradiol combination in postcoital contraception. III. Effect of preovulatory administration following the luteinizing hormone surge on ovarian steroidogenesis. *Fertil Steril* 1983;40:631-6.
- ³⁸ Croxatto HB, Devoto L, Durand M, Ezcurra E, Larrea F, Nagle C, Ortiz ME, Vantman D, Vega M, von Hertzen H. Mechanism of action of hormonal preparations used for emergency contraception: a review of the literature. *Contraception* 2001;**63**:111-21.
- Croxatto HB, Ortiz ME, Müller AL. Mechanisms of action of emergency contraception. *Steroids* 2003;**68**:1095-8.
- Trussell J, Raymond EG. Statistical evidence concerning the mechanism of action of the Yuzpe regimen of emergency contraception. *Obstet Gynecol* 1999;**93**:872-6.
- Hapangama D, Glasier AF, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. *Contraception* 2001;**63**:123-9.
- Durand M, del Carmen Cravioto M, Raymond EG, Durán-Sánchez O, De la Luz Cruz-Hinojosa L, Castell-Rodríguez A, Schiavon R, Larrea F. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception. *Contraception* 2001;64:227-34.
- Marions L, Hultenby K, Lindell I, Sun X, Ståbi B, Gemzell Danielsson K. Emergency contraception with mifepristone and levonorgestrel: mechanism of action. *Obstet Gynecol* 2002;**100**:65-71.
- Marions L, Cekan SZ, Bygdeman M, Gemzell-Danielsson K. Effect of emergency contraception with levonorgestrel or mifepristone on ovarian function. *Contraception* 2004;**69**:373-7.
- ⁴⁵ Croxatto HB, Brache V, Pavez M, Cochon L, Forcelledo ML, Alvarez F, Massai R, Faundes A, Salvatierra AM. Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. *Contraception* 2004;**70**:442-50.
- Durand M, Sépala M, del Carmen Cravioto M, Koistinen H, Koistinen R, González-Macedo J, Larrea F. Late follicular phase administration of levonorgestrel as an emergency contraceptive changes the secretory pattern of glycodelin in serum and endometrium during the luteal phase of the menstrual cycle. *Contraception* 2005;71:451-7.
- Kesseru E, Garmendia F, Westphal N, Parada J. The hormonal and peripheral effects of d-norgestrel in postcoital contraception. *Contraception* 1974;**10**:411-24.
- Müller AL, Llados CM, Croxatto HB. Postcoital treatment with levonorgestrel does not disrupt postfertilization events in the rat. *Contraception* 2003;67:415-19.
- Ortiz ME, Ortiz RE, Fuentes MA, Parraguez VH, Croxatto HB. Postcoital administration of levonorgestrel does not interfere with post-fertilization events in the new-world monkey *Cebus apella*. *Hum Reprod* 2004;**19**:1352-6.
- OPRR Reports: Protection of Human Subjects. Code of Federal Regulations 45CFR 46, March 8, 1983.
- Hughes EC (ed), Committee on Terminology, The American College of Obstetricians and Gynecologists, *Obstetric-Gynecologic Terminology*. Philadelphia PA: F.A. Davis Company, 1972.

- Statement on Contraceptive Methods. Washington DC: American College of Obstetricians and Gynecologists, July 1998.
- Kennedy KI, Trussell J. Postpartum contraception and lactation. In Hatcher RA, Trussell J, Stewart F, Nelson A, Cates W, Guest F, Kowal D. Contraceptive Technology: Eighteenth Revised Edition. New York NY: Ardent Media, 2004.
- Medical Eligibility Criteria for Contraceptive Use. Third Edition. Geneva: World Health Organization, 2004.
- Webb A, Taberner D. Clotting factors after emergency contraception. *Adv Contraception* 1993;**9**:75-82.
- Task Force on Post-Ovulatory Methods of Fertility Regulation. Efficacy and side effects of immediate postcoital levonorgestrel used repeatedly for contraception. *Contraception 2000*;**61**:303-8.
- Trussell J, Ellertson C, Stewart F. The effectiveness of the Yuzpe regimen of emergency contraception. *Fam Plann Perspect* 1996;**28**:58-64, 87.
- Raymond EG, Creinin MD, Barnhart KT, Lovvorn AE, Rountree W, Trussell J. Meclizine for prevention of nausea associated with emergency contraceptive pills: a randomized trial. *Obstetrics and Gynecology* 2000;**95**:271-7.
- Raymond EG, Goldberg A, Trussell J, Hays M, Roach E, Taylor D. Bleeding patterns after use of levonorgestrel emergency contraceptive pills.
- Raman-Wilms L, Tseng AL, Wighardt S, Einarson TR, Koren G. Fetal genital effects of first-trimester sex hormone exposure: a meta-analysis. *Obstet Gynecol* 1995;**85**:141-9.
- Bracken MB. Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. *Obstet Gynecol* 1990;**76**:552-7.
- Simpson JL, Phillips OP. Spermicides, hormonal contraception and congenital malformations. *Adv Contraception* 1990;**6**:141-67.
- Food and Drug Administration. Prescription drug products; certain combined oral contraceptives for use as postcoital emergency contraception. *Federal Regist* 1997;**62**:8610-2.
- Trussell J, Hedley A, Raymond E. Ectopic pregnancy following use of progestin-only ECPs [letter]. *J Fam Plann Reprod Health Care* 2003;**29**:249.
- Guerts, TBP, Goorissen, EM, Sitsen, JMA. *Summary of Drug Interactions with Oral Contraceptives*. Carnforth, England: Parthenon Publishing Group, Ltd., 1993.
- The Kaiser Family Foundation. Women's health care providers experiences with emergency contraception, June 2003. Available at URL: http://www.kff.org/womenshealth/3343-index.cfm. Accessed 28 July 2004.
- Glasier A, Baird D. The effects of self-administering emergency contraception. *N Engl J Med* 1998;**339**:1-4.
- Raine T, Harper C, Leon K, Darney P. Emergency contraception: advance provision in a young, high-risk clinic population. *Obstet Gynecol* 2000;**96**:1-7.
- Jackson RA, Schwarz EB, Freedman L, Darney P. Advance supply of emergency contraception: effect on use and usual contraception—a randomized trial. *Obstet Gynecol* 2003;**102**:8-16.
- Gold MA, Wolford JE, Smith KA, Parker AM. The effects of advance provision of emergency contraception on Adolescent women's sexual and contraceptive behaviors. *J Pediatr Adolesc Gynecol* 2004;**17**:87-96.

- Lo SS, Fan SYS, Ho PC, Glasier AF. Effect of advanced provision of emergency contraception on women's contraceptive behavior: a randomized controlled trial. *Hum Reprod* 2004;**19**:2404-10.
- Raine TR, Harper CC, Rocca CH, Fischer R, Padian N, Klausner JD, Darney PD. Direct access to emergency contraception through pharmacies and effect on unintended pregnancy and STIs: a randomized controlled trial. *JAMA* 2005;**293**:54-62.
- Hu X, Cheng L, Hua X, Glasier A. Advanced provision of emergency contraception to postnatal women in China makes no difference in abortion rates: a randomized controlled trial. *Contraception* 2005;**72**:111-6.
- Kosunen E, Sihvo S, Hemminki E. Knowledge and use of hormonal emergency contraception in Finland. *Contraception* 1997;**55**:153-7.
- Graham A, Moore L, Sharp D, Diamond I. Improving teenagers' knowledge of emergency contraception: cluster randomized controlled trial of a teacher led intervention. *Br Med J* 2002;**234**(7347):1179-84.
- Glasier A, Fairhurst K, Wyke S, Ziebland S, Seaman P, Walker J, Lakha F. Advanced provision of emergency contraception does not reduce abortion rates. *Contraception* 2004;**69**:361-6.
- Trussell J, Bull J, Koenig J, Bass M, Allina A, Gamble VN. Call 1-888-NOT-2-LATE: promoting emergency contraception in the United States. *J Am Med Wom Assoc* 1998;**53**(Suppl 2):247-50.
- Trussell J, Koenig J, Vaughan B, Stewart F. Evaluation of a media campaign to increase knowledge about emergency contraception. *Contraception* 2001;**63**:81-7
- Ellertson C, Trussell J, Stewart F, Winikoff B. Should emergency contraceptive pills be available without prescription? *J Am Med Wom Assoc* 1998;**53**(Suppl 2):226-9, 232.
- Grimes DA, Raymond EG, Scott Jones B. Emergency contraception over-the-counter: the medical and legal imperatives. *Obstet Gynecol*. 2001;**98**:151-5.
- Association of Reproductive Health Professionals. ARHP sign-on letter: Switch status of emergency contraceptive from Rx to OTC. Available at http://www.arhp.org/ec. Accessed 7 May 2004.
- Wells ES, Hutchings J, Gardiner JS, Winkler JL, Fuller DS, Downing D, Shafer R. Using pharmacies in Washington State to expand access to emergency contraception. *Fam Plann Perspect* 1998;**30**:288-90.
- Gardner JS, Hutchings J, Fuller TS, Downing D. Increasing access to emergency contraception through community pharmacies: lessons from Washington State. *Fam Plann Perspect* 2001;**33**:172-5.
- Marciante KD, Gardner JS, Veenstra DL, Sullivan SD. Modeling the cost and outcomes of pharmacist-prescribed emergency contraception. *Am J Public Health* 2001;**91**;1443-5.
- Emergency Oral Contraception. ACOG Practice Bulletin. Number 25. Washington DC: The American College of Obstetricians and Gynecologists, March 2001.
- Emergency Contraceptive Pills: Common Legal Questions about Prescribing, Dispensing, Repackaging, and Advertising. New York NY: The Center for Reproductive Law and Policy, 1999.
- Emergency Contraception: Client Materials for Diverse Audiences. Seattle WA: Program for Appropriate Technology in Health, 1998.

- Trussell J, Leveque JA, Koenig JD, London R, Borden S, Henneberry J, LaGuardia KD, Stewart F, Wilson TG, Wysocki S, Strauss M. The economic value of contraception: a comparison of 15 methods. *Am J Public Health* 1995;**85**:494-503.
- Trussell J, Koenig J, Stewart F, Darroch JE. Medical care cost savings from adolescent contraceptive use. *Fam Plann Perspect* 1997;**29**:248-55, 295.
- Trussell J, Wiebe E, Shochet T, Guilbert É. Cost savings from emergency contraceptive pills in Canada. *Obstet Gynecol* 2001;**97**:789-93.
- Trussell J, Shochet T. Cost-effectiveness of emergency contraceptive pills in the public sector in the USA. *Expert Rev Pharmacoeconomics Outcomes Res* 2003;**3**:433-40.
- Trussell J, Calabretto H. Cost savings from use of emergency contraceptive pills in Australia. *Aust N Z J Obstet Gynaecol* 2005;**45**:308-11.
- Brown SS, Eisenberg L (eds). *The Best Intentions: Unintended Pregnancy and the Well-Being of Children and Families*. Washington DC: National Academy Press, 1995.
- Ellertson C, Koenig J, Trussell J, Bull J. How many U.S. women need emergency contraception? *Contemp Ob Gyn* 1997;**42**:102-28.
- Jones RK, Darroch JE, Henshaw SK. Contraceptive use among U.S. women having abortions in 2000-2001. *Perspect Sex Reprod Health 2002*;**34**:294-303.
- Stewart FH, Trussell J. Prevention of pregnancy resulting from rape: A neglected preventive health measure. *Am J Prev Med* 2000:**19**(4):228-9.

Table 1. Twenty-One OCs that can be used for emergency contraception in the United States^a

Brand	Company	Pills per Dose ^b	Ethinyl Estradiol per Dose (µg)	Levonorgestrel per Dose (mg) ^c
Plan-B	Barr/Duramed	1 white pill	0	0.75
Ogestrel	Watson	2 white pills	100	0.50
Ovral	Wyeth-Ayerst	2 white pills	100	0.50
Cryselle	Barr/Duramed	4 white pills	120	0.60
Levora	Watson	4 white pills	120	0.60
Lo/Ovral	Wyeth-Ayerst	4 white pills	120	0.60
Low-Ogestrel	Watson	4 white pills	120	0.60
Levlen	Berlex	4 light-orange pills	120	0.60
Nordette	Wyeth-Ayerst	4 light-orange pills	120	0.60
Portia	Barr/Duramed	4 pink pills	120	0.60
Seasonale	Barr/Duramed	4 pink pills	120	0.60
Trivora	Watson	4 pink pills	120	0.50
Tri-Levlen	Berlex	4 yellow pills	120	0.50
Triphasil	Wyeth-Ayerst	4 yellow pills	120	0.50
Enpresse	Barr/Duramed	4 orange pills	120	0.50
Alesse	Wyeth-Ayerst	5 pink pills	100	0.50
Lessina	Barr/Duramed	5 pink pills	100	0.50
Levlite	Berlex	5 pink pills	100	0.50
Aviane	Barr/Duramed	5 orange pills	100	0.50
Lutera	Watson	5 white pills	100	0.50
Ovrette	Wyeth-Ayerst	20 yellow pills	0	0.75

Notes:

Plan-B is the only dedicated product specifically marketed for emergency contraception. Alesse, Aviane, Cryselle, Enpresse, Lessina, Levlen, Levlite, Levora, Lo/Ovral, Low-Ogestrel, Nordette, Ogestrel, Ovral, Portia, Seasonale, Tri-Levlen, Triphasil, and Trivora have been declared safe and effective for use as ECPs by the U.S. Food and Drug Administration. Outside the United States, more than 20 emergency contraceptive products are specifically packaged, labeled, and marketed. For example, Gedeon Richter and HRA Pharma are marketing in many countries the levonorgestrel-only products Postinor-2 and Norlevo, respectively, each consisting of a two-pill strip with each pill containing 0.75 mg levonorgestrel. Norlevo became available over-the-counter without a prescription in Norway in October 2000 and in Sweden in late 2001.

The treatment schedule is one dose within 120 hours after unprotected intercourse, and another dose 12 hours later. However, recent research has found that both doses of Plan B or Ovrette can be taken at the same time.

The progestin in Cryselle, Lo/Ovral, Low-Ogestrel, Ogestrel, Ovral, and Ovrette is norgestrel, which contains two isomers, only one of which (levonorgestrel) is bioactive; the amount of norgestrel in each tablet is twice the amount of levonorgestrel.

Appendix

Kaiser Family Foundation Survey 66

- OB/GYNs (2001)
 - Only 25% routinely discuss EC with patients
 - 80% prescribed ECPs last year (61% of whom did so only five or fewer times)
- Family Practice Physicians (2001)
 - Only 14% routinely discuss EC with patients
 - 36% prescribed ECPs last year (83% of whom did so only five or fewer times)
- Women ages 18-49 (2003)
 - Only 6% have ever used ECPs
 - 68% know there is something a woman can do in the next few days after unprotected sex to prevent pregnancy

Action Steps for Providers

- Ensure that all office staff (especially those answering the telephone) know that you provide EC
- Routinely discuss emergency contraception with clients
- Do not require clinical screening before prescribing ECPs
- Prescribe ECPs by telephone to clients
- Provide ECPs in advance to clients or give prescriptions in advance that can be filled when needed
- Discuss anti-nausea medicines with clients
- Extend 72-hour window when prescribing ECPs
- Join the directory of providers listed on the Emergency Contraception Website and the Emergency Contraception Hotline
- Advertise the availability of emergency contraception in your office/clinic

Emergency Contraception Resources

- Emergency Contraception Website: http://not-2-late.com
- Emergency Contraception Hotline: 1-888-NOT-2-LATE
- ARHP EC Train-the-Trainer PowerPoint slide set: http://www.arhp.org/ec/
- Emergency Contraceptive Pills: Common Legal Questions about Prescribing, Dispensing, Repackaging, and Advertising. New York NY: The Center for Reproductive Law and Policy, 1999. To order, call 212-514-5534.
- Emergency Oral Contraception. *ACOG Practice Bulletin*. Number 25. Washington DC: The American College of Obstetricians and Gynecologists, March 2001. To order, call 508-750-8400.

Statewide Hotlines and Websites: a prescription is called in to the woman's pharmacy of choice

- Connecticut (Planned Parenthood of Connecticut): 800-230-PLAN
- Georgia (Planned Parenthood of Georgia): 877-ECPills
- Georgia (Planned Parenthood of Georgia): www.ecconnection.org
- Illinois (Planned Parenthood/Chicago Area): 866-222-EC4U
- Illinois(Planned Parenthood/Chicago Area): www.plannedparenthoodchicago.com
- Illinois (Planned Parenthood—Springfield Area): 217-544-2744
- Indiana (Planned Parenthood of Greater Indiana): www.ppin.org/ecaccess/ecinfo.html
- Maine (Maine Family Planning Association): 800-887-4029
- Maryland (Planned Parenthood of Maryland): 877-99-GO-4-EC
- Massachusetts (Planned Parenthood League of Massachusetts): www.pplm.org
- Michigan (Planned Parenthood Mid-Michigan Alliance): 734-973-0710
- Minnesota (Boynton Health Service): 612-625-4607
- Montana (Intermountain Planned Parenthood): 800-584-9911
- New York (University of Rochester): 585-341-6568
- North Carolina (Planned Parenthood of Central North Carolina): 866-942-7762
- Oregon (Planned Parenthood of the Columbia/Willamette): www.ppcw.org
- Washington (Planned Parenthood of the Columbia/Willamette): www.ppcw.org
- Wisconsin (Family Planning and Reproductive Health Association): 877-975-9858