

Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy

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Introduction

Half of all pregnancies in the United States are unintended: 3.1 million occurred in 2001 alone, the last year for which data are available.¹ Emergency contraception, which prevents pregnancy after unprotected sexual intercourse, has the potential to significantly reduce the incidence of unintended pregnancy and the consequent need for abortion.² Emergency contraception is especially important for outreach to the 4.6 million women at risk of pregnancy but not using a regular method³ 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 pregnancy³ in case of condom slippage or breakage. Emergency contraceptives available in the United States include emergency contraceptive pills and the Copper T intrauterine contraceptive (IUC).^{4,5,6}

Emergency contraceptive pills

There are three types of ECPs: combined ECPs containing both estrogen and progestin, progestin-only ECPs, and ECPs containing an antiprogesterin (either mifepristone or ulipristal acetate). Only the first two are available in the United States. 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 two 0.75 mg doses 12 hours apart.^{7,8} One of these studies showed no difference in side effects between the two regimens,⁷ while the other found greater levels of headache and breast tenderness (but not other side effects) among study participants taking 1.5 mg of levonorgestrel at once.⁸ Increasingly, levonorgestrel is marketed internationally in a one-dose formulation (one 1.5 mg pill) rather than the two-dose formulation (two 0.75 mg tablets, taken 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.⁹) The only progestin-only products available in the United States are Next Choice, approved by the FDA in June 2009, and Plan B One-Step, approved by the FDA as an ECP in July 2009 (Table 1); this has replaced the two-pill predecessor Plan B, approved by the FDA in July, 1999.

Combined ECPs contain 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). 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. When dedicated ECPs are not available, certain ordinary birth control pills can be used in specified combinations as emergency contraception. In either case, the regimen is one dose followed by a second dose 12 hours later, where each dose consists of 1, 2, 4, 5, or 6 pills, depending on brand. Currently, 23 brands of combined oral contraceptives are approved in the United States for use as emergency contraception (Table 1).¹⁰ 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 also be used for emergency contraception.

The antiprogestin mifepristone has also been studied for use as an emergency contraceptive pill. Mifepristone is a first-generation progesterone receptor modulator that is approved for use in many countries for early first-trimester medication abortion. Mifepristone has been shown to be highly effective for use as emergency contraception, with few side effects (delayed menstruation following the administration of mifepristone is one notable side effect.^{7,12,13,14} However, the use of mifepristone as an abortion pill may limit its widespread acceptability for use for emergency contraception. Recently, a second-generation progesterone receptor modulator, ulipristal acetate (30 mg in a single dose), has been studied for use as emergency contraception and has been found to be highly effective and well-tolerated.^{15,16,17} It has been marketed for use as emergency contraception in Europe since October 2009.

Three published randomized trials compared the efficacy of 1.5 mg levonorgestrel and 10 mg mifepristone for use as emergency contraception. Two trials found no significant difference in efficacy of the two-dose (0.75 mg each) levonorgestrel regimen and mifepristone; pregnancy rates for the two regimens were respectively 1.8% and 1.5% in the first trial⁷ and 2.0% and 1.3% in the second.¹³ The first trial also included a one-dose (1.5mg) levonorgestrel regimen, which yielded a pregnancy rate of 1.5%. An earlier trial showed a significant difference between pregnancy rates for the two-dose levonorgestrel regimen (3.1%) and the 10 mg mifepristone regimen (1.4%).¹² It is possible that the divergent results from this trial are due to differences in the study population as well as differences in the composition of the study drugs themselves, which were locally manufactured in China. A recent meta-analysis of Chinese randomized trials found that a mid-dose (25 mg or 50 mg) of mifepristone had a lower failure rate than did levonorgestrel, but the delay in menses for the two regimens was similar.¹⁴

Two randomized trials compared the efficacy of levonorgestrel with the second-generation antiprogestin ulipristal acetate, one up to 72 hours after unprotected intercourse¹⁵ and the second up to 120 hours after.¹⁷ When these two studies were combined, ulipristal acetate was found to have a pregnancy rate 42% lower than levonorgestrel up to 72 hours and 65% lower in the first 24 hours. In the second randomized study, 30 mg ulipristal acetate prevented significantly more pregnancies than did levonorgestrel in the 72-120 hour subgroup. The reason seems to be that ulipristal acetate can prevent ovulation when taken closer to ovulation than can levonorgestrel. By the time the follicle reaches 18-20 mm (and ovulation should occur within 48 hours) and the probability of conception > 80%, ovulation is prevented by levonorgestrel in only 12% of cycles (versus 13% in the placebo group).¹⁸ In contrast ulipristal prevents ovulation in 59% of cycles.¹⁹

Meloxicam (a COX-2 inhibitor) 30 mg given for five consecutive days in the late follicular phase appears to be an effective emergency option. This regimen does not alter the endocrine profile of the cycle and causes no menstrual disturbance.^{20,21}

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. The latest WHO guidelines allow IUDs to be inserted up to day 12 of the cycle with no restrictions and at any other time in the cycle if it is reasonably certain that she is not pregnant.²² 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 with current sexually transmitted infections (STIs) are not 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,²³ and use of a copper IUD is not associated with an increased risk of tubal infertility among nulligravid women (whereas infection with chlamydia is).²⁴

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.^{25,26} 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. Accurate estimates of efficacy depend upon accurate recording of timing of intercourse and cycle day (so that timing of ovulation can be estimated). One study compared self-report of cycle day with urinary pregnanediol concentrations to demonstrate that over 30% of women presenting for ECPs had inaccurately dated their own menstrual cycles, believing themselves to be in the fertile phase of their cycle when they were not. In the same study, 60% reported more than one act of intercourse in the cycle, indicating that pregnancies attributed to ECP failure may actually be the result of intercourse earlier in the cycle.²⁷ Another study found that 99 women were between days -5 and +1 when the day of ovulation (day 0) was estimated as usual cycle length minus 13. However, hormonal data indicated that only 51 of these 99 (56%) were in fact between days -5 and +1.²⁸ In another recent study, cervical smears showed that more than one-third of women requesting ECPs had no sperm present in the vagina, and those with sperm present had fewer sperm than women attempting to become pregnant.²⁹ The risk of pregnancy for women requesting ECPs appears to be lower than assumed in the estimates of ECP efficacy, which are consequently likely to be 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.³⁰

Nine studies of the levonorgestrel regimen that included a total of nearly 10,500 women reported estimates of effectiveness (a reduction in a woman's chance of pregnancy) between 52% and 94%.^{7,8,9,12,13,15,17,31,32} 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.³³ 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.³⁴ 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 that among those who received the combined regimen.^{30,31,32} This estimate makes *no* assumption about the number of pregnancies that would have been observed in the absence of treatment. The results imply that (1) if the Yuzpe regimen is completely inefficacious, then the levonorgestrel regimen has an efficacy of 49% and (2) for every additional 2 percentage points of efficacy of the Yuzpe regimen, 1 percentage point of efficacy is added to the levonorgestrel regimen.

Several studies have indicated that both regimens are more effective the sooner after sex the pills are taken.^{7,8,32,35,36,37} Other studies of both regimens have not found this time effect,^{9,11,12,13,15,31,38,39,40} although sample sizes were often small. The initial studies included only women who used the regimens within 72 hours after intercourse.^{32,41} Consequently, some product package instructions, including that for Plan B One-Step and Next Choice, 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.^{7,9,39,40} Results of a simulation model demonstrate that the levonorgestrel regimen could not be effective on average when started after 96 hours without a post-fertilization effect; the reason is that with increasing delay, a greater proportion of women would be too near to ovulation.⁴² Nevertheless, individual women not past that threshold would benefit substantially even if there is no post-fertilization effect. No data are available establishing efficacy if ECPs are taken more than 120 hours after intercourse.

A pilot study of 41 women found that adding a Cox-2 inhibitor (meloxicam 15 mg) to 1.5 mg levonorgestrel significantly increased the proportion of cycles with no follicular rupture or ovulatory dysfunction (88% vs. 66%, $p=0.012$). Adding a Cox-2 inhibitor can disturb the ovulatory process after the onset of the LH surge.⁴³

More than 12,000 postcoital insertions of copper-bearing IUDs are known to have been carried out since the practice was introduced in 1976. With only 12 failures, this approach has a pregnancy rate of 0.1%.^{14,44} The effectiveness of using a levonorgestrel-releasing IUD (LNg-20) for emergency contraception has not been studied and is not recommended.

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.^{45,46,47,48} This mechanism of action 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 subsequent implantation of a fertilized egg.^{46,49,50,51} However, other more recent studies have found no such effects on the endometrium.^{45,52,53} 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.^{5,54,55,56} No clinical data exist regarding the last three of these possibilities. Nevertheless, statistical evidence on the effectiveness of combined ECPs suggests that that if the regimen is as effective as claimed, it must have a mechanism of action other than delaying or preventing ovulation.⁵⁷ However, if the effectiveness of combined ECPs was overestimated, which it seems to have been in that study,

the results would be less persuasive.³⁴ Nevertheless, the important point is that effectiveness and mechanism of action are not independent, a point emphasized in later work.⁴² For example, a regimen without a post-fertilization effect could not be 100% effective in typical populations, which will inevitably include some women who take it after fertilization has already occurred.

Early treatment with ECPs containing only the progestin levonorgestrel has been shown to impair the ovulatory process and luteal function.^{18,58,59,60,61,62} No effect on the endometrium was found in two studies,^{59,60} but in another study levonorgestrel taken before the LH surge altered the luteal phase secretory pattern of glycodeilin in serum and the endometrium.⁶³ However, this finding was not confirmed in two later studies explicitly designed to assess endometrial glycodeilin expression.^{64,65} The second of these studies also found no effect on other endometrial receptivity biomarkers or progesterone receptors. Levonorgestrel does not impair the attachment of human embryos to an in vitro endometrial construct and has no effect on the expression of endometrial receptivity markers.^{66,67} In a study conducted more than 30 years ago, levonorgestrel was found to interfere with sperm migration and function at all levels of the genital tract,⁶⁸ however, a study designed to assess this issue found that 1.5 mg levonorgestrel had no effect on the quality of cervical mucus or on the penetration of spermatozoa in the uterine cavity.⁶⁴ A recent study found an effect on sperm function only with much higher levels of levonorgestrel than are used for emergency contraception.⁶⁹

The reduced efficacy with a delay in treatment, even when use is adjusted for cycle day of unprotected intercourse,³⁶ suggests that interference with implantation is likely not an inevitable effect of ECPs. If ECPs did prevent all implantations, then delays in use should not reduce their efficacy as long as they are used before implantation.⁷⁰

Studies in the rat and the Cebus monkey demonstrate that levonorgestrel administered in doses that inhibit ovulation has no postfertilization effect that impairs fertility.^{56,71,72} Whether these results can be extrapolated to women is unknown. Based on those animal studies and on their own studies in women (including one in which no pregnancies were observed when levonorgestrel-only ECPs were taken before the day of ovulation whereas 4-5 would have been expected and three pregnancies were observed when ECPs were taken after ovulation when 3-4 would have been expected⁷³), Croxatto and colleagues have argued that most, if not all, of the contraceptive effect of both combined and levonorgestrel only ECPs can be explained by inhibited or dysfunctional ovulation. Based on their studies on human and animals, some are tempted to conclude that there is definitely no post-fertilization effect.⁷⁴ It is unlikely that this question can ever be unequivocally answered, and we therefore cannot conclude that ECPs never prevent pregnancy after fertilization. Even if there were an accurate test for fertilization, a finding that some fertilized eggs do not subsequently implant after ECPs are taken would not mean that ECPs can work after fertilization, since many, if not most, fertilized eggs naturally do not subsequently implant. Nevertheless, even if in some cases ECPs work by inhibiting subsequent implantation of a fertilized egg, these probably would be outnumbered by other cases in which fertilization of an egg that would not have subsequently implanted naturally is prevented because ECPs inhibited ovulation. Therefore, on balance, ECPs probably reduce the incidence of fertilized eggs that do not subsequently implant.

ECPs do not interrupt an established pregnancy, defined by medical authorities such as the United States Food and Drug Administration/National Institutes of Health⁷⁵ and the American College of Obstetricians and Gynecologists⁷⁶ as beginning with implantation. Therefore, ECPs are not abortifacient.

To make an informed choice, women must know that ECPs—like all regular hormonal contraceptives such as the birth control pill, the implant Implanon, the vaginal ring NuvaRing, the Evra patch, and the injectable Depo-Provera,⁷⁷ and even breastfeeding^{78,79,80,81}—may prevent pregnancy by delaying or inhibiting ovulation, inhibiting fertilization, or inhibiting subsequent implantation of a fertilized egg. At the same time, however, all women should be informed that the best available evidence is consistent with the hypothesis that levonorgestrel's ability to prevent pregnancy can be fully accounted for by mechanisms that do not involve interference with post-fertilization events.⁷⁰

Its very high effectiveness implies that emergency insertion of a copper IUD must be able to prevent pregnancy after fertilization.

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.⁸² 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,⁸³ progestin-only ECPs or insertion of a copper IUD may be preferable to use of combined ECPs for a woman 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.

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 regimens⁸⁴ 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 for 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.^{32,85} 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%).⁸⁶ 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.^{11,86} The levonorgestrel regimen has a significantly lower incidence of nausea and vomiting than the combined regimen; 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.³²

Three studies have been specifically designed to assess the effects of ECPs consisting of 1.5 mg levonorgestrel in a single dose on bleeding patterns. The first study found that when taken in the first three weeks of the menstrual cycle, ECPs 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 post-treatment menstrual cycle, but the second period was prolonged. Intermenstrual bleeding was uncommon after ECP use, although more common than among women who had not taken ECPs.⁸⁷ The second study compared the baseline cycle with the treatment and post-treatment cycles. Cycle length was significantly shortened by one day when ECPs were taken in the preovulatory phase of the cycle and was significantly lengthened by two days when ECPs were taken in the postovulatory phase. No difference in cycle length was observed for women who took ECPs during the periovulatory phase of the cycle (from two days before to two days after the expected day of ovulation). Menstrual period duration increased significantly when ECPs were taken in the periovulatory or postovulatory phase in both the treatment and post-treatment cycles. The duration of the post-treatment menstrual cycle remained significantly longer when ECPs were taken in the postovulatory phase. During the treatment cycle, 15% of women experienced intermenstrual bleeding; this was significantly more common when ECPs were taken in the preovulatory phase.⁸⁸ The third study examined the effects of two 0.75 mg levonorgestrel pills taken 12 hours apart.⁸⁹ When taken in the follicular phase, ECPs significantly shortened the cycle when compared with usual cycle length; no effect on cycle length was found when ECPs were taken in the periovulatory or luteal phase. The post-treatment cycle length was the same as the usual cycle length.

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, one study of 332 pregnant women who had used levonorgestrel-only ECPs in the conception cycle found no increased risk of birth defects.⁹⁰ Moreover, two observations provide reassurance for any concern about birth defects.⁵ 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.^{91,92,93} The FDA removed warnings about adverse effects of combined oral contraceptives on the fetus from the package insert years ago.⁹⁴

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.⁹⁵

Breastfeeding women

During the first 6 weeks postpartum, women who are fully breastfeeding and amenorrheic have little risk of pregnancy. There are no restrictions on use of ECPs by breastfeeding women.⁸² Only one study has examined levonorgestrel pharmacokinetics in plasma and milk of

lactating women who take 1.5 mg for emergency contraception. The authors conclude that to limit infant exposure to the period of maximum LNg excretion in milk, mothers should discontinue nursing for at least 8 hours, but not more than 24 hours, after taking ECPs.⁹⁶

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.⁹⁷ 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.

Ulipristal acetate is an antiprogestin. The implications for immediately starting hormonal contraceptives after taking it are unknown; specifically it is not known whether the regular instructions for abstaining or using condoms for 2 days (progestin-only pills) or 7 days (all other hormonal methods) are conservative enough.

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 contraceptive pill, Plan B, was approved a year later. A one-pill version Plan B One-Step, was approved in 2009, and a generic version of Plan B (Next Choice) was also approved in 2009. While availability of these products has helped, the two pharmaceutical companies initially 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 and subsequently by Teva Pharmaceuticals in December 2008, but Barr did not and Teva will not spend heavily on direct-to-consumer advertising. Neither will Watson Pharmaceuticals, the maker of Next Choice.

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.⁹⁸ As a consequence, many women do not know that emergency contraception is available, effective, and safe.⁹⁸

To help educate women and men about emergency contraception, the Association of Reproductive Health Professionals in Washington, D.C. and the Office of Population Research at Princeton University sponsor the Emergency Contraception Website (www.not-2-late.com). The Website has largely replaced the original Emergency Contraception Hotline, which was launched on February 14, 1996. Detailed information about emergency contraception is available on the Emergency Contraception Website, which was launched in October 1994 and now receives more than 150,000 visitors each month. The Website is completely confidential, available 24 hours a day in English and Spanish, and offers names and telephone numbers of providers of emergency contraception located near the user's zip code (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.⁹⁹ A paid public

education media campaign in Philadelphia and Seattle resulted in significant increases in knowledge about emergency contraception.¹⁰⁰

Additional barriers to ECP access persist and are perpetuated by U.S. institutions. That many hospital emergency departments do not provide emergency contraceptive services to women who have been raped is a tragic example of neglected preventive health care.^{101,102} Legal precedent also indicates that this failure constitutes inadequate care and confers to a woman in this situation the standing to sue the hospital.¹⁰³ It has been estimated that pregnancy following rape could potentially be reduced substantially if all women had access to EC after a sexual assault, a reduction of 22,000 pregnancies each year (though this is likely an overestimate for reasons given above).¹⁰⁴ Yet the Department of Justice makes no mention of emergency contraception in its 130-page *National Protocol for Sexual Assault Medical Forensic Examinations*, published in September, 2004.¹⁰⁵ Additionally, the Department of Defense Pharmacy and Therapeutics Committee removed the dedicated levonorgestrel ECP Plan B from the Basic Core Formulary (BCF) (medications which must be stocked at every full-service Medical Treatment Facility (MTF)) in May 2002, only one month after the drug had been added to the BCF¹⁰⁶ because of complaints from conservative members of Congress.¹⁰⁷ Whether the drug was stocked was left to the discretion of each MTF. Levonorgestrel ECPs were not available to all American soldiers serving overseas, which is of particular concern for women who are raped or face an unintended pregnancy for any reason, until Next Choice was added to the BCF on February 3, 2010.¹⁰⁸

Population impact of ECPs

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 would seem to demonstrate convincingly that making ECPs more widely available does not increase risk-taking or adversely affect regular contraceptive use.^{109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124} In the three studies that examined the impact of easier access to ECPs on rates of sexually transmitted infections, women randomly assigned to group given advance supplies of ECPs for later use should the need arise had the same incidence of infection as did women in the control group who had to obtain ECPs from a clinic.^{114,116,121,122} For example, in one randomized trial 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, did not use condoms or hormonal contraception less often, and did not exhibit higher rates of STIs.¹¹⁴ Another study demonstrated that educating teens about ECPs does not increase their sexual activity levels or use of EC but increases their knowledge about proper administration of the drugs.¹²⁵ However, reanalysis of one of the randomized trials suggests that easier access to ECPs may have increased the frequency of coital acts with the potential to lead to pregnancy.¹²⁶ Women in the increased access group were significantly more likely to report that they had ever used emergency contraception because they did not want to use either condoms or another contraceptive method.¹²⁷ Increased access to EC had a greater impact on repeat use among women who were at lower baseline risk of pregnancy.¹²⁸ This may explain in part why increased access to EC has had no measurable

benefit in clinical trials. Regardless, even if ECP availability does 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,^{122,124,129} although one demonstration project¹³⁰ and three clinical trials^{116,117,121} were specifically designed to address this issue. One 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. In the San Francisco trial, 45% of the women in the advance provision group who had unprotected intercourse during the study period did not use ECPs. In the Chinese trial, 30 women in the advance provision group did not use ECPs in the cycle in which they became pregnant. And in the Nevada/North Carolina trial, 33% of women in the advance provision group had unprotected intercourse at least once without using ECPs; 57 did not use ECPs in the cycle in which they became pregnant. In the demonstration project, 27 women with advance supplies became pregnant but never used ECPs.

Making Plan B available Over-the-Counter (OTC)

No medical reasons necessitate ECPs to be prescription-only products.^{131,132} Levonorgestrel ECPs are available OTC in Norway (2000), Sweden (2001), the Netherlands (2004), India (2005), and Canada (2008). In many other countries, ECPs can be obtained directly from a pharmacist without a prescription: In many other countries, ECPs can be obtained directly from a pharmacist without a prescription: Antigua, Aruba, Australia, Bahamas, Belgium, Belize, Benin, Burkina Faso, Cameroon, Chile, China, Congo, Denmark, Estonia, Finland, France, French Polynesia, Gabon, Ghana, Greece, Guinea-Conakry, Iceland, Israel, Ivory Coast, Jamaica, Latvia, Lesotho, Libya, Luxembourg, Mali, Mauritania, Mauritius, New Zealand, Niger, Portugal, Senegal, Slovakia, South Africa, Sri Lanka, St. Lucia, Switzerland, Tajikistan, Togo, Tunisia, and the United Kingdom.

In the United States, 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 available OTC.¹³³ 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. The independent Government Accountability Office concluded that the decision process was highly unusual and that the decision was made with atypical involvement from top agency officials and may well have been made months before it was formally announced.¹³⁴ 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, 2005 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

from 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.

This indefinite delay was heavily criticized.¹³⁵ Finally, on August 24, 2006, the FDA approved the nonprescription sale of Plan B for women and men aged 18 and older. Plan B One-Step was approved by the FDA as a nonprescription drug for women and men 17 and older in July 2009 (and Next Choice, a generic version of Plan B was approved in August 2009). Younger women will still need a prescription to buy the drug, and it will be kept behind the pharmacy counter, not on the shelf. The FDA decision is a qualified victory for women. Access is limited by whether a pharmacist is on duty and willing to dispense Plan B One-Step or Next Choice, and the lack of privacy may be a barrier to access for women who are embarrassed to ask a pharmacist for the drug. Further, the prescription requirement for young women obstructs timely access for many of the women most at risk for unintended pregnancy. Even so, nonprescription availability could facilitate access even for women aged 16 and younger, many of whom will likely circumvent the prescription requirement by getting parents, siblings, or older friends to buy it for them. The original age cutoff was chosen not based on any medical evidence that young women could not use emergency contraceptive pills safely or correctly, but rather, according to the FDA's Steven Galson, because it was easy for pharmacists to remember and enforce, since it is the same age limit placed on tobacco and nicotine-replacement products. Next Choice was approved by the FDA in June 2009 as a prescription medicine to women aged 17 and younger and in August 2009 as a prescription product to women aged 16 and younger and as a nonprescription product to women and men aged 17 and over.

In January 2005, the Center for Reproductive Rights filed suit in federal court against the FDA, alleging that the agency's failure to approve Plan B for over-the-counter use impermissibly denied women access to EC. In March 2009, The U.S. District Court for the Eastern District of New York in a blistering decision ordered the agency to reconsider its decision. It also ordered the FDA to act within 30 days to extend over-the-counter access to 17-year-olds. Judge Edward R. Korman was exceedingly blunt, stating that FDA had "acted in bad faith and in response to political pressure" and "repeatedly and unreasonably delayed issuing a decision on Plan B" and that the FDA's denial of nonprescription access to 17-year-olds "lacks all credibility" and was based on "fanciful and wholly unsubstantiated 'enforcement' concerns."¹³⁶ On April 22, 2009 the U.S. Food and Drug Administration announced that it would clear the way for Plan B's manufacturer to make it available without a prescription to 17-year-olds. And on July 13, 2009, the FDA approved Plan B One Step as a nonprescription drug for women and men aged 17 and over.

Two predictable, but unintended, negative outcomes have resulted from over-the-counter access to emergency contraception in the United States. One such consequence is the potential loss of opportunities for physicians to counsel patients about use of more effective, longer-term contraceptive methods when they present for emergency contraception.¹³⁷ Because emergency contraception is less effective than ongoing methods of hormonal contraception and IUDs, the

challenge remains for providers to find ways to encourage users of ECPs to initiate or continue a more effective ongoing method. Another consequence is an increase in price, from about \$25 per treatment to about \$45, and loss of insurance coverage in many, if not most, cases. This increase in cost could mean that even fewer women take emergency contraception when they are at highest risk of unintended pregnancy

Improving access to emergency contraception

Service delivery innovations can help to increase access to emergency contraception. One that benefits women aged 16 and under, who cannot purchase Plan B One-Step or Next Choice OTC, is enabling them to obtain ECPs directly from a pharmacist without having to see a physician, as is possible through state initiatives in 9 states (Alaska, California, Hawaii, Maine, Massachusetts, New Hampshire, New Mexico, Vermont, and Washington State.^{138,139,140}) This was an important innovation for all women before Plan B went OTC. Another alternative is screening by telephone or website, after which a prescription is called to the young 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.⁹⁸ The clinical practice bulletin issued by the American College of Obstetricians and Gynecologists¹⁴¹ should help clinicians achieve this goal. Information could be provided to women (and men!) in a culturally sensitive manner¹⁴² during counseling or by posters, brochures, audio or videocassettes, or wallet cards.

Cost effectiveness

Studies based on economic models have shown that 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.¹⁴³ Hormonal ECPs are cost effective regardless of whether they are provided when the emergency arises or provided beforehand as a routine preventive measure.^{10,144,145,146,147,148} Not only would making emergency contraception more widely available save medical care dollars, but additional social cost savings would result as well. 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.¹⁴⁹

All of these studies, however, have assumed that ECPs would actually be used after unprotected intercourse. But, as stated above, no published study has yet demonstrated that increasing access to ECPs reduces pregnancy or abortion rates in a population, at least in part because 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. Therefore, at the population level, advance provision of ECPs has not been demonstrated to be cost-effective. Whether ECPs are cost effective when they are provided after unprotected sex depends on what happens thereafter. If, as explicitly assumed in the economic models, a pregnancy averted by use

of ECPs is either avoided forever or postponed for two years, then the results hold. But, given the evidence from the advance provision trials that women do not use ECPs often enough when they are at risk, this assumption seems optimistic. A woman who averts a pregnancy using ECPs may experience another risky episode of unprotected intercourse shortly thereafter;¹⁵⁰ in that case, the effect of ECPs is simply to postpone a pregnancy for a short while.

Conclusion

Emergency contraception provides women with a last chance to prevent pregnancy after unprotected sex. Women deserve that last chance, and barriers to availability should be eliminated. But it is unlikely that expanding access will have a major impact on reducing the rate of unintended pregnancy, primarily because the incidence of unprotected intercourse is so high, ECPs are only moderately effective, and ECPs are not used often enough.

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Table 1. Oral contraceptives 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
<i>Progestin-only pills: take one dose^b</i>				
Plan B One-Step	Teva	1 white pill	0	1.5
Next Choice	Watson	2 peach pills	0	1.5
<i>Combined progestin and estrogen pills: take two doses 12 hours apart</i>				
Aviane	Teva	5 orange pills	100	0.50
Cryselle	Teva	4 white pills	120	0.60
Enpresse	Teva	4 orange pills	120	0.50
Jolessa	Teva	4 pink pills	120	0.60
Lessina	Teva	5 pink pills	100	0.50
Levora	Watson	4 white pills	120	0.60
Lo/Ovral	Akrimax	4 white pills	120	0.60
LoSeasonique	Teva	5 orange pills	100	0.50
Low-Ogestrel	Watson	4 white pills	120	0.60
Lutera	Watson	5 white pills	100	0.50
Lybrel	Wyeth	6 yellow pills	120	0.54
Nordette	Teva	4 light-orange pills	120	0.60
Ogestrel	Watson	2 white pills	100	0.50
Portia	Teva	4 pink pills	120	0.60
Quasense	Watson	4 white pills	120	0.60
Seasonale	Teva	4 pink pills	120	0.60
Seasonique	Teva	4 light-blue-green pills	120	0.60
Sronyx	Watson	5 white pills	100	0.50
Trivora	Watson	4 pink pills	120	0.50

Notes:

^a Plan B One-Step and Next Choice are the only dedicated products specifically marketed for emergency contraception. Aviane, Cryselle, Enpresse, Jolessa, Lessina, Levora, Lo/Ovral, LoSeasonique, Low-Ogestrel, Lutera, Lybrel, Nordette, Ogestrel, Portia, Quasense, Seasonale, Seasonique, Sronyx and Trivora have been declared safe and effective for use as ECPs by the United States Food and Drug Administration. Outside the United States, more than 100 emergency contraceptive products are specifically packaged, labeled, and marketed. Levonorgestrel-only ECPs are available either over-the-counter or from a pharmacist without having to see a clinician in 60 countries. Plan B One-Step and Next Choice are available over-the counter to women and men aged 17 and older.

- ^b The label for Plan B One-Step says to take the pill within 72 hours after unprotected intercourse. Research has shown that that all of the brands listed here are effective when used within 120 hours after unprotected sex. The label for Next Choice says to take one pill within 72 hours after unprotected intercourse and another pill 12 hours later. Research has shown that that both pills can be taken at the same time with no decrease in efficacy or increase in side effects and that they are effective when used within 120 hours after unprotected sex.
- ^c The progestin in Cryselle, Lo/Ovral, Low-Ogestrel and Ogestrel 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*⁹⁸

- 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

Emergency Contraception Resources

- Emergency Contraception Website: www.not-2-late.com
- ARHP EC Train-the-Trainer PowerPoint slide set: www.arhp.org/ec
- *Emergency Contraception*. ACOG Practice Bulletin, Number 69. Washington DC: The American College of Obstetricians and Gynecologists, December 2005. To order, call 508-750-8400. Also available in *Obstet Gynecol* 2005;**106**:1443-1451.

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): 800-682-9218, 642-5665, 539-2378
- Massachusetts (Planned Parenthood League of Massachusetts): www.pplm.org/clinic/pplm2.html
- Michigan (Planned Parenthood Mid-Michigan Alliance): 734-973-0710
- Minnesota (Boynnton Health Service): 612-625-4607
- Montana (Intermountain Planned Parenthood): 800-584-9911
- New Mexico (University of New Mexico Reproductive Health Program): 505-272-9304
- New York (Montefiore Medical Center): 917-641-5084
- North Carolina (Planned Parenthood of Central North Carolina): 866-942-7762
- North Carolina (Planned Parenthood Health Services): 800-230-PLAN, www.pphsinc.org/ec
- North Dakota (Boynnton Health Service): 612-625-4607
- Oregon (Planned Parenthood of the Columbia/Willamette): www.ppcw.org
- South Carolina (Planned Parenthood Health Services): 800-230-PLAN, www.pphsinc.org/ec
- South Dakota (Boynnton Health Service): 612-625-4607
- Washington (Planned Parenthood of the Columbia/Willamette): www.ppcw.org
- West Virginia (Planned Parenthood Health Services): 800-230-PLAN, www.pphsinc.org/ec
- Wisconsin (Family Planning and Reproductive Health Association): 866-ECFIRST (866-323-4778)