Emergency Contraception:
A Last Chance to Prevent Unintended Pregnancy

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Introduction

Half of all pregnancies in the United States are unintended: 3.2 million occurred in 2006 alone, the last year for which data are available.[1] Emergency contraception offers women a last chance to prevent pregnancy after unprotected intercourse. Emergency contraception is especially important for outreach to the 4.5 million women at risk of pregnancy but not using a regular method[2] 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 8.6 million women who rely on condoms for protection against pregnancy[2] 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).[3-5] The levonorgestrel-releasing intrauterine system (sold as Mirena in the United States) is currently being studied for use as EC.

Emergency contraceptive pills

There are three types of ECPs: combined ECPs containing both estrogen and progestin, progestin-only ECPs, and ECPs containing an antiprogestin (either mifepristone or ulipristal acetate). All three are available in the United States. 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.

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 combined, dedicated (meaning it was specially packaged for use as EC) EC product (Preven) was approved by the FDA in 1998 but withdrawn from the market in 2004.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, 26 brands of combined oral contraceptives are approved in the United States for use as emergency contraception (see Table 1). Research has demonstrated the safety and efficacy of an alternative regimen containing ethinyl estradiol and the progestin norethindrone;[6] this result suggests that oral contraceptive pills containing progestins other than levonorgestrel may also be used for emergency contraception.

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, 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 progestin-only products available in the United States include are Plan B One-Step (1.5 mg), approved by the FDA in July 2009 (Table 1), and several generic forms of Plan B One-Step including Next Choice One Dose, My Way, Take Action and AfterPill; two-dose LNG EC pills are no longer sold in the US.

The second-generation antiprogestin 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.[10-13] It has been marketed for use as emergency contraception in Europe since October 2009; it was approved by the FDA in August 2010 and is available for sale by prescription only, marketed under the brand name ella. Ulipristal acetate EC (sold as ellaOne) is available without prescription in Europe.

The antiprogestin mifepristone has also been extensively 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.)[14] However, the use of mifepristone as an abortion pill may limit its widespread acceptability for use for emergency contraception, and it is currently available only in Armenia, China, Russia, and Vietnam.

Meloxicam (a COX-2 inhibitor) 30 mg given for five consecutive days in the late follicular phase appears to be an effective emergency contraceptive option. This regimen does not alter the endocrine profile of the cycle and causes no menstrual disturbance.[15,16] (In contrast, the COX-2 inhibitor celecoxib appears to have no potential for emergency contraception.[17])

Copper-bearing IUDs

Implantation occurs 6-12 days following ovulation.[18] Therefore, copper IUDs can be inserted up to 5 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 8 days after intercourse. Because of the difficulty in determining the day of ovulation, however, many protocols recommend insertion up to only 5 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.[19] A copper IUD can also be left in place to provide effective ongoing contraception for up to 12 years. But IUDs are not ideal for all women. Women with active 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,[20] and use of a copper IUD is not associated with an increased risk of tubal infertility among nulligravid women (whereas infection with chlamydia is).[21]

New research about levonorgestrel IUDs as emergency contraception is emerging. One study compared copper IUDs and oral levonorgestrel EC pills with concomitant placement of a levonorgestrel IUD.[22] More women in this study chose oral LNG EC plus LNG IUD (121 women) over the copper IUD (67 women) at the time of their visit. There were no pregnancies in the

copper IUD group, and one pregnancy in the LNG group, which was determined to be an existing luteal phase pregnancy rather than a failure. This study may be too small to widely recommend this approach, but it is a promising area of future research.

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.[23,24] 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.[25] 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.[26] 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.[27]

Emergency contraceptive pills

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.[28]

Twelve studies of the levonorgestrel regimen that included a total of more than 13,500 women reported estimates of effectiveness (a reduction in a woman's chance of pregnancy) between 52% and 100%.[7-10,12,37,38,29- 33] A meta-analysis of eight studies of the combined (estrogen-progestin) 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.[34] 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.[35] 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.[28-30] 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.

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 with ovulatory dysfunction (88% vs. 66%, p=0.012). Adding a COX-2 inhibitor can disturb the ovulatory process after the onset of the luteinizing hormone (LH) surge.[36]

Three randomized trials published in English 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 trial[7] and 2.0% and 1.3% in the second.[37] 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%).[38] 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 meta-analysis of 20 Chinese randomized trials found that a mid-dose (25 mg or 50 mg) of mifepristone had a lower failure rate than did levonorgestrel; for the 13 trials that reported side effects, mifepristone was more tolerable but the delay in menses was greater for mifepristone.[14] A meta-analysis of 11 randomized trials (9 Chinese, 1 UK[37] and one multinational[7]) found that low dose (<25mg) mifepristone was more effective than levonorgestrel, but when only the 4 high-quality studies were included, mifepristone was not superior.[14] One Chinese trial found that the antiprogestin gestrinone was as effective as 10 mg mifepristone.[39]

The antiprogestin ulipristal acetate (30 mg in a single dose) is the most effective ECP option in the United States and Europe, with reported estimates of effectiveness ranging from 62% to 85%.[10-13] Two randomized trials compared the efficacy of levonorgestrel with the second-generation antiprogestin ulipristal acetate (UPA), one up to 72 hours after unprotected intercourse[10] and the second up to 120 hours after.[11] When these two studies were combined, the odds of pregnancy for UPA were 42% lower up to 72 hours and 65% lower in the first 24 hours.[12] In the second randomized study, 30 mg UPA prevented significantly more pregnancies than did levonorgestrel in the 72-120 hour subgroup. The reason seems to be that when ovulation is imminent, UPA is more effective than levonorgestrel in delaying it. By the time the leading follicle reaches 15-17 mm, follicular rupture is prevented within 5 days no more often after levonorgestrel administration than after placebo administration.[40] In contrast, when taken when the leading follicle reaches 18-20 mm (and ovulation should occur within 48 hours) and the probability of conception exceeds 30%, UPA prevents follicular rupture within 5 days of

administration in 59% of cycles, compared with 0% in placebo cycles.[41] The antiprogestins UPA and mifepristone are probably equally effective.

Copper IUDs

More than 7,000 postcoital insertions of copper-bearing IUDs have been reported in the literature since the practice was introduced in 1976. With only 10 known failures, this approach has a pregnancy rate of 0.1%.[42] The effectiveness of using a levonorgestrel-releasing IUD (LNG-20) for emergency contraception is being studied.

Factors Impacting Effectiveness

Treatment Delay: Several studies have indicated that both the combined and levonorgestrel regimens are more effective the sooner after sex the pills are taken.[7,8,30,31,43-45] Other studies of both regimens have not found this time effect,[6,9,10,37,38,29,46-48] although sample sizes were often small. The initial studies included only women who used the regimens within 72 hours after intercourse.[30,49] Consequently, some product package instructions, including that for Plan B One-Step and its generic counterparts such as Next Choice One Dose and Take Action, and older guidelines advise use only within that time frame. Some recent studies indicate that the regimens continue to be moderately effective if started between 72 and 120 hours.[7,8,9,31,47,48] However, a pooled analysis of four WHO trials of the levonorgestrel regimen shows no decline in efficacy until day 5, when it may offer no protection at all.[50] Analysis of the pooled data from the two Phase III trials of ulipristal acetate showed no statistically significant effect of treatment delay (0-24h 25-48h, 49-72h, 73-96h, 97-120h) on pregnancy rates ($p = 0.91$).[51] 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.[52] 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.

Body Mass Index: Analysis of data from the two randomized trials of the ulipristal acetate (UPA) and levonorgestrel (LNG) regimens found that when compared with women who were not obese, obese women taking LNG had a significantly higher risk of pregnancy whereas women taking UPA did not. LNG showed a rapid decrease of efficacy with increasing body mass index (BMI), reaching the point where it appeared no different from pregnancy rates expected among women not using EC at a BMI of 26 compared with a BMI of 35 for UPA.[53] The label for NorLevo (a 1.5 mg LNG) was changed in Europe in November 2013 to reflect the findings from further analyses of these data; the label stated: "In clinical trials, contraceptive efficacy was reduced in women weighing 75 kg or more and levonorgestrel was not effective in women who weighed more than 80 kg."[54] However, the European Medicines Agency, after reviewing additional data from three WHO trials[7,30,31] that did not find reduced efficacy with increasing weight or BMI, removed that statement from the Norlevo label in July 2014.[55] In May 2016, the US FDA similarly announced that the evidence was too limited to merit a label change, and encouraged EC manufacturers to further study this question.[56] This is an active area of pharmacokinetic

research: one recent study found that the serum concentration of LNG 1.5 mg was about 50% lower in obese women compared with normal BMI women.[57] The same study found that doubling the dose of LNG EC (from 1.5 mg to 3.0 mg) appeared to produce serum concentration levels similar to those in normal weight women who had taken the regular dose (1.5 mg). This is a small pharmacokinetic study that did not measure endpoints more directly related to effectiveness (ovulation or pregnancy), but it suggests that obesity does affect the bioavailability of LNG EC and that doubling the dose of LNG EC for obese women may be a reasonable approach. The effect of weight on the efficacy of combined ECPs has not been studied.

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.[58-61] 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.[59,62-64] However, other more recent studies have found no such effects on the endometrium.[58,65,66] 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.[4,67-69] 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.[70] However, if the effectiveness of combined ECPs was overestimated, which it seems to have been in that study, the results would be less persuasive.[35] Nevertheless, the important point is that effectiveness and mechanism of action are not independent, a point emphasized in later work.[52] 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.[40,71-75] No effect on the endometrium was found in two studies,[72,73] but in another study levonorgestrel taken before the LH surge altered the luteal phase secretory pattern of glycodelin in serum and the endometrium.[76] However, this finding was not confirmed in two later studies explicitly designed to assess endometrial glycodelin expression.[77,78] The second of these studies also found no effect on other endometrial receptivity biomarkers or progesterone receptors. In another study levonorgestrel taken before the LH surge increased serum and intrauterine concentrations of glycodelin at the time of ovulation; since glycodelin inhibits fertilization, this result may indicate an additional mechanism of action when ovulation is not inhibited.[79] 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.[80,81] 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;[82] 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.[77] A recent study found an effect on sperm function only with much higher levels of levonorgestrel than are used for emergency contraception.[83]

The reduced efficacy with a delay in treatment, even when use is adjusted for cycle day of unprotected intercourse,[44] 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.[84]

Studies in the rat and the Cebus monkey demonstrate that levonorgestrel administered in doses that inhibit ovulation has no postfertilization effect that impairs fertility.[69,85,86] Whether these results can be extrapolated to women is unknown. Croxatto and colleagues have argued that most, if not all, of the contraceptive effect of levonorgestrel-only ECPs can be explained by inhibited or dysfunctional ovulation, based on the existing animal and human studies, including two studies comparing observed and expected pregnancies when levonorgestrel-only ECPs were administered before and after ovulation. In the first study, no pregnancies were observed when ECPs were taken before the day of ovulation (in contrast to the 4 pregnancies that would have been expected without use of ECPs), whereas 3 pregnancies occurred when ECPs were taken after the day of ovulation (versus 3.5 expected pregnancies).[87] In a follow-up study no pregnancies were observed when ECPs were taken before the day of ovulation (in contrast to the 16 pregnancies that would have been expected without use of ECPs, whereas when ECPs were taken on or after the day of ovulation, 8 pregnancies occurred (*versus* 8.7 expected pregnancies).[33] A 2013 review concluded that levonorgestrel-only ECPs have no post-fertilization effect,[88] and the label for NorLevo (a 1.5mg LNG EC product available outside the United States that is identical to Plan B One-Step and its generic forms) has been updated to reflect the current evidence. The new label states: "The primary mechanism of action is blockade and/or delay of ovulation via suppression of the luteinizing hormone (LH) peak. Levonorgestrel interferes with the ovulatory process only if it is administered before the onset of the LH surge. Levonorgestrel has no emergency contraceptive effect when administered later in the cycle."[54]

One study has demonstrated that ulipristal acetate (UPA) can delay ovulation.[41] in this study, 34 women were treated when the size of the leading follicle was at least 18 mm. Each woman contributed one cycle treated with placebo and another with UPA. Follicular rupture failed to occur within 5 days following UPA treatment in 20 (59%) subjects while normal ovulation was observed in all women within 5 days after placebo intake. Follicular rupture failed to occur within 5 days after treatment with UPA in all women treated before onset of the LH surge, in 79% of women treated after the onset of the LH surge but before the LH peak, and in 8% of women treated after the LH peak. Another study was designed to assess whether UPA EC has similar efficacy when used before and after ovulation. The researchers measured pregnancy rates in women who took UPA within 120 hours of unprotected sex. The women were classified as pre-ovulatory or post-ovulatory based on several parameters, including serum LH, estradiol and progesterone levels, presence and size of a lead ovarian follicle >10 mm in mean diameter, and self-reported cycle length. Among women in the pre-ovulatory group, 77.6% of expected pregnancies were prevented, while in women who took UPA EC post-ovulation 36.4% of pregnancies were prevented. The pregnancy rate in the pre-ovulatory group was significantly lower than would be expected without the use of EC, while the rate in the

post-ovulatory group was not different than would have been expected if the women had not used any EC. This result builds on earlier work suggesting that the primary mechanism of action of UPA EC is interference with ovulation.[13] Other studies have focused on potential effects of UPA on the endometrium: one found that ulipristal acetate altered the endometrium, but whether this change would inhibit implantation is unknown.[89] Another study found that UPA, at the dosage used for EC, does not affect human embryo implantation process, in an *in vitro* endometrial construct.[90]

ECPs do not interrupt an established pregnancy, defined by medical authorities such as the United States Food and Drug Administration/National Institutes of Health[91] and the American College of Obstetricians and Gynecologists[92] 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,[93] and even breastfeeding[94-97]—prevent pregnancy primarily by delaying or inhibiting ovulation and inhibiting fertilization, but it is not scientifically possible to definitively rule out that a method may inhibit implantation of a fertilized egg in the endometrium. At the same time, however, all women should be informed that the best available evidence is that the ability of levonorgestrel and ulipristal acetate ECPs to prevent pregnancy can be fully accounted for by mechanisms that do not involve interference with post-fertilization events.

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 U.S. Medical Eligibility Criteria for Contraceptive Use (US MEC), there are no situations in which the risks of using combined or progestin-only ECPs outweigh the benefits (the US MEC does not include ulipristal acetate yet).[98] The US MEC 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,[99] ulipristal acetate or 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 regimens[100] 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. The label for ella

states that "Repeated use of ella within the same menstrual cycle is not recommended, as safety and efficacy of repeat use within the same cycle has not been evaluated."[101] However, a pharmacodynamics study of repeated use of UPA EC (every 7 days for 8 weeks) showed no safety concerns, indicating that UPA can be safely used more than once per cycle. The same study found that the majority of women in a smaller subgroup ovulated at least once during this period, suggesting that this may not be an effective longer-term method.[102] In addition, recent comprehensive review by CDC/WHO did not suggest any special safety concerns for the use of any type of ECPs among women with particular medical conditions or personal characteristics, such as pregnancy, lactation or frequent ECP use.[103]

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.[30,104] 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%).[105] 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.[6,105] 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.[30]

Three studies have been specifically designed to assess the effects of ECPs consisting levonorgestrel on bleeding patterns. All three found that the length of the menstrual cycle can be shortened when treatment occurs early in the cycle. The first study found that when taken in the first three weeks of the menstrual cycle, 1.5 mg levonorgestrel in a single dose significantly shortened that cycle as compared both to the usual cycle length and to the cycle length 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. However, when this regimen was taken later in women's cycles it had no effect on cycle length, but it did cause prolongation of bleeding during the next menstrual period. The ECPs had no effect on the length of the post-treatment cycle, but bleeding during the second period was prolonged. Intermenstrual bleeding was uncommon after ECP use, although more common than among women who had not taken ECPs.[106] The second study compared the baseline cycle with the treatment and post-treatment cycles when 1.5 mg levonorgestrel was administered in a single dose. 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). In both the treatment and post-treatment cycles, the duration of bleeding during the menstrual period increased significantly when ECPs were taken in the periovulatory or

postovulatory phase. The length of the post-treatment 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.[107] The third study examined the effects of two 0.75 mg levonorgestrel pills taken 12 hours apart.[108] 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.[109] Moreover, two observations provide reassurance for any concern about birth defects.[4] 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.[110-112] The FDA removed warnings about adverse effects of combined oral contraceptives on the fetus from the package insert years ago.[113]

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.[114,115]

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 combined or progestin-only ECPs by breastfeeding women.[98] 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.[116] One study compared outcomes among women who took progestin-only ECPs (after a breastfeed) and among women who used progestin-only oral contraceptives; there no adverse maternal and infant effects and no effect of continuation of breastfeeding among the women who took ECPs.[117] The label for ellaOne states "The effect on newborn/infants has not been studied. A risk to the breastfed child cannot be excluded. After intake of ellaOne breastfeeding is not recommended for one week. During this time it is recommended to express and discard the breast milk in order to stimulate lactation."[54] European guidelines have been updated to reflect that ellaOne is not contraindicated for breastfeeding women, but that breastmilk should not be given to a baby for a week after a woman has taken the product.[118]

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.[119] 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. Therefore there are implications for immediately starting progestin-containing hormonal contraceptives after taking it. One randomized double-blind placebo controlled study found no difference in the time (14 days) to achieve ovarian quiescence between the placebo group and the group who took combined oral contraceptives for 14 days; this finding implies that women should abstain or use a condom for 14 days when quick-starting combined hormonal contraceptives.[120] A second randomized cross-over study examined women who quick-started a desogestrel progestin-only oral contraceptive (75µg desogestrel, not available in the US) after taking UPA or a placebo.[121] No significant differences were found in time to ovarian quiescence or cervical mucus penetrability. That same study addressed the issue of whether quick-starting a progestin-only oral contraceptive reduces the efficacy of UPA and concluded that it impairs the ability of UPA to delay ovulation by at least five days. The FDA updated the ella package label to include warnings regarding the co-administration of ella and hormonal contraception. The label now states that if a woman wishes to use hormonal contraception after using ella, she should do so no sooner than 5 days after the intake of ella and that she should use a reliable barrier method until the next menstrual period. The label also now states that because ella and the progestin component of hormonal contraceptives both bind to the progesterone receptor, using them together may impair the ability of ella to delay ovulation. The European Medicines Agency (the European equivalent of the FDA) has decided not to modify its clinical recommendations for ella as it felt that the data were too limited.

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. A second generic product, Levonorgestrel Tablets, entered the market in 2010, two more products (Next Choice One Dose and My Way), one-pill products) were approved in 2012. Additional generic products, including Take Action and AfterPill, have become available recently. While availability of these products has helped, the 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 has Actavis Pharmaceuticals, the maker of Next Choice One Dose and ella (ella is now distributed in the United States by Afaxys Pharmaceutical). Nevertheless, among women aged 15-44 who have

ever had intercourse, the fraction who had ever used ECPs increased from 2% in 2002 to 10% in 2006-2008.[2]

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 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 900,000 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). An Arabic version of the website is available 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.[122] A paid public education media campaign in Philadelphia and Seattle resulted in significant increases in knowledge about emergency contraception.[123]

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.[124-126] Legal precedent also indicates that this failure constitutes inadequate care and confers to a woman in this situation the standing to sue the hospital.[127] 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).[128] Yet the Department of Justice made no mention of emergency contraception in its 130-page *National Protocol for Sexual Assault Medical Forensic Examinations*, published in September 2004;[129] this omission was partially rectified in the 2012 Prison Rape Elimination Act final rule that mandates that "inmate victims of sexual abuse while incarcerated must be offered timely information about, and timely access to, emergency contraception,"[130] and finally rectified in the second edition *of the National Protocol for Sexual Assault Medical Forensic Examinations*, published in April 2013.[131] 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 BCF[132] because of complaints from conservative members of Congress.[133] 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.[134]

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. 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. Published evidence would seem to demonstrate convincingly that making ECPs more widely available does not increase risk-taking or adversely affect regular contraceptive use.[135-152] In the four 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.[141,143,148,149] 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.[141] 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.[153] 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.[154] 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.[155] Increased access to EC had a greater impact on repeat use among women who were at lower baseline risk of pregnancy.[156] This finding 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. More recently, ecological studies comparing outcomes before and after ECPs became available without a prescription in the United States provide conflicting information about whether easier access to ECPs is associated with changes in behavior: one study found that women were 5% more likely to report multiple sexual partners after ECPs became available without a prescription,[157] but another study by the same author found exactly the opposite effect.[158] A third study suggested that condom use among public school students declined by 5-7% when ECPs became available without a prescription, highlighting the importance of education about STI transmission.[159]

On the other hand, only one[151] of 15 published studies has demonstrated that increasing access to ECPs can reduce pregnancy or abortion rates in a population,[160,161] although one demonstration project[162] and four clinical trials[143,144,148,151] 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.[143] And in the Nevada/North Carolina trial, 33% of women in the advance provision group had unprotected intercourse at least once without using ECPs.[148] The single exception occurred among women using the lactational amenorrhea method in Egypt.[151] Women in the advance provision group had a lower pregnancy rate (0.8% *versus* 5.0%, p=0.0002) in the first six months postpartum, but the reason is that these women were far more likely to start using an ongoing contraceptive; the authors argue that using ECPs allowed the women time to get to a clinic for ongoing contraception.

One study found no effect on birth or abortion rates in the United States as a result of Plan B being made available without prescription for those aged 18 and over.[163] A second study found a modest reduction in abortion rates among women aged 18-19 but no reduction among women aged 20-24 after the change;[164] the result for those aged 18-19 is unconvincing because the magnitude of the drop from 2000-2001 to 2002-2006 (before the change) is the same as that from 2002-2006 (before the change) to 2007-2009 (after the change).

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

No medical reasons indicate that ECPs should be prescription-only products.[165,166] Levonorgestrel ECPs are available OTC in Norway (2000), Sweden (2001), the Netherlands (2004), India (2005), Canada (some provinces, 2008) and Bangladesh (2012). In the United States, one-step ECPs are available OTC (2013). In many other countries, ECPs can be obtained directly from a pharmacist without a prescription. In Europe, UPA EC is available without prescription (as of 2015).

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.[167] 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.[168] 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.[169] Finally, on August 24, 2006, the FDA approved the nonprescription sale of Plan B for women and men aged 18 and older This age cutoff was not chosen 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.

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."[170] 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. On February 7, 2011, Teva submitted actual-use study data and label-comprehension study data on females <18 to the FDA. On December 7, 2011, the FDA was set to approve OTC status for Plan B with no age restriction based on the studies submitted by Teva. However, this action was overruled by the Secretary of Health and Human Services Kathleen Sebelius. Teva then filed an amended application to make Plan B One-Step available without prescription to consumers aged 15 and over and to allow it to be available in the family planning section of a pharmacy rather than behind the pharmacy counter; proof of age would still be required at checkout. On April 30, 2013, the FDA approved this amended application. In the meanwhile, on April 4, 2013, U.S. District Judge Edward R. Korman ordered the FDA to allow over-the-counter sales of LNG ECPs with no age restriction. In a scathing rebuke to the Obama administration, he stated that "the secretary's action was politically motivated, scientifically unjustified, and contrary to agency precedent."[171] On May 1, 2013, the Department of Justice announced that it would appeal his ruling, and subsequently did appeal and requested a stay of the order until the case was heard. On June 5, 2013, 2nd Circuit Court of Appeals ordered that the FDA must comply with Judge Korman's ruling to make 2-pill formulation of LNG EC available without restriction but granted a stay regarding 1-pill formulation.[172] On June 10, in a letter to Judge Korman, the Department of Justice said it would comply with his demand that Plan B One-Step be made available OTC with no age restriction.[173] Two days later, Judge Korman approved the Obama Administration's plan to make Plan B One-Step (and only Plan B One-Step) available OTC with no age restriction.[174]

In August 2013, Plan B One-Step became available without prescription to males and females with no age restriction. In most pharmacies it is located on the shelf in the family planning aisle; some pharmacies may choose to keep it in a locked cabinet. One-pill generics (such as Take Action, My Way and Next Choice One Dose) are now approved for sale on the shelf as well. Until April 2016, a required use recommendation on generic packaging stated that the product is intended for use by women aged 17 and older (although this was <u>not</u> intended as an

enforceable restriction). Teva's exclusivity on OTC sale to all ages expired in April 2016, so generic manufacturers are no longer required to include this language on their packaging, although some old stock main remain on shelves for several months. As far as we understand, two-pill generics are no longer sold in the United States (but the age restriction on the sale remains for any two-pill generics that are still in stock; two-pill generics must be sold behind the counter and a prescription was required for women under the age of 17).

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.[175] Because emergency contraceptive pills are 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. However, new legislation in Maryland (called the Contraceptive Equity Act), which passed on 2016 and will be implemented in January 2018, will require insurers to cover OTC contraceptive medications, including EC; hopefully this model will spread to other parts of the US.

Improving access to emergency contraception

Service delivery innovations can help to increase access to emergency contraception. In some states (Alaska, California, Hawaii, Maine, Massachusetts, New Hampshire, New Mexico, Vermont, and Washington State[176-178]) collaborative practice agreements allow pharmacists to directly dispense emergency contraceptive pills without prescription. Since levonorgestrel EC products are now available OTC, these agreements are no longer necessary for younger women to access LNG EC; however such agreements could be expanded to include ella (some already do). Ella may be purchased online for $67 following a medical screener through the website www.ella-kwikmed.com or its companion website, www.prjktruby.com. An online source for the FDA-approved LNG EC product AfterPill is www.afterpill.com; here, consumers can purchase one pack for $20 plus $5 shipping, or 3 packs for $60 plus $5 shipping.

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, particularly the more effective methods. One recent study found that only 29% of healthcare providers across specialties who treat women of reproductive age had heard of UPA EC, and only 7% recommended or provided it. Among reproductive health specialists, 52% were aware of UPA EC and 14% offered it.[179] Another challenge for UPA EC is that it is not always routinely stocked in pharmacies; a study in Hawaii found that while 82.4% of pharmacies stocked the OTC option for EC (LNG), only 2.6% had UPA immediately available.[180]

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 12 years thereafter, producing savings if used as an ongoing method of contraception for as little as four months after emergency insertion.[181] Hormonal ECPs are cost effective regardless of whether they are provided when the emergency arises or provided beforehand as a routine preventive measure.[182- 189] 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.[190]

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;[191] 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. Pills 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]
Antiprogestin pills: take one pill				
ella[d]	Actavis	1 white pill	0	0
Progestin-only pills: take one dose[b]				
Plan B One-Step	Teva	1 white pill	0	1.5
Generic one-dose pills (Including My Way, Next Choice One Dose, Take Action and AfterPill)	Various	1 pill	0	1.5
Combined progestin and estrogen pills: take two doses 12 hours apart				
Altavera	Sandoz	4 peach pills	120	0.60
Amethia	Actavis	4 white pills	120	0.60
Amethia Lo	Actavis	5 white pills	100	0.50
Amethyst	Actavis	6 white pills	120	0.54
Aubra	Afaxys	5 white pills	100	0.50
Aviane	Teva	5 orange pills	100	0.50
Camrese	Teva	4 light blue-green pills	120	0.60
CamreseLo	Teva	5 orange pills	120	0.50
Chateal	Afaxys	4 white pills	120	0.60
Cryselle	Teva	4 white pills	120	0.60
Enpresse	Teva	4 orange pills	120	0.50
Introvale	Sandoz	4 peach pills	120	0.60
Jolessa	Teva	4 pink pills	120	0.60
Lessina	Teva	5 pink pills	100	0.50
Levora	Actavis	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	Actavis	4 white pills	120	0.60
Lutera	Actavis	5 white pills	100	0.50
Lybrel	Wyeth	6 yellow pills	120	0.54
Nordette	Teva	4 light-orange pills	120	0.60

Ogestrel	Actavis	2 white pills	100	0.50
Portia	Teva	4 pink pills	120	0.60
Quasense	Actavis	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	Actavis	5 white pills	100	0.50
Trivora	Actavis	4 pink pills	120	0.50

Notes:

[a] The oral contraceptive pills listed above have been declared safe and effective for use as ECPs by the United States Food and Drug Administration. One-pill EC products (such as Plan B One-Step, Next Choice One Dose, My Way, and Take Action) are available over-the counter without restrictions. ella is prescription-only regardless of age. 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. For a worldwide directory of pills that can be used for emergency contraception, see http://ec.princeton.edu/worldwide/default.asp#country.

[b]The labels for one-pill LNG EC products (including Plan B One-Step, Next Choice One Dose, My Way and Take Action) say to take the pill within 72 hours after unprotected intercourse. Research has shown that they are effective when used within 96 hours after unprotected sex. The label for Levonorgestrel Tablets 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 96 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.

[d] ella contains 30 mg ulipristal acetate.