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Emergency contraception review: evidence-based recommendations for clinicians

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Abstract

Several options for emergency contraception are available in the United States. This article describes each method, including efficacy, mode of action, safety, side effect profile and availability. The most effective emergency contraceptive is the copper IUD, followed by ulipristal acetate and levonorgestrel pills. Levonorgestrel is available for sale without restrictions, while ulipristal acetate is available with prescription only, and the copper IUD must be inserted by a clinician. Although EC pills have not been shown to reduce pregnancy or abortion rates at the population level, they are an important option for individual women seeking to prevent pregnancy after sex.

Keywords

Emergency contraception; morning-after pill; levonorgestrel; ulipristal acetate; copper IUD

Introduction

Preventing unintended pregnancy is a significant concern at the public health level and is critically important for individuals seeking to determine the number and spacing of their children. Unprotected sex occurs for multiple and complex reasons; these include sexual assault or reproductive coercion, lapse in adherence to an ongoing method of contraception, a contraceptive mishap (such as condom breakage), and lack of contraceptive use. Fortunately, several options are available for contraception that can be used after unprotected sex has already occurred; these methods, collectively referred to as emergency contraception, include different types of pills and the copper IUD. Here, we describe these methods, including their efficacy, mode of action, safety, side effect profile, availability, and any special issues relevant to each method.

Overview of EC Options

The most commonly-available emergency contraceptive option is levonorgestrel 1.5 mg, sold in the United States as Plan B One-Step (Teva Pharmaceuticals, North Wales, PA) and in generic form including Take Action (Teva Pharmaceuticals, North Wales, PA), Next Choice One-Dose (Actavis Pharmaceuticals, Parsippany, NJ), My Way (Gavis Pharmaceuticals, Somerset, NJ), and Levonorgestrel Tablets (Perrigo, Allegan, MI). After years of regulatory battles, in August 2013, Plan B One-Step was approved for sale without restrictions to women and men of any age on store shelves. In February 2014, the Food and Drug Administration (FDA) approved generic versions of Plan B One-Step for unrestricted sale (until recently, these were available without prescription only to those aged 17 or older).

The other type of dedicated emergency contraceptive pill (ECP) available in the U.S. contains 30 mg ulipristal acetate, and is marketed as ella (Actavis Pharmaceuticals, Parsippany, NJ). Ella is available by prescription only for women of any age. In addition to these dedicated ECPs, many types of oral contraceptive pills can be used (in various combinations, depending on pill formulation) as EC – this is often referred to as the Yuzpe method. The Yuzpe method is less effective and causes more side effects than levonorgestrel or ulipristal acetate ECPs. A list of the oral contraceptive pills that can be used as EC can be found at <http://ec.princeton.edu/questions/dose.html>. The copper intrauterine device (IUD), available in the US under the trade name ParaGard T-380 (Teva Pharmaceuticals, North Wales, PA) is the most effective option for emergency contraception, and has been used as EC for more than 35 years. Although studies are currently underway, no published data are available about use of the levonorgestrel intrauterine system (sold in the United States as Mirena (Bayer Healthcare Pharmaceuticals, Whippany NJ)) as EC, and this use is not recommended at this time.

Other options for emergency contraception are available in other countries, or are under investigation as potential new methods. Mifepristone, available as EC in doses of 10 to 25 mg in a small number of countries, is safe and effective but is not currently available for use as EC in the US. When added to 1.5 mg levonorgestrel, the COX-2 inhibitor meloxicam (15 mg) has been shown to block follicular rupture even after the ovulatory process has been stimulated by the gonadotropin surge,¹ and administration of meloxicam alone (15 or 30 mg for five days) has been shown to be effective in disrupting ovulation in a pilot study;² these are not yet marketed anywhere as EC products.

Efficacy

For ongoing contraceptive methods, efficacy is usually measured as the number of pregnancies that occur among users over a given period of time. In contrast, the efficacy of emergency contraceptives is usually expressed as the proportion of expected pregnancies that are averted by the method. A complex set of assumptions must be made to produce estimates of EC efficacy, the most important of which is how many pregnancies would have occurred if EC had not been used. This assumption is often flawed and imprecise; therefore estimates based on it are also imprecise. Here, we present failure rates of EC from clinical

trials (rather than the proportion of expected pregnancies averted), including comparative data showing the relative effectiveness of different methods.

The copper IUD is by far the most effective option for emergency contraception; a review of 42 studies showed that the pregnancy rate after insertion of the copper IUD for EC is less than 0.1%,³ indicating that it averts almost all expected pregnancies. The copper IUD has the added benefit of providing at least 12 years of highly effective ongoing contraception if left after placement for EC.

Ulipristal acetate is the most effective ECP available in the United States. In clinical trials, failure rates for ulipristal acetate range from 0.9% to 2.1%.⁴⁻⁶ Pregnancy rates following use of levonorgestrel ECPs in clinical trials range from 0.6% to 3.1%.^{4,6-17} A meta-analysis of two studies comparing ulipristal and levonorgestrel ECPs found that the odds of pregnancy among users of ulipristal were 42% lower than among users of levonorgestrel in the first 72 hours after sex, and 65% lower in the first 24 hours after sex.⁶ The greater efficacy of ulipristal is most likely due to the fact that it is effective at disrupting ovulation even after the luteinizing hormone (LH) surge has begun, while levonorgestrel is ineffective after the start of the LH surge.^{17,18}

Combined oral contraceptive pills that can be used for EC, which contain both estrogen and progestin, are the least effective EC method. Failure rates reported from clinical trials range from 2.0% to 3.5%.^{13,14,19} In trials comparing the combined regimen with the dedicated levonorgestrel regimen, the pregnancy rate among users of the combined regimen was about twice that of women who used levonorgestrel ECPs.^{13,14,20}

Although ECPs are effective at reducing pregnancy risk for individuals, they have not been shown to reduce rates of unintended pregnancy or abortion at the population level.^{21,22} This finding may be due in part to the fact that, even when provided with ECPs in advance of need, women do not use them every time they are at risk. In one trial, 45% of women who were given an advance supply of ECPs who had unprotected sex did not use ECPs;²³ in another trial, 33% of women with an advance supply of ECPs had unprotected sex at least once without using ECPs.²⁴ Given that most women do not have an advance supply of ECPs at home, and must go to a clinic or pharmacy to purchase ECPs after the fact, the proportion of women who have unprotected sex without using ECPs is likely substantially higher than found in these trials. Another explanation is that women who have EC readily available may increase their coital frequency or decrease their use of other contraceptives. Most studies find no evidence of such behavior change, but it was documented in one randomized trial.²⁵

While these findings suggest that ECPs are not a solution for reducing rates of unintended pregnancy and abortion at the population level, ECPs are nevertheless an important option for individual women who have had unprotected sex. Clinicians should remind patients about this option, especially those who are using short-term or user-dependent methods. Because levonorgestrel ECPs are now available directly from pharmacies without a prescription, clinicians may not see their patients at the time that they need EC, and therefore may wish to integrate reminders about the importance of EC into routine visits. The copper IUD is an excellent option for women who are likely to experience multiple

episodes of unprotected sex, as it is highly effective at preventing pregnancy following an act of unprotected sex, as well as all subsequent acts of unprotected sex for at least 12 years. A recent study that followed women who sought EC at a clinic for one year showed that those who chose the copper IUD for EC became pregnant half as often by the end of the year as those who chose levonorgestrel ECPs, demonstrating the longer-term benefits of postcoital use of the copper IUD.²⁶

Efficacy and Body Weight

The efficacy of ECPs may be reduced in women of higher body weight. Although no studies have been specifically conducted to assess the relationship between weight and efficacy of EC products, a 2011 analysis showed decreased efficacy for women with higher body mass index (BMI) for both levonorgestrel and ulipristal EC; among women with a BMI of 30 kg/m² or higher, the failure rate was 5.8% for those using levonorgestrel and 2.6% for those using ulipristal. A model developed by the authors showed that levonorgestrel may be ineffective for women with a BMI of 26 kg/m², and ulipristal may be ineffective for women with a BMI of 35 kg/m².¹⁰ No studies have been conducted to determine whether increasing the dose would improve efficacy; therefore, offering a higher dose is not recommended. If possible, women weighing more than 165 lbs should be offered ulipristal or the copper IUD. The copper IUD is the most effective EC option, and efficacy does not appear to be affected by the user's weight. However, barriers to access may make it difficult for women to obtain ulipristal or a copper IUD quickly after unprotected sex; in this case, it may be worthwhile for the woman to take levonorgestrel ECPs, regardless of her weight, if she is able to afford it.

Efficacy and Drug interactions

Specific data about interactions of ECPs with other drugs are not available; however, experts assume that interactions would be similar to those with regular oral contraceptive pills. Drugs that reduce the efficacy of oral contraceptive pills, such as rifampin, griseofulvin, certain anticonvulsant drugs, Saint John's wort, and certain antiretroviral drugs may also reduce the efficacy of levonorgestrel, ulipristal acetate, and combined ECPs.²⁷ Women using these medications who need EC should be offered the copper IUD as EC as a first-line option, as the efficacy of the copper IUD is not affected. If women using these medications prefer to use levonorgestrel EC (or if it is the only method readily available), some clinical guidelines recommend doubling the dose to 3 mg.²⁸ Ulipristal is not recommended in women using enzyme-inducing drugs.

Because ulipristal is a progesterone receptor modulator, and therefore blocks progestin, it may reduce the efficacy of other hormonal contraceptives containing progestin. Study of this relationship is underway, but results have not yet been published. A conservative approach for women continuing or starting progestin-only methods after use of ulipristal is additional precautions (abstinence or a barrier method) for 14 days following use of ulipristal.²⁸

Regimen Timing

All emergency contraceptive pills (ECPs) should be taken as soon as possible after unprotected sex. ECPs work by interfering with ovulation, and because women frequently do not know precisely when they are at the most fertile period of their menstrual cycle,²⁹ prompt use may improve the chance of preventing or disrupting ovulation.

The original levonorgestrel regimen consisted of two 0.75 mg pills, to be taken 12 hours apart. The two-pill regimen has almost entirely been replaced by the single-pill product (1.5 mg), but patients may encounter the two-pill regimen occasionally and should be advised to take both pills together as soon as possible after sex. Although the package insert indicates use for only 72 hours after unprotected sex, some research has shown levonorgestrel ECPs to be effective up to 4 days after sex and ineffective thereafter,³⁰ while other analyses suggest that levonorgestrel ECPs are effective up to 5 days after sex, but with declining efficacy.⁶

Clinical guidelines recommend insertion of an IUD within 5 days of unprotected intercourse,³¹ or within 5 days of ovulation (if ovulation can reasonably be determined).^{28,32,33} However, a recent analysis showed that the copper IUD is highly effective at any point in the menstrual cycle, as long as a negative urine pregnancy test result is obtained prior to insertion of the IUD.³⁴

Women who seek EC from a clinician but prefer to not to use a copper IUD for EC should be offered another form of highly effective ongoing contraception. Studies have demonstrated that simultaneously offering EC and quick-starting depot-medroxyprogesterone acetate is safe and effective;^{35–37} similar protocols for the levonorgestrel intrauterine system or etonogestrel implant could significantly reduce longer-term pregnancy risk. A recent pilot study in Scotland found that a simple intervention in which pharmacists provided women presenting for EC with a cycle of progestin-only pills significantly increased the probability of the women using effective contraception six to eight weeks following EC use.³⁸

Repeated Use of ECPs

ECPs are not intended for deliberate repeated use or use as a routine method of contraception because far more effective (and cost-effective) methods are available. Women who present for emergency contraception should be offered a copper IUD or another ongoing method of their choosing if they do not want to become pregnant. No specific data are available about the efficacy or safety of the available ECP regimens when used frequently over a long period of time. However, at least 11 studies have confirmed that levonorgestrel 0.75 mg administered multiple times per cycle causes no serious adverse events.³⁹ These data provide reassurance that using the levonorgestrel regimen as often as needed to prevent pregnancy after unprotected sex is safe.

Repeated use of ulipristal in the dose used for emergency contraception (30 mg) has not been specifically studied, but ulipristal in daily doses of 5 mg and 10 mg over the course of several weeks has been studied for treatment of uterine fibroids and appears to be safe and

well-tolerated.⁴⁰ The National Institute of Child Health and Human Development is beginning to investigate daily use of ulipristal acetate in doses of 5 mg or 10 mg as a daily oral contraceptive.⁴¹

Whether the efficacy of levonorgestrel ECPs is reduced by recent or subsequent use of ulipristal, which is a progesterone receptor modulator, is unknown. Therefore, if a woman who has recently used the levonorgestrel regimen has a subsequent need for emergency contraception, she should be advised to use levonorgestrel again or have a copper IUD inserted. Despite the lack of clear evidence to support or refute repeated use of ulipristal in the same cycle, the label for ulipristal EC products recommends against using the product more than once within the same cycle. If a woman who has recently used ulipristal has a subsequent need for emergency contraception, she should consider a copper IUD if that is acceptable and available; if an IUD is unacceptable or unavailable, some guidelines support use of levonorgestrel ECPs if another episode of unprotected intercourse occurs following use of ulipristal.²⁸

Mechanism of Action

The question of how levonorgestrel ECPs work to prevent pregnancy has been studied extensively. Two recent studies demonstrate that levonorgestrel ECPs, if taken before the luteinizing hormone (LH) surge has begun, can inhibit the LH surge, thereby disrupting the ovulatory process, but are ineffective thereafter.^{17,18} In these studies, a combined total of 492 women presenting for EC were monitored using blood serum and ultrasound to assess their cycle day. Among those who took EC before ovulation, none became pregnant, whereas 20 pregnancies would have been expected. Those who took EC on the day of ovulation or after became pregnant at the rate that would have been expected if no contraception had been used (11 women became pregnant, and 11 or 12 pregnancies would have been expected). These studies conclude that, because levonorgestrel ECPs are ineffective after ovulation has occurred, they do not interfere with the implantation of fertilized eggs. Levonorgestrel ECPs have been postulated to interfere with sperm function, tubal transport of sperm or egg, or endometrial receptivity, but evidence of these mechanisms is inconsistent across studies.⁴² Levonorgestrel ECPs have no effect if taken after implantation has occurred; the regimen does not affect an existing pregnancy or increase rates of miscarriage.^{43,44}

Ulipristal acetate has been shown to prevent ovulation both before and after the LH surge has started (but before the LH peak), delaying follicular rupture for at least 5 days.⁴⁵ In this study, ulipristal did not prevent ovulation in the vast majority of women treated with ulipristal after the LH peak. The fact that ulipristal is effective after the start of the LH surge, while levonorgestrel is not, may account for its greater effectiveness. Published post-marketing surveillance data for ulipristal acetate show no increased risk of miscarriage among women who took ulipristal when they were already pregnant, or became pregnant due to failure of ulipristal; in addition, exposure to ulipristal in utero did not increase the risk of birth defects among babies born.⁴⁶

The precise mechanism of action of the copper IUD is unknown. Copper ions released into the uterine cavity may inhibit sperm function,⁴² and the presence of the IUD may also induce an inflammatory response that could impair transport of gametes or the fertilized egg or inhibit implantation. These effects may contribute to its near-perfect effectiveness as a method of emergency contraception.

Safety and Contraindications

ECPs are not dangerous under any known circumstances or in women with any particular medical conditions. According to the Center for Disease Control's Medical Eligibility Criteria for Contraceptive Use, no circumstances exist under which the risks of using combined or levonorgestrel ECPs outweigh the benefits.³³ These criteria do not yet include ulipristal, but ulipristal would most likely receive the same safety rating. Recognized contraindications to oral contraceptives do not apply to ECPs. Furthermore, women with a history of cardiovascular disease, migraines, liver disease, and women who are breastfeeding may use levonorgestrel ECPs.³³ The U.S. label for ulipristal acetate recommends against use by breastfeeding women; however, European guidelines have been updated to reflect that ulipristal may be used by breastfeeding women, but that breastmilk should not be given to a baby for a week following its use.⁴⁷ Breastfeeding women using ulipristal should be advised to pump and discard the milk for a week to maintain supply.

History of ectopic pregnancy is not a contraindication for use of ECPs. A systematic review found that when ECPs fail, the proportion of pregnancies that are ectopic does not exceed the proportion of ectopic pregnancies in the general population.⁴⁸ Like all contraceptive methods, ECPs reduce the absolute risk of ectopic pregnancy by preventing pregnancy in general.

Concerns about pelvic inflammatory disease (PID) following insertion of an IUD may limit providers' willingness to offer IUDs to women seeking EC. Current guidelines recommend against IUD insertion in women known to currently have PID, purulent cervicitis, active gonorrhea or Chlamydia infection.³² However, a study of nearly 58,000 IUD insertions found a low absolute risk of PID following IUD insertion, regardless of whether patients were screened within one year before insertion, within eight weeks before insertion, on the day of insertion, or not screened at all.⁴⁹ This study suggests that, for women presenting for IUD insertion, it is reasonable to simultaneously insert an IUD and screen high-risk patients for STIs, then promptly treat those with positive results. For patients at low risk of sexually transmitted infections, who are also at very low risk of PID, requiring two visits (one to test for STI and another to insert the IUD) places significant and unnecessary burdens of inconvenience and cost on the patient. Two-visit protocols have been shown to reduce the proportion of women who ultimately receive an IUD.⁵⁰

Side effects

Emergency contraceptive pills have an excellent safety profile, and no deaths or serious complications have been causally linked to any ECP regimen. ECPs may cause some side effects that are typically mild and transient. The most common side effect of ECPs is changes in the menstrual period that follows use of ECPs. These changes may vary

depending on when in the cycle the pills are taken, according to three studies designed to study the effects of levonorgestrel ECPs on the menstrual cycle.^{51–53} These studies show that when levonorgestrel ECPs are taken early in the cycle, they shorten cycle length, but when they are taken later in the cycle, they may have no effect on cycle length or may prolong the length of the cycle. In a study comparing ulipristal and levonorgestrel ECPs, menstruation occurred on average one day earlier than expected for users of levonorgestrel ECPs, and two days later than expected for users of ulipristal ECPs.⁶

Users of the copper IUD may experience changes in bleeding patterns as well, particularly heavier menstrual bleeding. However, evidence suggests that some of these changes decrease over time for many users.⁵⁴ Counseling that helps women anticipate changes in bleeding patterns, as well as the fact that these changes may subside over time, may improve both uptake and retention of the IUD. Patients may experience pain during the insertion process, as well as increased cramping following insertion. About 5% of women experience expulsion of their IUD within the first year of use,⁵⁵ and must have a new IUD placed or switch to a different form of contraception if they desire ongoing pregnancy prevention.

Nausea (rarely accompanied by vomiting) occurs in less than 20% of women using the levonorgestrel regimen,^{7,56} and in about 12% of women using the ulipristal regimen.^{5,6} These newer regimens induce nausea and vomiting far less often than the combined estrogen-progestin regimen; the combined regimen causes nausea in about 50% of users, and vomiting in 20%.¹⁴ If vomiting occurs within two or three hours after taking a dose of ECPs, some experts recommend that the dose should be repeated.²⁸

Access and Availability

Levonorgestrel ECPs are the most widely available EC method in the US. Restrictions on the availability of levonorgestrel ECPs have no medical basis, yet the process of gaining approval for unrestricted over-the-counter sale has been long, arduous, and fraught with political interference. After years of complicated and frequent regulatory changes, all one-pill levonorgestrel ECPs are approved for sale on the shelf with no restrictions. Although the label for generic ECPs indicates that the product is for women age 17 and older, proof of age and point of sale restrictions no longer apply.⁵⁷

The cost of levonorgestrel ECPs is a considerable barrier for many women, as the out-of-pocket cost for branded product is \$48 on average, while the average cost of generics is approximately \$41.⁵⁸ Women may be able to have this product covered by their insurance; patients should be reminded to check with their insurance provider to determine whether a prescription is needed for insurance coverage.

The alternative dedicated ECP in the US, ulipristal acetate, is available by prescription only. The prescription requirement creates multiple potential barriers to access, as women must be aware that this more effective product is available, contact a healthcare provider to prescribe it, and find a pharmacy that has the medication in stock or can order it for next-day delivery. Ulipristal is likely to be covered by health insurance, but patients should check with their provider to ensure that it is included in their insurance company's formulary and is available at a nearby pharmacy.

The copper IUD is the most effective EC option, but it can also be the most difficult to obtain. The use of IUDs is growing in the United States, but awareness of its use as EC is low. A 2012 study showed that, among clinicians participating in a California State family planning program, 85% of clinicians never recommended the copper IUD for EC.⁵⁹ The same study showed that the majority of providers required two visits for an IUD insertion, which is burdensome for patients and medically unnecessary. In addition, some outdated attitudes about IUDs inhibit providers from offering IUDs to all women, particularly young and nulliparous women. IUDs are safe and effective for women of any age, regardless of whether they have had a previous pregnancy; the American College of Obstetricians and Gynecologists recommends IUDs and implants as a first-line contraceptive option for nearly all women, and encourages same-day insertion protocols.⁶⁰ Cost has historically been a substantial barrier to accessing IUDs. However, the Preventive Services Provision of the Affordable Care Act, which requires that all FDA-approved contraceptives be covered by insurance plans with no co-pay, should improve access to IUDs for many women. Uninsured women may be able to obtain an IUD from a subsidized family planning clinic.

Conclusion

The availability of several options for emergency contraception is a benefit to all women who are at risk for pregnancy following unprotected sex. Although many women obtain levonorgestrel ECPs directly from a pharmacy without consulting a clinician, clinicians have an important role in reminding women that they have options for preventing pregnancy even after unprotected sex has occurred. Patients should be counseled that the copper IUD is the most effective option for emergency contraception; if this option is not acceptable or available, same-day provision of highly effectively long-acting methods should be offered if ongoing pregnancy prevention is desired by the patient.

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