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Emerging Options for Emergency Contraception

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Abstract: Emergency post-coital contraception (EC) is an effective method of preventing pregnancy when used appropriately. EC has been available since the 1970s, and its availability and use have become widespread. Options for EC are broad and include the copper intrauterine device (IUD) and emergency contraceptive pills such as levonorgestrel, ulipristal acetate, combined oral contraceptive pills (Yuzpe method), and less commonly, mifepristone. Some options are available over-the-counter, while others require provider prescription or placement. There are no absolute contraindications to the use of emergency contraceptive pills, with the exception of ulipristal acetate and mifepristone. This article reviews the mechanisms of action, efficacy, safety, side effects, clinical considerations, and patient preferences with respect to EC usage. The decision of which regimen to use is influenced by local availability, cost, and patient preference.

Keywords: emergency contraception, levonorgestrel, intrauterine device, emergency contraceptive pills

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Introduction

Approximately forty percent of all pregnancies worldwide are unintended, with higher unintended pregnancy rates in developing (57 per 1,000 women aged 15–44 years of age) vs developed regions (42 per 1,000 women aged 15–44 years of age).^{1,2} Emergency contraception (EC) is an important tool in preventing unintended pregnancies and is now widely available in most countries. Early regimens, described as the Yuzpe method, consisted of taking higher doses of estrogen/progesterone combination oral contraceptives. This method was found to be less effective and the side effect profile higher than with newer methods.³ Currently there are several options, including pills: progestin-only (levonorgestrel), progesterone modulators (ulipristal acetate), antiprogestosterone synthetic steroids (mifepristone), and the copper intrauterine device (IUD). In many countries, levonorgestrel has been given over-the-counter status, allowing earlier and easier access. While the mechanism of action of many of these methods is not completely understood, most are thought to work by delaying or preventing ovulation, and thus are not considered abortifacients. Of the previously described methods, the copper IUD is the most effective. The following is a review of the various options for EC. See Table 1 for a summary.

Mechanism of action

The mechanism of action of EC methods is incompletely understood. Although the time of ovulation may be difficult to predict, the fertile window extends from 5 days before ovulation (the lifespan of a sperm within the female genitourinary (GU) tract) to the day of ovulation (after which time the ovum deteriorates)⁴ (Fig. 1). The highest rates of conception begin 2 days before and continue up to the day of ovulation.⁴ Most methods are thought to prevent pregnancy by delaying or inhibiting ovulation.^{5,6} Other proposed mechanisms include alterations in hormone levels, changes in the endometrial environment, and inhibition of fertilization.^{7–9}

The copper IUD is the most effective form of post-coital emergency contraception, and can be used up to 5 days after unprotected intercourse without change in efficacy. Unlike the pills described below, the mechanism of the copper IUD is somewhat different. Pre-fertilization effects are prominent.¹⁰ The copper composition can be toxic to both the ovum and

the sperm.^{10,11} Additionally, the foreign body induces a chronic inflammatory response, leading to release of cytokines and integrins.¹² These inflammatory markers cause both a spermicidal effect and inhibit implantation even if fertilization does occur.¹⁰ The copper IUD may also be effective after fertilization occurs; although the mechanism is not completely understood, these post-fertilization effects usually take place before the embryo even enters the uterus.¹⁰ The copper IUD has an additional benefit, in that it can be employed for up to 12 years and used as a form of long-acting reversible contraception preventing future unintended pregnancies.¹³

Levonorgestrel (LNG) is a progestin-only pill licensed in many countries around the world. As with the other forms of emergency contraception, the exact mechanism is not fully understood. Studies indicate that LNG suppresses ovulation by delaying the luteinizing hormone (LH) surge (Fig. 1).^{14–17} In order to be effective, it must be administered before the LH surge begins. It is thus reasonable to infer that LNG is less effective when given closer to the time of ovulation.¹⁴ However, one study found that LNG increases the amount of glycodeilin in the body, which can theoretically prohibit fertilization after ovulation has occurred.¹⁸ Still, studies indicate that after ovulation occurs, LNG has only minor effects on corpus luteum function, and is thought to be ineffective once fertilization has transpired.⁶ Studies in rats and monkeys have demonstrated no post-fertilization effects of LNG, and most experts agree that the majority of levonorgestrel's effects derive from inhibition of ovulation.^{19,20}

Ulipristal acetate (UPA), a progesterone receptor modulator, was granted market authorization by the European Medicines Agency in 2009, and was approved by the US Food and Drug Administration (FDA) in 2010. UPA has a mechanism similar to that of LNG. Specifically, UPA delays follicular rupture by approximately 5 days, thus inhibiting or delaying ovulation.²¹ When ovulation is delayed by 5 days, the lifespan of sperm within the female GU tract, the chances of fertilization are greatly decreased. As with LNG, it should be administered before ovulation occurs in order to be effective. However, unlike LNG, UPA may be effective after the LH levels have already begun to rise.²¹ UPA generally works best when given before the LH surge, but it continues



Table 1. Methods of emergency contraception.

Method	Dose	Timing after intercourse	Adverse effects	Relative contra-indications	Absolute contra-indications*	Notes
Copper IUD	Single IUD	0–120 hours	Pain, bleeding	Bleeding disorders, ovarian cancer, high individual likelihood of exposure to gonorrhea/chlamydia, AIDS	Current pregnancy, active pelvic infection, copper allergy, undiagnosed vaginal bleeding, pelvic tuberculosis, Wilson's disease, known or suspected pelvic malignancy, uterine abnormalities that distort the uterine cavity	Efficacy decreased in morbidly obese Efficacy decreases with time
Levonorgestrel	1.5 mg or 0.75 mg × 2 (equal efficacy)	0–72 hours (may be used up to 120 hrs with decreased efficacy, and off-label)	Nausea, vomiting, headache, menstrual changes	None	None	Efficacy decreased in morbidly obese Efficacy decreases with time
Ulipristal acetate	30 mg	0–120 hours	Nausea, vomiting, headache, menstrual changes	Renal/hepatic impairment, uncontrolled asthma, breast feeding (can pump and discard milk for 36 hours)	Sensitivity to Lactose monohydrate (including galactose intolerance)	Efficacy decreased in morbidly obese Limited safety data in < age 18 No change in efficacy with time (up to 120 hours) Availability limited to Armenia, China, Russia, and Vietnam
Mifepristone	10–50 mg	0–120 hours	Nausea, vomiting, headache, menstrual changes	Adrenal failure, steroid therapy, bleeding disorders, porphyria	None	Higher side effect profile
Yuzpe method	Combination estrogen/progesterone pill-dose depends on pill brand used	0–72 hours	Nausea, vomiting, headache, menstrual changes	None	None	

Notes: *An established pregnancy is a contraindication to all of the above. While LNG and UPA are not abortifacients, an established pregnancy is a contraindication as they will not be efficacious. For the copper IUD, pregnancy is a contraindication as there is an increased risk of septic abortion and serious pelvic infection. For ulipristal acetate, it is contraindicated in pregnancy as animal studies showed increase pregnancy loss.⁵¹ Low doses of mifepristone are used for EC. High doses of mifepristone (200 to 600 mg) are used as an abortifacient either alone or with misoprostol, a prostaglandin analogue.

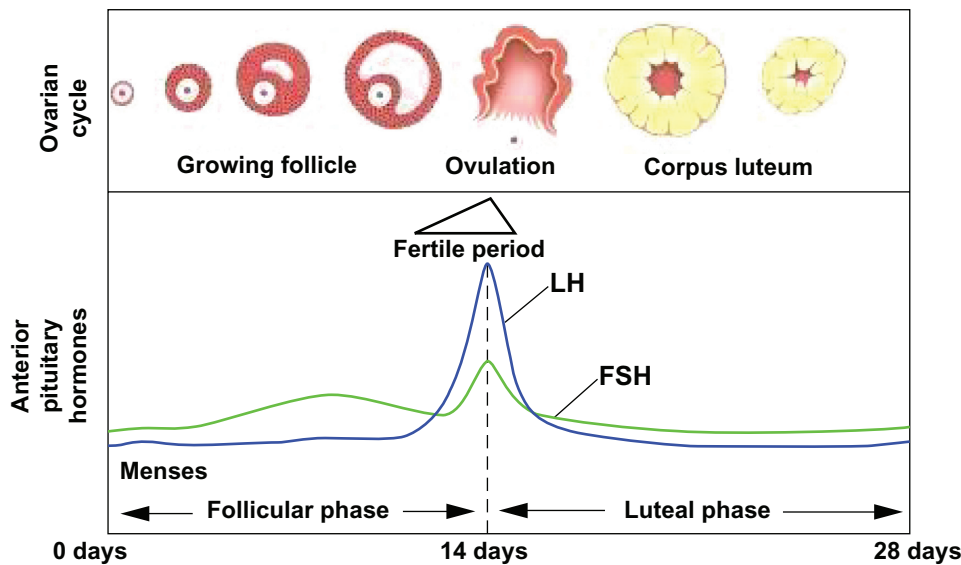


Figure 1. Diagram of hormonal fluctuations in the menstrual cycle.

Notes: Day 0 of the menstrual cycle is the first day of menstruation. During the follicular phase LH and FSH (both released by the anterior pituitary) levels begin to rise, and peak at approximately day 14, as an egg is released from the lead follicle (top picture). The 'fertile period' begins approximately 5 days before the LH surge, and ends the day after, as the egg rapidly degenerates if not fertilized. LNG and the Yuzpe regimen are effective only if given before the LH surge. UPA continues to be effective until the LH surge peaks. The copper IUD continues to be effective throughout the cycle. Menstrual cycle times can vary widely by individual, thus making exact timing of the fertile period difficult to calculate.

to be effective until LH levels peak. In addition to delaying or inhibiting ovulation, UPA also causes hormonal changes—specifically, a drop in LH levels and a resultant increase in menstrual cycle length.²¹ Some studies have shown endometrial changes after UPA administration, but the significance of these remains unclear.^{22,23}

Mifepristone, an anti-progestin synthetic steroid, is best known as an abortifacient in large doses (200 to 600 mg) in early pregnancy. It has also been studied, mostly in China, as an emergency contraceptive option within 120 hours of unprotected sexual activity at much lower doses (10 to 50 mg).^{24–26} The mechanism of mifepristone as an emergency contraceptive usually occurs pre-implantation and thus is not considered an abortifacient in this context. As with other emergency contraceptive options, the effect of mifepristone varies based on the timing of administration within the menstrual cycle.⁶ During the follicular phase, mifepristone delays the estrogen rise, LH surge, and ovulation. In addition, it suppresses endometrial development and follicle development. These effects of mifepristone ultimately lead to inhibition of ovulation.^{6,27} After ovulation, mifepristone inhibits endometrial development and blocks the expression of necessary endometrial receptors. The endometrium remains immature, thus preventing implantation from

effectively occurring.^{6,27} Mifepristone is the only pill that, at higher doses (200 to 600 mg), is effective once implantation occurs and can stop an early pregnancy from continuing, thus considered an abortifacient in this context.^{28,29} Mifepristone licensure and use as an emergency contraceptive is currently limited to Armenia, China, Russia, and Vietnam.^{30,31}

The Yuzpe method is the oldest form of post-coital emergency contraception, and was first described in 1974. This method utilizes a combination estrogen and progestin.³² In the 1970s, unlicensed use of a combination of oral contraceptive pills added to the accessibility of this regimen. When utilized during the first half of the menstrual cycle, the Yuzpe method delays or inhibits ovulation. The Yuzpe method is only effective if follicles are not already well developed.⁸ Some studies suggest that there may be secondary mechanisms of action, including disruption of luteal function, alteration of the endometrial environment, depression of sex steroid levels, alterations in cervical mucus physiology, and inhibition of fertilization.^{8,9}

Efficacy

There is strong evidence that all forms of emergency contraception are effective at the individual level. The copper IUD is the most effective of all forms of emergency contraception. A systemic review article



by Cleland, et al³³ of 42 studies analyzed patients that had copper IUDs inserted 2–10 days after unprotected intercourse. From a total of 7,034 patients around the world who had post-coital IUD insertions, there were only 10 pregnancies, with a failure rate of only 0.14% (95% CI = 0.08%–0.25%).³³ There is some evidence that copper IUDs are more effective if they contain at least 380 mm² of copper.^{34,35} The copper IUD is the only form of emergency contraception that continues to provide ongoing contraception for years when left in place.¹³ While the copper IUD is the most effective form of EC and is often offered in family planning and women's clinics, it requires expertise and equipment necessary for insertion. This expertise is not available immediately at many sites.

The most common EC pill offered is LNG. A double-blind controlled trial involving 1998 women compared LNG with the Yuzpe method. This trial found that the crude pregnancy rate was 1.1% in the LNG group and 3.2% in the Yuzpe method group, yielding a relative risk of 0.36 (95% CI = 0.18–0.70). The estimated efficacy, when used within 72 hours of intercourse was 85% for LNG, compared with 57% in the Yuzpe method group. The efficacy (based on estimates of conception probabilities) of LNG decreased with time: from 95% at 24 hours to 58% when taken between 49–72 hours.³ Earlier administration of LNG is imperative; the recommended regimen involves administration of LNG within the first 72 hours. While LNG can be used up to 120 hours after unprotected sex, a downward gradient in efficacy has been observed during the 49–72 hour time period. The odds ratio of pregnancy, if given five days after unprotected intercourse (compared to one day), is almost 6.^{3,36,37} Additionally, LNG is ineffective once fertilization has occurred. LNG can be administered as a single dose regimen (1.5 mg), or less commonly as a two-dose regimen (0.75 mg q 12 hours) with no significant difference in pregnancy rate between these two regimens.²⁵ It is important to note that the efficacy of LNG decreases as body mass index increases, with a four-fold risk of pregnancy in obese women compared to women with a normal body mass index.³⁸

UPA has similar efficacy to LNG. Two randomized, non-inferiority, clinical trials compared the efficacy of UPA and LNG. One trial enrolled 1672

women, and found that pregnancy occurred in 0.9% (CI = 0.2%–1.6%) of the UPA group and 1.7% (95% CI = 0.8%–2.6%) of the LNG group. UPA averted 85% of unwanted pregnancies, indicating a similar efficacy when compared to LNG.³⁹ A second trial involved 2221 women given emergency contraception within 5 days of unprotected intercourse. In the UPA group, there was a reported 1.8% (95% CI = 1.0%–3.0%) pregnancy rate; in the LNG group, there was a reported 2.6% (95% CI = 1.7%–3.9%) pregnancy rate.⁴⁰ A meta-analysis combining the two trials was performed in order to increase the power, revealing a significantly lower pregnancy rate with UPA when compared to LNG. A subgroup analysis of the 203 women who received emergency contraception between 72 and 120 hours after unprotected intercourse, revealed that all 3 pregnancies in this subgroup had received LNG.⁴⁰ This difference in efficacy between 72 and 120 hours is attributed to the fact that UPA is able to delay ovulation in the immediate preovulatory period, when LNG is ineffective.⁴¹ As with LNG, there was a trend toward decreased effectiveness of UPA in obese women; however, the current data is not statistically significant, with a 95% CI of 0.89–7.00.⁴⁰ UPA is sold in over 60 countries.⁴²

Mifepristone, less commonly used for emergency contraception, has been compared to both the Yuzpe method and LNG. Two randomized controlled studies studied the difference between 600 mg of mifepristone and the Yuzpe method. In both of these studies, none of the women who received mifepristone became pregnant.^{43,44} One study compared low dose mifepristone (10 mg) to 1.5 mg LNG in a single dose, and LNG 0.75 mg in 2 doses; pregnancy rates in this study were 1.5% with mifepristone, 1.5% with single-dose LNG, and 1.8% with two-dose LNG, leading to the conclusion that there is no difference in efficacy.²⁵ One study found no significant difference in efficacy between three different doses of mifepristone (10, 50 and 600 mg).⁴⁵ Therefore, the lowest dose is recommended. Mifepristone is currently used only in Armenia, China, Russia, and Vietnam for this indication.³¹

Despite being the least effective of all forms of emergency contraception, the Yuzpe method remains in use, as it is easily accessible to women who are already on select forms of oral contraception.⁴⁶



A review of eight studies showed an estimated range of effectiveness between 56.4% and 89.3%. The reduced risk of pregnancy with the Yuzpe method is 74.1% (95% CI = 62.9%–79.2%).⁴⁷ As with other forms of post-coital contraception, this method is most effective the sooner it is completed after unprotected intercourse.

Safety and side effects

Emergency contraceptive methods are considered safe. Most cause alterations in hormone levels and changes in menstrual bleeding patterns. Side effects are relatively mild with most agents and may include nausea, vomiting, and headache. Of all methods, the Yuzpe method has the highest incidence of side effects, namely nausea and vomiting. There are no absolute contraindications for the most commonly used forms of EC, the progestin-only pills. Absolute contraindications exist for the copper IUD and mifepristone as detailed below. Pregnancy is noted as a contraindication to progestin-only ECPs, because they are unlikely to be effective after a pregnancy has been established. Studies have shown very little risk to a pre-existing pregnancy from LNG and the Yuzpe method.^{48–50} There are too few pregnant patients in the UPA studies to make a determination, but animal studies cited in the product insert reported pregnancy loss; therefore, UPA is classified as Pregnancy Category X.⁵¹ The product insert instructs that if pregnancy cannot be excluded on the basis of history and/or physical exam, a pregnancy test is recommended prior to use.⁵¹

The most common side effects with the copper IUD are pain during the insertion process and increased menstrual bleeding.⁵² Non-steroidal anti-inflammatory drugs (NSAIDs) and local anesthesia are commonly utilized if discomfort is experienced during the procedure. Absolute contraindications to copper IUD placement are the same as with routine insertion and include pregnancy (due to increased risk of septic abortion and serious pelvic infection), undiagnosed vaginal bleeding, malignant gestational trophoblastic disease, active pelvic inflammatory disease, pelvic tuberculosis infection or purulent cervicitis, copper allergy, Wilson's disease, known or suspected pelvic malignancy, and uterine abnormalities that distort the uterine cavity.⁵³

LNG is generally well tolerated. The most common side effects with LNG are nausea (23%) and

vomiting (5.6%). Less common events include fatigue, dizziness, headache, and mastalgia. Disruption in the menstrual cycle pattern may also occur.

UPA has a similar side effect profile when compared to the other hormonal emergency contraceptive pills. Headache is the most common side effect, occurring in 19% of patients.⁴¹ Other side effects include nausea, fatigue, dizziness, and lower abdominal pain.³⁹ In addition, menstrual cycle length increased by approximately 2.8 days, with no change in duration of menstrual bleeding.⁵⁴ UPA is metabolized by the kidney and the liver, therefore UPA is contraindicated in severe kidney or liver disease. UPA use in severe, uncontrolled asthma is a relative contraindication, as UPA has some antagonist effect at glucocorticoid receptors. Since ella and ellaOne[®] one contain lactose monohydrate, they should not be offered to those with rare errors of galactose metabolism.⁴¹ If UPA is used while breast feeding, breast milk should be discarded for 36 hours, as it is a lipophilic compound, and therefore could be secreted in breast milk. Data from rat and rabbit studies show increased perinatal deaths for the offspring of those exposed to UPA. In those animals that survived, however, there were no increased fetal malformations.⁵¹ As noted previously, if pregnancy cannot be ruled out based on patient history, a pregnancy test prior to administration is recommended.⁵¹ Data is limited for pregnant women, but preliminary data from a meta-analysis and post-marketing surveillance suggests that there is little harm to the fetus.⁴⁰ If a patient becomes pregnant after taking ellaOne[®], the provider should enter the patient into the HRA Pharma ellaOne[®] pregnancy registry (<http://www.hra-pregnancy-registry.com/en/>, accessed 11/19/12). Patients should be counseled that oral contraceptives may be less effective throughout the current cycle, and an alternate method of birth control should be used throughout the current cycle.

Side effects of mifepristone include nausea, vomiting, headache, dizziness, fatigue, mastalgia, lower abdominal pain, and diarrhea. Studies indicate that a larger dose of mifepristone correlates with a longer delay to menses.⁴⁵ Absolute contraindications to mifepristone use include chronic adrenal failure, steroid therapy, severe asthma, bleeding disorders, known hypersensitivity to prostaglandins or mifepristone, and porphyria.⁵⁵



The Yuzpe method has more pronounced side effects than the other regimens for emergency contraception. 50% of women develop nausea, and 20% develop vomiting. Antiemetic medications are recommended if the Yuzpe method is used. Changes in menstrual bleeding and mastalgia also occur.⁴³ Although there is a theoretical concern for increased risk of venothromboembolism with high dose estrogen therapy, current studies do not support any increased risk with brief use of estrogen.⁵⁶ Prescribers should consider alternatives if patients have relative contraindications to combined estrogen/progesterone therapy.

Clinical Considerations

Recommendations as to which ECP to use depends on a number of factors, including timing of presentation after unprotected sexual intercourse, patient factors (such as obesity, allergies, and concurrent medications), cost, and availability.

Timing of unprotected sexual intercourse

While all methods are highly effective within 72 hours of unprotected sexual intercourse, UPA may be more effective in those who present 72–120 hours.⁴⁰ While LNG can be administered after 72 hours and before 120 hours, it is less effective, and is not currently labeled for use as such. The copper IUD does not decrease in efficacy over the 120 hours.

Patient factors

Weight: While BMI > 30 kg/m² is not considered a contraindication to ECPs, both LNG and UPA were found to be less effective in patients with BMI > 30. Although no studies have looked at this specifically, sub-group analysis from a meta-analysis showed a statistically significant increase in risk of failure in the LNG group: OR 4.41 in the LNG group and 2.62 in the UPA group for obese women with BMI > 30.⁴⁰ UPA was more efficacious than LNG in obese women; UPA may therefore be preferred to LNG in this population, although more studies are needed. The efficacy of the copper IUD does not change with BMI, and therefore this method may be preferred in women with BMI > 35.

Uncontrolled asthma: In those patients with uncontrolled asthma on glucocorticoids, LNG is preferable to UPA, as UPA blocks glucocorticoid receptors and may theoretically worsen asthma (although there are no studies specifically looking at this).

Concomitant medications: Since UPA and LNG are metabolized by the CYP3A4 microsomal system, medications which induce the CYP3A4 system (such as barbiturates, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's Wort, and topiramate) may decrease levels of UPA, but the actual effect of these interactions is unclear.⁵¹ Some experts recommend against concomitant use of these medications and UPA.⁵⁷ Where readily available, insertion of a copper IUDs may be preferable in a patient who has taken any of these medications in the past 28 days.⁵¹ Theoretically, drugs that inhibit the CYP3A4 system (such as anti-retrovirals used for HIV post-exposure prophylaxis, itraconazole, and clarithromycin) may inhibit the metabolism of UPA, and lead to increased levels of UPA. Currently there is scant literature evaluating this interaction in vivo. Medications that decrease the pH of the stomach (including antacids, H₂ blockers and proton pump inhibitors) may decrease the absorption and efficacy of UPA; therefore, discussion with patients regarding the potential decreased efficacy in these situations is warranted.⁵¹

Breastfeeding: Most EC is safe when breastfeeding. Mifepristone should not be used in women who are breastfeeding. UPA is a lipophilic compound, and therefore could be excreted in breast milk. If UPA is taken, most experts recommend discarding breast milk for 36 hours.

After EC is given, and when appropriate, contraception should be started to prevent further episodes of unplanned pregnancies ('quick start' contraception). As LNG and UPA may prevent or delay ovulation, subsequent episodes of unprotected sexual intercourse, may lead to pregnancy; therefore, it is recommended in all cases that patients use a barrier method to prevent unintended pregnancies after ECPs. Since UPA is a progesterone receptor modulator, it could theoretically interfere with OCPs that contain progestones. When progesterone containing OCPs are started immediately, patients should also be advised to use barrier protection or abstain from sexual activity until the next menstrual cycle.⁵¹ Providers should remind patients that EC does not prevent HIV or other sexual transmitted infections and stress the importance of barrier protection. Patients who do not experience a menstrual cycle one week after her usual expected menstrual cycle or three weeks after taking



ECPs should take a pregnancy test and/or seek medical care.

Place in Therapy

Increased access has led to increased use of emergency contraception methods.⁵⁸ Emergency contraception is offered, provided, and/or dispensed in emergency rooms, outpatient clinics and pharmacies. EC can also be provided in advance, allowing earlier and easier access. Women can receive ECPs and copper IUDs through family planning, public health, and other outpatient clinics. Dedicated emergency contraceptive pill products are available in over 140 countries worldwide.⁵⁹ In over 60 of these countries including Ireland, Bangladesh, Kazakhstan, South Africa, Israel, and the United Kingdom, ECPs are over-the-counter and can be obtained in pharmacies without a prescription.⁵⁹ In France, ECPs are free of charge to minors and can be dispensed anonymously from pharmacies.⁵⁹ Some countries have age restrictions and prescription requirements, such as the US where Plan B One-Step[®] (levonorgestrel) is over-the-counter for men and women 17 years of age and older, but requires a prescription for females under 17-years-old.⁶⁰

In addition to outpatient clinics and pharmacies, emergency rooms play an important role in access to ECPs for women, especially those seeking medical care after a sexual assault. In many countries around the world, such as the United States, Argentina, Brazil, Chile, Ecuador, Mexico, Sri Lanka, Zimbabwe, and South Africa, governments and hospitals have created protocols and guidelines that include counseling about and provision of ECPs for sexual assault survivors.⁶¹ In the US, medical groups such as the American Medical Association and the American College of Obstetricians and Gynecologists, as well as the US Centers for Disease Control and Prevention, recommend that ECPs be offered routinely after sexual assault.^{62–64} Emergency departments in 17 states and the District of Columbia are required by law to provide EC related services to sexual assault victims upon request.⁶⁰ International organizations such as the United Nations High Commissioner for Refugees Health and Community Section in collaboration with the World Health Organization and the Interagency Working Group on Reproductive Health in Refugee Situations have produced protocols that emphasize

the importance of access to and provision of ECPs to refugees following rape.⁶¹

Patient Preference

Preference for the different types of EC largely depends on patient and provider knowledge, as well as availability and access. Two large studies from China, where almost 60% of all married women use IUDs for contraception, and a small pilot study from the US showed that women who received the copper IUD for EC found it an acceptable option.⁶⁵ Continuation rates ranged from 61%–94%, depending on the follow-up time and parity of participant.^{52,66,67} The copper IUD is the most effective form of EC, has been used as EC for over 35 years, can provide up to 12 years of reversible contraception, and does not decrease in efficacy over the duration of time when it can be used.^{33,52,67,68} Despite the long-term contraceptive benefits of the copper IUDs, this method remains underutilized. The necessity of IUD placement by a trained health care provider, high up-front costs, lack of provider and patient knowledge regarding the IUD's effectiveness and use as a form of EC, all contribute to the relatively low use of the copper IUDs as a form of EC.^{69–71} Two studies from the US of adolescents and young women presenting to family planning clinics reported that when counseled on IUDs for EC, 13%–15% of them would choose an IUD, with increased numbers if provided on the same day and at free cost.^{69,72} The copper IUD is also cost effective in the long term given decreased healthcare costs due to lower unintended pregnancy rates compared to oral levonorgestrel pills.⁷³ These studies suggest that with increased provider and patient education, lower costs, and improved access to trained providers, there may be more women who choose copper IUDs for emergency contraception.

ECPs are more widely available and are the most common type of EC used worldwide. Studies indicate, however, that they are still underutilized, and thus are not associated with a reduction in the unintended pregnancy or abortion rate at the population level.^{58,74} Utilization of ECPs remains low in many countries around the world. In the United States, data from the National Survey of Family Growth from 2006–2008 showed that even after ECPs became available without a prescription for people 17 years of age and older, the number of women who reported



using ECPs remained below 10% (9.7%).⁷⁵ In other countries, Demographic and Health Survey data from 2005–2009 indicated a higher use of EC, though still under 25% of unmarried sexually active women reported use: 21.7%, 15%, 11%, and 10%, in Albania, Ukraine, Kenya, and Colombia respectively.^{76–78}

Factors Affecting ECP Use: Knowledge, Prescriptive Practices, and Access

Successful use of emergency contraception requires accurate knowledge about the different EC methods by both providers and patients, prescriptions when necessary for obtaining ECPs, and access to the different methods. Studies from over a decade ago show poor knowledge about EC among healthcare providers (HCP) and patients as well as a lack of counseling about and dispensing of ECPs by HCPs. For example, a study published in 2000 reported only 20% of pediatricians ever prescribing ECPs while another study in 2001 revealed that only 17% of pediatricians routinely counseled adolescents about the availability of EC.^{79,80} Two studies in 1998 of adolescents in the US, revealed that only one third (28% in one study and 30% in the other) of the respondents had heard of EC.^{81,82} More recent studies have shown some improvement in the number of patients who have heard of EC, though less so among populations at higher risk of unplanned pregnancies such as adolescents. A literature review published in 2012 on male knowledge about ECPs in the US showed that 38% of adolescent males and 65%–100% of adult males were familiar with EC.⁸³ 48% of pregnant teens presenting for an abortion to clinics in Shanghai had heard about EC.⁸⁴ Slightly higher rates were found at a teen clinic in Hawaii (56%)⁸⁵ and among sexually active teens in Switzerland (89% of girls and 75% of boys).⁸⁶ In sub-Saharan Africa, knowledge about EC ranged from 57% of rural women in Ghana to between 47% and 84% of female students at 2 different universities in Ethiopia.^{87–89}

Unfortunately, despite awareness of the availability of emergency contraception, knowledge about timing, and appropriateness continues to be an issue. A study from 2004 reported that 77% of women presenting to an inner-city emergency department in the US having heard of EC, although 25%–50% of them did not have sufficient knowledge to use it effectively.⁹⁰

Similarly, two studies from 2009 showed an increase in the number of providers aware of the method, but there remained a lack of accurate medical knowledge about the method.^{91,92} 71% of family medicine providers in Pakistan had heard of EC.⁹¹ Despite the widespread knowledge of the product, only 40% had prescribed it, 24% felt it was an abortifacient, and 42% were unsure if it was an abortifacient.⁹¹ 85% of pediatric emergency medicine physicians in the US reported prescribing ECPs to adolescents but 43% of respondents answered > 50% of knowledge based questions about EC incorrectly.⁹² Nearly all of the 448 Jamaican and Barbadian health care providers surveyed had heard of EC, but only one in five knew it could be prescribed as often as needed.⁹³

There also continues to be a bias towards restricting EC access to adolescents despite its proven efficacy and safety as well as recommendations for improved access for high-risk populations such as adolescents.^{62,94} A study of Nicaraguan pharmacists showed that the majority of them sold EC at least once a week (92%) and 65% of them were willing to provide them to all women in need, but only 13% would dispense to minors.⁹⁵ A qualitative study of physicians and nurses working in three large academic, urban, free-standing pediatric emergency rooms in the US found that nurses commonly expressed views that adolescents who may need EC are irresponsible and that EC should only be used after an assault and very few nurses, physicians, or NPs supported advance prescription for EC.⁹⁶

“Advance provision” of emergency contraception refers to providing patients with ECPs or a prescription for ECPs for patients to fill as needed in the future. Advanced provision has been shown to increase the use of ECPs in multiple studies.^{58,74,97–101} Concerns that advanced provision will increase rates of sexually transmitted infections and unprotected sexual activity have proven to be unfounded.^{98,102–104} However, although EC is effective in reducing unplanned pregnancy on an individual level, studies including a Cochrane meta-analysis indicate that emergency contraception pills, even with advanced provision, are not associated with a reduction in the unintended pregnancy, or abortion rates at a population level.^{58,74,105} Reported reasons for underuse of emergency contraception methods at an individual level include failure to recognize the risk of conception, misunderstanding about the appropriate



time frame to use emergency contraception, lack of knowledge on where to obtain the medication, and perceived risk or stigma.^{58,106} Although EC has not affected pregnancy and abortion rates at a population level, medical, policy and public health groups continue to recommend advanced provision for vulnerable populations such as adolescents.^{62,107}

Access to emergency contraception has also been influenced by politics, which has been tied to gender issues and individuals' and groups' beliefs about abortion and contraception. These factors determine whether providers and hospitals offer ECPs, as well as if ECPs are provided by pharmacies over-the-counter with or without pharmacist intervention, by prescription only, or sold freely. Access can also depend on whether the government believes EC to be a form of contraception or a form of abortion. For example in Peru, the Ministry of Health (MINSA) issued a resolution (No. 167-2010) categorizing EC as a contraceptive method allowing Peruvian public health facilities to distribute ECPs to women for free.¹⁰⁸ Soon after, a petition was filed and MINSA issued a subsequent resolution (No. 652-2010) that prohibits free distribution of EC, making EC essentially inaccessible.¹⁰⁹

In 1998, Mexico first began considering the inclusion of emergency contraception as part of their public health services but it did not officially become part of the Health Sector List of Essential Medications until 2005.¹¹⁰ At that time, the Catholic Church threatened to excommunicate women who used EC as well as those who provided it.¹¹⁰ Chile first introduced ECPs in 2001 by prescription but lawsuits were quickly filed by groups opposing EC.¹¹¹ Due to legal issues, political pressure and opposition from religious groups, it was not until 2010 that ECPs were made affordable and available in pharmacies and public health clinics for all women 14 years of age and older.^{59,111} The US FDA delayed approving behind the counter status for EC (for those over age 17) for three years despite evidence of efficacy and safety. EC remains prescription only for those under age 17, despite recommendations to eliminate age restrictions from FDA experts.¹¹²

Conclusion

In 2008, there were approximately 208 million pregnancies worldwide, of which approximately 41% were unintended.¹ As availability of EC can decrease the number of unintended pregnancies, many medical

groups, nonprofit organizations and experts in a variety of fields, including but not limited to the American Academy of Pediatrics, The United Nations Population Fund, The World Health Organization, and The International Federation of Gynecology and Obstetrics, advocate for easy access to emergency contraceptive pills.⁵⁹ ECPs are safe and there are no absolute contraindications for usage of LNG or the Yuzpe method and few relative contraindications to UPA, low dose mifepristone, and the copper IUD. The copper IUD, LNG, UPA, and low dose mifepristone are highly effective in preventing unintended pregnancies when used as directed. Providers working with women in clinics, emergency departments, and pharmacies should be familiar with the availability of medications, as well as options for provision. Patient preference, provider capability, and local availability will influence which options are most preferable.

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Abbreviations

LH, Luteinizing hormone; IUD, Intrauterine device; LNG, Levonorgestrel; NSAIDs, Non-steroidal anti-inflammatory drugs; ECPs, Emergency contraceptive pills; EC, Emergency contraception; HCP, Healthcare provider; UPA, Ulipristal acetate.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and



confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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