UPDATE on EMERGENCY CONTRACEPTION

Precis:

Emergency contraceptive options include combined and progestin-only pills, ulipristal acetate, and the copper intrauterine device.

Abstract:

Emergency contraception (EC) is any method used after sexual intercourse to prevent pregnancy. This article provides an overview of the history of EC methods and describes the current availability of oral and intrauterine EC. Oral forms include the Yuzpe regimen (combining ethinyl estradiol and levonorgestrel), levonorgestrel–only pills, and ulipristal acetate, which is a new emergency contraceptive drug recently approved by the US Food and Drug Administration. The copper T-380A intrauterine device can also be used for EC. Information about dosing, timing, access, and other considerations in the provision of EC is covered. Clinicians should be aware of all available options in order to counsel women in need of EC appropriately.

UPDATE on EMERGENCY CONTRACEPTION

INTRODUCTION

Emergency contraception (EC) is any contraceptive method used after sexual intercourse to prevent pregnancy. References to the concept of postcoital contraception date back to ancient times, with common instructions being to sneeze, jump backwards, and otherwise attempt to expel semen immediately after sexual intercourse [1-3]. Modern clinicians have undoubtedly heard other myths about ways to prevent pregnancy after sex. Indeed, one such myth, douching with a carbonated beverage, produced published laboratory-based research to evaluate its presumed effectiveness [4-6]. The beginnings of modern effective EC however date to the 1920s, when veterinarians administered high-dose estrogens to animals to prevent pregnancies from unintended mating [7]. Possibly the first documented use in humans was in mid 1960s when physicians in the Netherlands gave estrogens to a 13-year-old girl who had been raped.[3]

Emergency contraception should be offered to every woman who reports unprotected intercourse, whether voluntary or forced. Currently available options in the United States are listed in Table 1. The purpose of this article is to update clinicians about options for and management of the drugs and devices available in the United States for emergency contraception.

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Table 1: Comparison of Emergency Contraceptive Methods

Emergency Contraceptive Method	Brand names	Route and dose	Pregnancy Rate after Use	Maximum time for Use	Access Issues	Provides ongoing contraception	US MEC category [a]	Other considerations
Copper T380A	ParaGard	Intrauterine	0.1%-0.2%	Up to 5 days after unprotected intercourse; Up to day 12 of a regular menstrual cycle; At other times of cycle if not more than 5 days after ovulation	Office visit needed, experienced provider, cost of IUD or insurance coverage for IUD	Yes	1 or 2 except: Sexual assault victims at high risk for STI: 3 Pregnancy: 4	
Levonorgestrel	Plan B One Step; Next Choice	150 mcg orally in 1 or 2 doses[b]	1.7%-2.6%[c]	Up to 5 days (120 hours) after unprotected intercourse, may be somewhat less effective from 72 – 120 hours	Non-prescription for women 17 and older; Prescription required for women under age 17	No	1 or 2	May be less effective at higher body weight but is more effective than not using it at all.
Ulipristal	*ella*	30 mg	0.9%-	Up to 5	Prescription	No	Not yet	*May* reduce

acetate		orally in one dose	1.8%[c] 2.6% from 48-72 hours[d]	days; Effectiveness does not wane between 72 and 120 hours.	required		included	the contraceptive action of progestin-containing hormonal contraceptive methods because of its affinity for binding to the progesterone receptor; reliable barrier contraception should be used until next menses
Ethinyl estradiol and levonorgestrel hormonal contraceptives (Yuzpe regimen)	Various[e]	Two doses orally of various options[e]	2%-3%	Up to 72 hours[f]	Prescription required	No	1 or 2	Higher rates of nausea and vomiting compared to other oral regimens. Consider prescribing an anti-emetic.

Abbreviations: MEC, *Medical Eligibility Criteria for Contraceptive Use;* STI, sexually transmitted infection

Sources: Centers for Disease Control and Prevention [46] , Food and Drug Administration [22] ,Glasier [45] ,Trussell[51] , World Health Organization [62] , Wu [59] ,

[a] US MEC Categories:

Category 1: a condition for which there is no restriction

Category 2: a condition for which the advantages of using the method generally outweigh the theoretical or proven risks

Category 3: a condition for which the theoretical or proven risks usually outweigh the advantages of using the method

Category 4: a condition that represents an unacceptable health risk if the contraceptive method is used.

[b] A single dose has been shown to be as effective as 2 doses, although some package labeling continues to state it should be taken in 2 doses.

[c] Rates taken from clinical trials that compared levonorgestrel and ulipristal acetate and calculated actual risk, not relative risk.

[d] This rate was taken from a single-arm trial that evaluated the effectiveness of ulipristal acetate beyond 72 hours.

[e] These regimens are not the first choice, due to associated rates of nausea and vomiting. If these are the only option available for a woman, the number of pills and dosing from 19 different branded combined oral contraceptive products is available from the Princeton University Office of Population Research and Association of Reproductive Health Professionals and can be accessed at http://ec.princeton.edu/questions/dose.html.)

[f] No studies have evaluated effectiveness beyond 72 hours.

The oral form of EC, the so-called “morning after pill”, is the most commonly used EC method and can be taken at any time in the first 3 to 5 days after unprotected sex to prevent pregnancy (not just “the morning after”).

Formulations for Emergency Contraception

Combined Estrogen-Progestin Formulations

In the mid to later 20th century, women in need of EC typically received either high-dose diethylstilbestrol, conjugated estrogens, or ethinyl estradiol, administered over several days after unprotected sex. These regimens were replaced in the 1980s by the so-called Yuzpe regimen, named for the Canadian physician who first described it [8]. This regimen involved 2 doses of oral contraceptive pills containing both ethinyl estradiol and norgestrel; each dose contained 200 mcg of ethinyl estradiol and 1.0 mg of norgestrel. In 1997, the US Food and Drug Administration (FDA) concluded that the Yuzpe regimen was safe and effective for off-label use as postcoital EC [9]. At the time, 6 branded hormonal oral contraceptive products were listed in instructions for providing an appropriate dose of the 2 hormones for EC. In 1998, the FDA approved a dedicated product (Preven) that packaged 4 pills as an emergency contraception kit [10]. Preven was discontinued in May 2004. Although use of combined EC has largely been replaced by the single hormone products discussed in the next sections, current authoritative EC resources continue to list 19 branded oral contraceptives that can be used to provide an EC dose if the preferred products are not available. [11] Although all of the oral contraceptive regimens currently recommended for EC contain ethinyl estradiol and levonorgestrel (the biologically active enantiomer of norgestrel), at least one study

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has suggested that a combination of ethinyl estradiol and norethindrone may work as well [12].

Progestin-only Formulations

In the 1970s, several studies evaluated high-dose progestins used peri- and postcoitally as an ongoing primary contraceptive method, but interest waned due to the cycle irregularities that accompanied continued or frequent use of the method [13-16]. However, this experience, along with the common side effect of nausea and vomiting with use of combined EC regimens containing ethinyl estradiol, led to consideration of progestin-only treatments as EC. Levonorgestrel-only EC was evaluated in a number of studies in the 1990s, including a large trial by the World Health Organization (WHO), that compared this progestin-only regimen to the Yuzpe regimen containing both a progestin and ethinyl estradiol. These studies demonstrated the effectiveness and lower side effect rates of the levonorgestrel-only dosing. [17,18] Following these findings, the combined EC product was gradually withdrawn from the market in favor of levonorgestrel-only products. As previously noted, authoritative resources still provide the correct dosing of the Yuzpe combined EC regimen for those unable to access progestin-only products. [11]

The original branded levonorgestrel –only product (Plan B, approved in 1999) contained 2 doses of 0.75 mg of levonorgestrel taken 12 hours apart. A 2002 WHO study [19] found that progestin-only EC can be taken in a single dose of 1.5 mg total; one current branded product offers this single dose (Plan B One Step, approved in 2009, which has replaced the original branded product). The other branded product retains the 2-dose regimen (Next Choice, approved in 2009), but based on existing research, both

doses can be taken at once. The current FDA-approved labeling for the branded products states that the dose should be taken within 72 hours of unprotected sex. However, data from the WHO study also suggested that progestin-only oral EC can be taken up to 120 hours after intercourse and still maintain some effectiveness, although there is a decline in effectiveness with delay.[19]

Emergency contraception dosing with levonorgestrel provides a higher dose (1.5 mg) than is typical in progestin-only daily contraceptives; one would have to take 40 separate tablets of a norgestrel progestin-only contraceptive pill to approximate the single-dose emergency contraceptive pill [11]. The dose is also higher than the daily dose one would get in hormonal contraceptives that contain levonorgestrel; the Yuzpe regimen dosing of the various combined EC products requires taking anywhere from 4 to 10 pills to achieve a total of 1.0 to 1.2 mg of levonorgestrel in 2 doses.[11] The branded levonorgestrel-only emergency contraceptive products contain a total of 1.5 mg.

Antiprogestin Formulations

Antiprogestins are progesterone receptor antagonists, or progesterone receptor modulators, that counteract the effects of progesterone, which is a critical component of the events that lead to fertilization and the establishment of pregnancy. Mifepristone is an antiprogestin and highly effective as a postcoital emergency contraceptive. A single dose of mifepristone in a range of 25 to 50 mg is more effective for EC than levonorgestrel regimens, and can be used up to 120 hours after unprotected intercourse [20]. There are fewer side effects than observed with other methods. Because mifepristone is a component of the medication regimen to induce abortion, there are non-medical pressures against its wider availability, and it is currently not available for

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use as an emergency contraceptive in the United States (it is available as an emergency contraceptive in China and Russia). Note that the FDA-approved dose of mifepristone for medication abortion is 600mg; dosing for EC purposes is less than 10% of this and does not function as an abortifacient.[21]

A second generation antiprogestin, ulipristal acetate (UPA), has been studied as an EC agent and was approved for this use in Europe in 2009 and by the FDA in 2010 [22]. This is a new drug with limited post-marketing experience and is available only by prescription, as a 30 mg single oral dose (brand name *ella*). Animal studies demonstrated that UPA and mifepristone are roughly equipotent; thus this drug will not function as an abortifacient at the approved dose.[23]

Several comparative clinical studies with large populations provided the efficacy and safety data that led to approval of the drug. An early randomized trial of nearly 1700 women compared a 50 mg dose of UPA (note that the current FDA-approved dose is 30 mg) to the 1.5 mg EC dose of levonorgestrel. The pregnancy rate in the UPA group was 0.9% (95% confidence interval [CI], 0.2%-1.6%) as compared to 1.7% in the levonorgestrel group (95% CI, 0.8%-2.6%) [24]. Another study with more than 2200 women used a 30 mg oral dose of UPA and compared outcomes to 1.5 mg single dose of levonorgestrel. In the evaluable UPA sample, the pregnancy rate was 1.8% (95% CI, 1.0%-3.0%), compared to 2.6% (95% CI, 1.7%-3.9%) in the levonorgestrel group. In this study there were 203 women who took EC after 72 hours but within 120 hours of unprotected intercourse. There were 3 pregnancies in the delayed dosing group, and all were in the levonorgestrel arm.[25] An observational prospective study evaluated efficacy of a single 30 mg dose of UPA from 48 to 72 hours after unprotected sex (after which

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the efficacy of levonorgestrel begins to wane) up to 120 hours. There were 1241 women in the evaluable sample, and the overall pregnancy rate was 2.6% (95% CI, 1.4%-3.1%). The pregnancy rate was 2.3% when dosing occurred between 48 and 72 hours, 2.1% when dosing occurred between 72 and 96 hours, and 1.3% from 96 to 120 hours [26]. In summary, the available research demonstrates that UPA is an effective emergency contraceptive, with lower failure rates than levonorgestrel and effectiveness up to 120 hours.

Other Drugs as Emergency Contraceptives

Several animal and human studies suggest that cyclooxygenase-2 (COX-2) inhibitors can prevent or delay follicular rupture. Meloxicam (Mobic), given as 30 mg a day for 5 consecutive days, produced dysfunctional ovulation in half of 22 women treated during the late follicular phase (when a leading follicle reached a size of 18 mm) [27]. Larger clinical studies to assess effectiveness and risk are needed. Currently, use of meloxicam as EC is investigational and should not be recommended in clinical practice. Meloxicam carries a black box warning about cardiovascular and gastrointestinal risks and is currently approved by the FDA only for the treatment of osteoarthritis and rheumatoid arthritis.[28] Other FDA-approved EC regimens do not carry such risks.

Mechanism of Action of Oral Emergency Contraception Products

The generally accepted mechanisms of action for progestin-only EC, as well as for the combined EC products, include inhibition of ovulation, disruption of follicular development, and interference with the maturation of the corpus luteum. When levonorgestrel EC is taken prior to the day before a woman's LH surge, it suppresses the surge completely and thus she does not ovulate. When it is taken closer to or during

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the LH surge, it blunts or delays the surge and renders the ova resistant to fertilization.[29-34]

Some have theorized that levonorgestrel EC produces histological/biochemical alterations of the endometrium, thereby impairing its receptivity to implantation. More recent studies have demonstrated little to no effect on the endometrium.[35,36] Other suggested mechanisms of action include alteration of sperm or egg transport, interference with fertilization, and/or cervical mucus changes, but none of these has been verified by clinical data. There is no evidence that levonorgestrel EC can interrupt an established pregnancy that has already implanted in the uterine lining.[37,38]

As is true of levonorgestrel regimens, the likely primary mechanism of action of ulipristal acetate is inhibition or delay of ovulation. Studies have shown that when this drug is administered before the onset of the LH surge, there is no follicular rupture evident for 5 days after treatment. When administered after the onset of the surge, but before the peak, 79% of women treated showed no follicular rupture while 60% of women still had an intact dominant follicle present on day 5 after treatment (vs. 0 in a placebo group) [39]. The apparent ability of the drug to inhibit follicular rupture after the LH surge may explain its continued effectiveness on days 4 and 5 after unprotected sex. Dosing in the early luteal phase decreases endometrial thickness, but the clinical consequences of this are unknown. [40]

Side Effects and Concerns Related to Use of Oral Emergency Contraception

Physical Effects. Reported side effects with oral EC use are mild and resolve quickly. Women taking combined EC (the Yuzpe regimen) have the highest rates of nausea and vomiting (50% and 20% respectively). [41] Following treatment with levonorgestrel

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regimens, about 20% of women will experience headaches, approximately 14% will experience painful menstruation, and approximately 12% will experience nausea. [25] In clinical trials of UPA, the most frequently reported side effects were headache, nausea, abdominal pain, dysmenorrhea, fatigue, and dizziness. Most were considered “mild or moderate” and resolved spontaneously. This side effect profile is very similar to that of a single oral dose of levonorgestrel.

Cycle Length. Bleeding patterns can be altered after use of oral EC, and this seems to be dependent on when in the cycle dosing occurs. Use of levonorgestrel EC early in the cycle (pre-ovulatory phase) shortens the time to the next period. Some but not all studies have shown that levonorgestrel EC taken in the luteal phase can lengthen the time to the next period by an average of 2 days. There is some evidence of a slight increase in intermenstrual bleeding or spotting after oral levonorgestrel EC, and of slightly prolonged bleeding during the next menses after use. [42] Findings are similar for UPA use. About 7% of women will have their period a week or so earlier than expected, and about 19% will have their period delayed by a week or more. Cycle length of the first period after administration may be longer by about 2 days but will return to normal by the next month.[26,43]

Ongoing Contraception. Fertility returns rapidly after oral EC use, and effective contraception should be continued or initiated as soon as possible. While there are no data about use of UPA with standard hormonal contraceptives, there are some theoretical concerns that UPA, because of its affinity for binding to the progesterone receptor, may reduce the contraceptive action of progestin-containing hormonal contraceptive methods. [22] There are at present no data to support or refute this

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theoretical concern. According to current practice guidelines from the Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit in the United Kingdom (where UPA has been available longer than in the United States) [44] , reliable barrier method of contraception should be used with subsequent acts of intercourse that occur in the same cycle (until the next menses), even if another hormonal contraceptive method is begun right after EC dosing.

Obesity. Concerns have been raised about effects of obesity on hormonal contraceptives due to observations about potential alterations in the metabolism of some drugs due to obesity and possible reduced effectiveness of contraceptives in obese women. Recent secondary analysis of data suggests that the overall risk of pregnancy after oral EC use may be more than threefold greater for obese women compared to women with normal body mass index (odds ratio [OR] 3.6; 95% CI, 1.96–6.53). This differs according to the type of oral EC used: the risk of pregnancy was greater for obese women taking levonorgestrel (OR 4.4; 95% CI, 2.05–9.44) than for obese women taking UPA (OR 2.6; 95% CI, 0.89–7.00). [45] These findings suggest that women in need of EC who have a high body mass index should be offered UPA rather than levonorgestrel if they wish an oral treatment, or should be offered an intrauterine device for maximum efficacy. However, these observations have not been confirmed, and offering any method of EC is preferred to leaving obese women at risk of unintended pregnancy.

Breastfeeding. Lactation is not affected by the use of oral EC. There are no restrictions on combined EC or levonorgestrel EC during breastfeeding.[46] It should be noted that women are not likely to ovulate before 4 to 6 weeks postpartum,. For women who

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continue to completely breastfeed, the likelihood of ovulation is low as long as certain breastfeeding criteria are met: the woman must be less than 6 months postpartum, not have resumed menstruating, and must be exclusively breastfeeding, with no or very little supplementation and nursing episodes about every 4 hours, including nighttime. Questions arise whether expressing or pumping milk has the same neuroendocrine effect on prolactin and other hormones that suppress ovulation as does having the infant suckle at the breast. One older study demonstrated striking differences in the ability of various breast-pumping methods to produce the necessary prolactin rise in breastfeeding mothers, with battery-operated pumps the least effective, and electric pulsatile hospital grade pumps the most similar to actual breastfeeding.[47] A standard global reference states that because manual expression does not elicit the same hormonal response as suckling, the likelihood of ovulation suppression will decrease if expression or supplementation replaces suckling for more than approximately 10% of feeds. [48] Thus, a mother who feeds her infant only breast milk but without nursing at the breast may be at risk of ovulation and potential unintended pregnancy; providers should educate women about this.

One study of 12 women compared levonorgestrel concentrations in milk to those in plasma. Milk levels were lower (mean milk to plasma ratio 0.28), and the authors estimated the infant's exposure to levonorgestrel as 1.6 micrograms on the day of dosing and markedly lower (0.2-0.3 micrograms) on the next 2 days. These authors concluded that in order to limit infant exposure to maximum excretion in milk, mothers should discontinue nursing for at least 8 hours (but not more than 24 hours).[49] However, the *US Medical Eligibility Criteria for Contraceptive Use* (MEC) do not place any

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restrictions on use of EC formulations during breastfeeding.[46] No studies have looked at the excretion of UPA in human milk, and the drug is not yet included in the US guidelines for contraceptive management. Animal studies have shown that it is detected in milk of lactating rats. Effects, if any, on an infant are unknown. The manufacturer recommends avoiding use of UPA during lactation.

Drug interactions. Notable adverse interactions with other drugs have not been demonstrated with UPA or levonorgestrel, but theoretically any drug or herbal product that can induce or inhibit cytochrome p450 liver enzymes may affect plasma concentrations of these drugs and should be avoided. Such cautions are typical of those that accompany use of hormonal contraceptives. Inducers include: barbiturates, bosentan (Tracleer), carbamazepine (Tegretol), felbamate (Felbatol), griseofulvin, oxcarbazepine (Trileptal), phenytoin (Dilantin), rifampin, topiramate (Topomax), and St. John's Wort. Inhibitors include itraconazole (Sporanox) or ketoconazole (Nizoral).

Safety of Oral Emergency Contraception

Contraindications. There is no evidence that the risks of either combined or levonorgestrel-only oral EC outweigh the benefits of use. The US MEC classify both combined EC and levonorgestrel-only EC as category 1 or 2 for all conditions. Category 1 means there are no restrictions on use, and category 2 means that advantages generally outweigh any risks of use[46]. Ulipristal acetate is not yet included in the US or WHO MEC.

The US MEC note that given the low dose and short exposure to these products, oral EC or levonorgestrel-only EC can be used by women who might have contraindications to ongoing use of hormonal products. Given that UPA is a new drug,

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there is not the same long history of use as there is with the hormones contained in contraceptives to allow extrapolation of risks and benefits to be made. However, dosing with UPA however is also of very short duration.

Frequent or continued use. There are no safety concerns with frequent use of levonorgestrel-only products; the only possible exception is frequent or repeated use in women for whom the US MEC list cautions or contraindications to the use of progestin-only ongoing contraceptives. [46] This would also apply to repeated use of hormonal contraceptives as EC. As previously noted, efforts to develop levonorgestrel-only pills as a peri- or postcoital ongoing primary contraceptive were stopped due to unacceptable cycle irregularity, but not for safety reasons. A recent Cochrane review of the studies of pericoital contraception with levonorgestrel calculated a pooled Pearl Index of about 5 pregnancies per 100 woman years [50] when women used EC dosing of levonorgestrel as a primary contraceptive. However, many of the studies in this review were deemed of suboptimal quality. Trussell has estimated that if a typical woman used progestin-only EC for a year, she would have a 20% chance of pregnancy over that year. [51] Not only would she enjoy better contraceptive efficacy with a continuous long-acting contraceptive method, she would also find it less expensive than purchasing multiple packages of EC. No data are available regarding repeated use of UPA.

Pregnancy. In the event of EC failure and subsequent pregnancy, there are no conclusive studies of adverse effects of EC use. However, observational data about use of oral contraceptives that were inadvertently taken in early pregnancy do not suggest concern, and the FDA removed warnings about possible adverse effects of hormonal contraceptives on the developing fetus 15 years ago [52]. There was no increased risk of

birth defects in one study that followed more than 300 women who became pregnant after taking levonorgestrel EC.[53] There is no evidence that using levonorgestrel EC increases the risk of ectopic pregnancy [54]

There are few data about UPA, but there is no evidence of adverse effects in the small number of women who became pregnant during the clinical trials. There will likely be a registry to report possible adverse effects as the drug begins to be prescribed more widely. However, if taken as directed, any oral EC provides a short duration of drug exposure before embryonic development or even implantation, so adverse effects are extremely unlikely. There is no evidence of an increase in the risk of ectopic pregnancy after oral UPA use.

Provision of Oral Emergency Contraception

Combined Hormonal Products. There is no currently marketed combined EC product. These methods are no longer the preferred method of EC, due to the high rates of nausea and vomiting associated with their use. However, guidance about how to use hormonal contraceptive pills as EC (the Yuzpe regimen) can easily be found on a website dedicated to EC (http://ec.princeton.edu/questions/dose.html) and can be used in instances where women need EC but local pharmacies do not carry dedicated products.

Levonorgestrel-only Products. Levonorgestrel is a drug with a long record of safety and use in contraceptive products. The single-dose regimen of this drug clearly met FDA standards for safety and effectiveness required for over-the-counter (OTC) availability,[55] but efforts to make it available without a prescription met with lengthy delays at the FDA and considerable controversy and charges about political agendas. A Citizen's Petition (in 2001) and a manufacturer's application (in 2003) to have the drug approved for OTC

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access finally resulted (in 2006) in FDA approval for OTC access to levonorgestrel EC for women aged 18 years and older. Continued legal challenges to the FDA position led to a lowering of the age for OTC availability in 2009 to women aged 17 and older. An application to remove all age restrictions was filed in 2011 and as of this writing, a decision is pending.[56]

Over-the-counter approval of EC does not necessarily translate into access for many women. A discussion of health care provider refusal to dispense or prescribe contraceptives, including EC, is beyond the scope of this paper. However it is important for providers to realize that in addition to a number of federal laws that permit health care professionals and institutions to refuse to provide care related to abortion and sterilization services, 13 states also have laws that permit refusal to provide contraceptive services. Ten states allow individual health care providers to refuse to provide services related to contraception; 6 states explicitly permit pharmacists to refuse to dispense contraceptives, and 5 other states have broad refusal clauses that may apply to a variety of health care providers and pharmacists. Nine states also allow health care institutions to refuse to provide contraceptive services.[57] Even without such legislation, individual providers and pharmacists may claim a religious objection to providing these services. Before referring women in need of EC to a local pharmacy, providers in some areas might be advised to ensure that the pharmacy stocks and will dispense the medication.

At present women can obtain levonorgestrel EC from a pharmacy without a prescription if they can verify they are 17 years of age or older; younger women will need a prescription. Advance purchase of a package of EC, and advance prescription to

younger women will facilitate access and avoid delay in EC dosing. The product may be available at lower cost through clinics. The 1.5 mg dose should be taken as soon as possible after, and within 5 days of, unprotected intercourse.

Ulipristal acetate. Ulipristal acetate is a prescription-only product and should be available in pharmacies, although (as is true of all the oral products) demand will predict any individual pharmacy's stock. It should be priced in the general range of the branded levonorgestrel product. As a prescription-only drug, it may be covered by insurance when the other product is not. Advance prescription will facilitate access and avoid delay in taking the medication. There is an online ordering option through a website devoted to enabling access to EC (http://ec.princeton.edu/get-ec-now.html). Based on data from the clinical trials, the product labeling for UPA states that a single 30 mg oral dose of ulipristal acetate should be taken as soon as possible within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure.

Education about Oral Emergency Contraception

Women who need EC should be advised that in currently approved doses and based on contemporary scientific research, none of these regimens are abortifacients. Timing of the dose is especially important, and both combined ECand levonorgestrel-only EC are most effective if taken within 72 hours of unprotected sex (although they remain somewhat less effective until 120 hours). Ulipristal acetate has higher efficacy than levonorgestrel for 120 hours after unprotected sex. Women should be counseled that they should initiate on ongoing contraceptive method, as repeated use of EC will be expensive and increase the rate of side effects, especially bleeding. Because the timing of taking EC is critical to its efficacy in preventing unintended pregnancy, purchase or

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prescription of EC should be done in advance, so a woman has it at hand when she needs it.

DEVICES

Intrauterine Contraceptives as Emergency Contraception

The copper-bearing intrauterine device (IUD, ParaGard) is an emergency contraceptive option. A properly placed IUD causes an increase in copper, white blood cells, prostaglandins, and other chemicals in the uterine and tubal fluid that impairs sperm function [58]. A distinct advantage of this option over oral EC is that the woman has continued effective long-acting contraception.

The copper IUD is a long available contraceptive method. There are few absolute contraindications to its initiation for ongoing contraception, most relating to current pregnancy, uterine or cervical malignancy or infection, and anatomic abnormalities that would preclude proper placement [46]. It has been studied as an emergency contraceptive as well. A prospective multicenter study in 18 family planning clinics in China followed the outcomes of 1963 women who had a copper IUD inserted for EC. All had had unprotected intercourse within 120 hours; follow-up was at 1 week after expected menses, and then at 1, 3, and 12 months following insertion. There were no known pregnancies at 3 months. Even if all of the 38 women lost to follow-up prior to the first evaluation had become pregnancy, the pregnancy rate would have been between 1% and 2%. Of those followed for the full 12 months, the calculated pregnancy rate was 0.23 pregnancies per 100, far less than the 1% to 3% pregnancy rates calculated for various oral EC regimens and products. [59] The advantages of the copper IUD over oral levonorgestrel are supported by an interim analysis of a US study comparing EC users

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choosing the copper IUD or oral levonorgestrel. Women selecting the IUD were more likely to be using an effective method of contraception (80% vs 50%, *P*<.001) and less likely to have an unplanned pregnancy (2.6% vs 7.0%, *P*=.04) in the first 6 months after presenting for EC and selecting the IUD than women who selected oral levonorgestrel. [60]

The levonorgestrel intrauterine system (LNG-IUS, Mirena) has not been evaluated as an emergency contraceptive and should not be used for that purpose.

Mechanism of Action of the Copper Intrauterine Device as Emergency Contraception

Although it has been theorized that the presence of the foreign body in the uterus acts primarily by preventing implantation of a fertilized egg, studies have demonstrated an absence of fertilized, normally dividing ova in the tubes of women using an IUD, [61] and the noticeable decrease in all pregnancies among IUD users (including ectopic pregnancies that implant outside the uterus) supports that the contraceptive effect is not related to implantation, but rather to fertilization [61]. The WHO Selected Practice Recommendations state that an IUD may be inserted up to day 12 of the menstrual cycle with no restrictions, and after that only if one is reasonably certain the women is not pregnant [62] The IUD can be inserted up to 5 days after ovulation to prevent fertilization. Once the fertilized egg is implanted, which occurs 6 to 12 days after ovulation, the IUD will not function as EC. Clearly it is difficult to know exactly when a woman ovulates, so most experts will say that the copper IUD can be inserted up to 5 days after unprotected sex [62].

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Side Effects and Concerns related to Intrauterine Device Use for Emergency Contraception

Side effects are the same whether the IUD is placed as an interval insertion for contraception or as an emergency contraceptive: counseling the patient about physical side effects (cramping) or changes in bleeding patterns would be the same as when initiating this method for any woman. There are no concerns about breastfeeding, drug interactions, or obesity.

Active cervical infection is a contraindication to insertion and thus identification of asymptomatic STI infection may be a concern; many local practice guidelines mandate pre-screening for sexually transmitted infection of the cervix before an IUD can be inserted. This creates a barrier to immediate insertion of the IUD, as would be imperative for its use as EC. Such testing however can be done at the time of IUD insertion, and those women who test positive can be recalled for prompt treatment. In one older study, 10% of women with undetected chlamydia at time of insertion developed pelvic inflammatory disease (PID), but the risk of PID after insertion was not different between those who had a positive chlamydia test and those whose test was negative [64]. In a recent US study offering the copper IUD as EC, testing for sexually transmitted infection was done at the time of insertion. Among 197 women receiving the IUD, there were 8 cases of *Chlamydia trachomatis* discovered (no cases of *Neisseria gonorrhoeae*), and none of the women with chlamydia developed PID [65] If a woman receiving an IUD has a positive STI test, she should be treated but the IUD can be left in situ unless symptoms fail to improve or worsen on appropriate therapy [62].

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Many providers worry that IUDs are not as well tolerated in nulliparous women, who may comprise a large proportion of women who request EC, or would be expelled more often from the nulliparous uterus. A review of 15 studies of women using copper IUDs showed that expulsion rates in nulliparous women ranged from 3.3 - 6.2 per 100 insertions, and removals for bleeding and/or pain in nulliparous women ranged from 9 to 59 per 100 insertions [66]. These data suggest that the vast majority of nulliparous women will not expel the IUD and that most will tolerate the device quite well.

Another concern expressed by providers who may not have inserted many IUDs in nulliparous women is that insertion might be more difficult, and failed insertions more common in this group of women. In the Chinese study of copper IUDs for EC, [59] the authors reported that 1.5% of women (29/1963) experienced difficult insertion requiring local anesthesia; this was not broken down by parity. They also reported that 14% of nulliparous women (compared to 5.6% of parous women) required cervical dilation for insertion. In another study, done in the United States, there was a 19.6% failed insertion rate in nulliparous women. [60] There is no evidence that priming the cervix with misoprostol before insertion is effective, and it may delay insertion (for the purpose of EC) and increase adverse side effects from absorption of the misoprostol. [67-70]

Safety of the Copper Intrauterine Device as Emergency Contraception

The US MEC place the IUD in category 1 (no restrictions on use) or 2 (advantages generally outweigh risks of use) for most conditions [46]. However, the MEC rate the use of the copper IUD for EC as a category 3 (risks generally outweigh advantages of use) in women who have been raped who might be at high risk for a sexually transmitted infection and as category 4 (unacceptable health risk) for

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pregnancy. Nulliparous women [71] and adolescents [72] who desire highly effective contraception are candidates for the IUD. The US FDA removed restrictions on copper IUD use regarding parity in 2005, and the both the US and WHO MEC list the device as a category 2 for nulliparous women. There is no evidence that use of an intrauterine device will increase the risk of PID once placed. The copper IUD reduces the risk of ectopic pregnancy because it is so effective at preventing pregnancy; however, if a women becomes pregnant with an IUD in place, the possibility of ectopic implantation should be considered. If a woman experiences an IUD failure and wishes to continue the pregnancy, the IUD should be removed if possible to reduce the risk of infection.

Provision of a Copper Intrauterine Device as Emergency Contraception

Offering the copper IUD is the first step to having women consider it as an EC option. A study in Utah asked women aged 18 to 45 years presenting for EC at 4 family planning clinics in the state whether they would be willing to get a long acting reversible contraceptive method for EC instead of pills; 34% expressed an interest, and 37% of these were still interested when they learned that it was an intrauterine device being proposed. Overall 13% of those surveyed would have been willing to have an IUD for EC even with additional waiting time and undergoing a pelvic examination and insertion procedure [63]

If an IUD is offered, the woman should be medically eligible according to practice standards set by the US MEC [46]. A good sexual and menstrual history is important to rule out the possibility of pregnancy from previous acts of intercourse. A highly sensitive urine pregnancy test will help to rule out an existing early pregnancy. There must be a provider available who can insert the device, and practice and financial guidelines must

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be developed to facilitate immediate insertion. The device generally can be inserted within 5 days of unprotected intercourse.

SUMMARY AND CONCLUSION

Emergency contraception is an important means of preventing unintended pregnancy. The most comprehensive and current source of information about EC for patients and clinicians is the EC Web site run by the Office of Population Research at Princeton University and the Association of Reproductive Health Professionals. This Web site can be accessed at www.not-2-late.com.

Clinicians should ensure that women are aware of their EC options and be prepared to provide such options promptly should a woman request it. Assessment of need, risk, and identifying the woman's plans for ongoing contraception will allow the provider in assisting a woman make appropriate decisions about her EC options. Availability of oral options in one's local community should be evaluated, and women referred to pharmacies that have oral options in stock and do not place restrictions on dispensing them. Providers who are inexperienced in the provision of the IUD option should identify colleagues to whom woman can be promptly referred. Removing barriers to EC access and use will provide women with a last chance to prevent pregnancy after unprotected intercourse.

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Table 1: Comparison of Emergency Contraceptive Methods

Emergency Contraceptive Method	Brand names	Route and dose	Pregnancy Rate after Use	Maximum time for Use	Access Issues	Provides ongoing contraception	US MEC category [a]	Other considerations
Copper T380A	ParaGard	Intrauterine	0.1%-0.2%	Up to 5 days after unprotected intercourse; Up to day 12 of a regular menstrual cycle; At other times of cycle if not more than 5 days after ovulation	Office visit needed, experienced provider, cost of IUD or insurance coverage for IUD	Yes	1 or 2 except: Sexual assault victims at high risk for STI: 3 Pregnancy: 4	
Levonorgestrel	Plan B One Step; Next Choice	150 mcg orally in 1 or 2 doses[b]	1.7%-2.6%[c]	Up to 5 days (120 hours) after unprotected intercourse, may be somewhat less effective from 72 – 120 hours	Non-prescription for women 17 and older; Prescription required for women under age 17	No	1 or 2	May be less effective at higher body weight but is more effective than not using it at all.
Ulipristal	*ella*	30 mg	0.9%-	Up to 5	Prescription	No	Not yet	*May* reduce

acetate		orally in one dose	1.8%[c] 2.6% from 48-72 hours[d]	days; Effectiveness does not wane between 72 and 120 hours.	required		included	the contraceptive action of progestin-containing hormonal contraceptive methods because of its affinity for binding to the progesterone receptor; reliable barrier contraception should be used until next menses
Ethinyl estradiol and levonorgestrel hormonal contraceptives (Yuzpe regimen)	Various[e]	Two doses orally of various options[e]	2%-3%	Up to 72 hours[f]	Prescription required	No	1 or 2	Higher rates of nausea and vomiting compared to other oral regimens. Consider prescribing an anti-emetic.

Abbreviations: MEC, *Medical Eligibility Criteria for Contraceptive Use;* STI, sexually transmitted infection

Sources: Centers for Disease Control and Prevention [46] , Food and Drug Administration [22] ,Glasier [45] ,Trussell[51] , World Health Organization [62] , Wu [59] ,

[a] US MEC Categories:

Category 1: a condition for which there is no restriction

Category 2: a condition for which the advantages of using the method generally outweigh the theoretical or proven risks

Category 3: a condition for which the theoretical or proven risks usually outweigh the advantages of using the method

Category 4: a condition that represents an unacceptable health risk if the contraceptive method is used.

[b] A single dose has been shown to be as effective as 2 doses, although some package labeling continues to state it should be taken in 2 doses.

[c] Rates taken from clinical trials that compared levonorgestrel and ulipristal acetate and calculated actual risk, not relative risk.

[d] This rate was taken from a single-arm trial that evaluated the effectiveness of ulipristal acetate beyond 72 hours.

[e] These regimens are not the first choice, due to associated rates of nausea and vomiting. If these are the only option available for a woman, the number of pills and dosing from 19 different branded combined oral contraceptive products is available from the Princeton University Office of Population Research and Association of Reproductive Health Professionals and can be accessed at http://ec.princeton.edu/questions/dose.html.)

[f] No studies have evaluated effectiveness beyond 72 hours.

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