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Review article

Society of Family Planning Clinical Recommendation: Emergency contraception

Jennifer Salcedo[a,*], Kelly Cleland[b], Deborah Bartz[c], Ivana Thompson[d]

[a] Department of Obstetrics and Gynecology, New York Medical College, Valhalla, NY, United States
[b] American Society for Emergency Contraception, Lawrenceville, NJ, United States
[c] Department of Obstetrics and Gynecology, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, United States
[d] Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, United States

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ABSTRACT

Emergency contraception (EC) refers to several contraceptive options that can be used within a few days after unprotected or under protected intercourse or sexual assault to reduce the risk of pregnancy. Current EC options available in the United States include the copper intrauterine device (IUD), levonorgestrel (LNG) 52 mg IUD, oral LNG (such as Plan B One-Step, My Way, Take Action), and oral ulipristal acetate (UPA) (ella). These clinical recommendations review the indications, effectiveness, safety, and side effects of emergency contraceptive methods; considerations for the use of EC by specific patient populations and in specific clinical circumstances and current barriers to emergency contraceptive access. Further research is needed to evaluate the effectiveness of LNG IUDs for emergency contraceptive use; address the effects of repeated use of UPA at different times in the same menstrual cycle; assess the impact on ovulation of initiating or reinitiating different regimens of regular hormonal contraception following UPA use; and elucidate effective emergency contraceptive pill options by body mass indices or weight.

1. Background

Emergency contraception (EC) refers to contraceptive options that can be used within a few days after an episode of unprotected or under protected intercourse or sexual assault to reduce the risk of pregnancy. Current EC options available in the United States include the copper intrauterine device (IUD), levonorgestrel (LNG) 52 mg IUD, oral LNG (such as Plan B One-Step, My Way, Take Action), and oral ulipristal acetate (UPA) (ella). All EC options are effective, safe, and generally well tolerated. Oral methods are accessible without a clinic visit [1–4]. EC differs from medication abortion which is used to end an established pregnancy.

Unprotected or under protected intercourse and sexual assault are common. Of patients who specifically seek out EC, approximately 40% report multiple episodes of unprotected intercourse in the cycle prior to presentation, and 14% report at least one episode of unprotected intercourse six or more days prior to seeking EC [5,6]. Additionally, approximately 19% of women in the United States report a history of rape or attempted rape in their lifetime, with ethnic minority women, individuals with a history of military service, and sexual minority and transgender individuals reporting higher rates [7–9].

Patients present to various settings to inquire about or access EC, including emergency departments, clinics, urgent care centers, and pharmacies. Health care providers working in such settings should be knowledgeable about EC options and facilitate the provision of these methods in a time-sensitive manner. Many patients face geographic, logistical, financial, and sociocultural barriers to safe abortion care, making EC a critical resource to help patients avoid unintended pregnancies.

2. Clinical questions

2.1. What options are available for EC?

2.1.1. Emergency contraceptive pills (ECPs)

Dedicated oral ECPs containing UPA 30 mg or LNG 1.5 mg, both as a single dose, are available in the United States and Europe. UPA can be effectively used up to 120 hours after unprotected intercourse while oral LNG can be effectively used up to 96 hours (and possibly up to 120 hours) after unprotected intercourse [10]. In a few countries, oral mifepristone in doses of 10 to 25 mg is available commercially as EC [11]. The Yuzpe method is a form of EC that comprises two doses of combined oral contraceptive pills

* Corresponding author.
E-mail address: jsalcedo4@nymc.edu (J. Salcedo).

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containing 100 to 120 mcg ethinyl estradiol (EE) and 0.5 to 0.6 mg LNG per dose [12]. Given the resulting nausea from this high dose of EE, as well as the availability of other more convenient products marketed specifically for EC, the Yuzpe method is likely used infrequently in current clinical practice.

2.1.1.1. Mechanism. ECPs work by preventing or delaying ovulation and are ineffective after ovulation has occurred. Two studies demonstrated that when LNG ECPs are taken on or before the day of ovulation, no pregnancies occurred. However, when taken after the day of ovulation, the number of pregnancies expected without EC occurred (based on the cycle timing of the individuals in the study) [13,14]. In a crossover pharmacodynamic study, 34 women were treated with UPA ECPs or placebo when the leading follicle was at least 18 mm. Follicular rupture failed to occur among all women treated with UPA ECPs before the luteinizing hormone surge began, in 79% after the surge began but before the peak, and in 8% of women treated after the luteinizing hormone peak [15]. In another study, researchers measured pregnancy rates among women who took UPA ECPs within 120 hours of unprotected intercourse and were classified as preovulatory or postovulatory. The observed pregnancy rate in the preovulatory group was significantly lower than expected with 77.6% of expected pregnancies prevented ($p < 0.0001$), while the rate in the postovulatory group was as expected with 36.4% of expected pregnancies prevented ($p = 0.281$) [16]. Although the United States Food and Drug Administration (FDA) recently addressed the labeling of LNG ECPs, approved labeling for UPA ECPs states that these products can interfere with implantation [17,18]. Two newer systematic reviews do not support this assertion [19–21].

2.1.1.2. Efficacy. In clinical trials, pregnancy rates following UPA ECP use within 120 hours of intercourse range from 0.9% to 1.8% [22–26]. Similar effectiveness is seen when LNG ECPs are taken up to 96 hours following unprotected intercourse. It is unclear whether protection against unintended pregnancy is provided when LNG ECPs are taken 96 to 120 hours after unprotected intercourse [10]. In comparative trials, UPA is more effective than LNG. In a combined analysis of two randomized trials comparing the effectiveness of UPA to LNG ECPs, the odds of pregnancy following UPA were 65% lower when taken in the first 24 hours following unprotected intercourse, and 42% lower up to 72 hours after unprotected intercourse, compared to LNG [2,16,22,24,26]. This difference in efficacy is best explained by UPA's ability to delay ovulation after the luteinizing hormone surge has begun (at which point LNG ECPs are no longer effective) before the luteinizing hormone peak [27].

2.1.2. IUDs

2.1.2.1. Types. The copper IUD and the LNG 52 mg IUD can be effectively initiated up to 120 hours after unprotected intercourse as EC. Copper IUDs have been used for decades as EC, while the LNG 52 mg IUD has recently demonstrated effectiveness as EC [4,28].

2.1.2.2. Mechanism. The primary mechanism of the copper IUD is interference with sperm maturation and motility [29]. However, the nearly one hundred percent efficacy of the emergency copper IUD indicates that if fertilization does occur, postfertilization effects (such as induction of a foreign-body reaction in the uterus through alteration of cytokines in the endometrial lining which can inhibit implantation) may also contribute to its mechanism of action [27]. LNG IUDs may work as EC by similarly inducing a foreign-body reaction or through known effects of LNG, such as thickening of cervical mucus, interference with sperm maturation and function, and alterations to oviduct transport [29–32].

2.1.2.3. Efficacy. The copper IUD used as EC is significantly more effective than ECPs, with a pregnancy rate of 0.09% [33,34]. A randomized, noninferiority trial of 638 patients investigated the efficacy of the LNG 52 mg IUD for EC compared to the copper IUD within 5 days of unprotected intercourse. The trial demonstrated a 0.5% (95% CI 0.01% to 1.7%) failure rate for the LNG 52 mg IUD as compared to a 0% (95% CI 0%–1.1%) failure rate for the copper IUD. The LNG 52 mg IUD was found to be noninferior to the copper IUD for EC [28]. The investigators did not estimate anticipated pregnancy rates based on cycle timing of unprotected intercourse in the study. Additional studies investigating the LNG IUD for EC may further strengthen the external validity of these findings [35]. *We recommend that the LNG 52 mg IUD be offered as a first-line EC option, along with other EC methods (GRADE 1B).* IUD for EC patients should be counseled regarding the risk of ectopic pregnancy should an IUD fail, as well as the risks of pregnancy in the setting of an IUD, such as miscarriage and intrauterine infection [36].

We recommend that clinicians counsel individuals considering EC on the following:

- *The copper IUD is more effective than ECPs (GRADE 1A).*
- *UPA ECPs are more effective than LNG ECPs (GRADE 1A).*
- *LNG and UPA ECPs prevent pregnancy through preovulatory effects (GRADE 1A).*
- *The LNG 52 mg IUD is noninferior to the copper IUD for EC within 5 days of unprotected intercourse (GRADE 1B).*

2.2. What are the indications for EC?

Patients seek EC to reduce their risk of pregnancy after unprotected or under protected intercourse and sexual assault. Such situations include, but are not limited to: intercourse during which no contraception was used; intercourse surrounding contraception failure (such as a broken condom) or incorrect use (such as recently missed oral contraceptive pills); intercourse during which the contraception used is viewed to have suboptimal effectiveness (such as a barrier method); sexual assault; suspected contraceptive sabotage; and intercourse during fertile days in one's cycle, as tracked by calendars or period tracking applications.

The World Health Organization (WHO) identifies several specific clinical situations for which EC can be recommended. These clinical scenarios are listed in Table 1 [37]. As detailed in this document, the risks of EC use are low. If a patient requests EC outside of the listed criteria for use, we recommend engaging in a shared decision-making process to assist the patient in choosing an option that best meets their goals.

2.3. What clinical considerations may impact the use of EC?

2.3.1. Medical conditions

Given the potential for EC to decrease morbidities associated with mistimed or unwanted pregnancy, the risk of all currently available EC methods should be compared to the risks of pregnancy in the setting of medical conditions. For patients with hypercoagulable conditions or a history of VTE, the estrogen-containing Yuzpe method has not been found to significantly change Factor VII or antithrombin levels, unlike longitudinal combined oral contraceptive use. No cases of venous thromboembolism secondary to estrogen-containing EC use have been reported [38].

Acute or chronic illnesses associated with significant vomiting or malabsorption may result in decreased effectiveness of ECPs. The UPA prescribing information and the Centers for Disease Control and Prevention Selected Practice Recommendations for Contraceptive Use recommend repeat ECP dosing when vomiting occurs within 3 hours of pill intake, the maximum amount of time required to achieve peak plasma concentrations in the setting of recent high-fat food intake [18,36].

Table 1
World Health Organization indications for emergency contraception use

Sexual intercourse when no contraceptive has been used	
Sexual assault when the person was not protected by an effective contraceptive method	
Sexual intercourse where there is concern for contraceptive failure or misuse, including:	
Condoms	Breakage, slippage, or incorrect use
Combined hormonal contraceptive pills	Three or more consecutively missed pills or Three days late during the first week of the cycle
Progesterone-only contraceptive pills	Three or more hours late from usual pill use time or more than 27 h after the previous pill
Desogestrel-only contraceptive pills	Twelve or more hours from usual pill use time or more than 36 h after the previous pill
Norethisterone enanthate injection	Two or more weeks late for injection
Depot-medroxyprogesterone acetate injection	Four or more weeks late for injection
Combined injectable contraceptive	Seven or more days late for injection
Cervical cap or diaphragm	Dislodgement, breakage, tearing, or early removal
Withdrawal	Failed withdrawal
Spermicide	Failure to melt prior to intercourse
Fertility awareness methods	Miscalculation of abstinence period, or failure to abstain or use a barrier on the fertile days
Intrauterine device or implant	Device expulsion

Data from selected practice recommendations for contraceptive use. 3rd ed. Geneva: World Health Organization; 2016.

Immunosuppressed patients should be considered appropriate candidates for IUDs for EC, given the current understanding of IUD mechanisms of action, absence of evidence for systemic inflammation following LNG IUD placement, and evidence for a sterile intrauterine inflammatory response after IUD insertion in solid organ transplant and patients with other immunosuppressive conditions. Additionally, while there are concerns for increased upper genital tract infection risk with the IUD insertion process, such infections are rare, and the risk of infection is not increased in immunosuppressed patients [39]. Although the CDC US Medical Eligibility for Contraceptive Use (US MEC) states that IUD insertion is not recommended unless other methods are not available or acceptable in patients with complicated solid organ transplant, such as graft failure, rejection, or cardiac allograft vasculopathy, this recommendation is based on theoretical concern with no published evidence of increased infectious morbidity with IUD placement in such patients. Clinicians should pursue a shared decision-making approach with patients in these circumstances [40–44].

2.3.2. Weight and BMI

Multiple studies demonstrate no changes in the failure rate for the copper IUD or the LNG 52 mg IUD for EC based on body weight or BMI [28,35,45,46]. However, patient BMI and weight appear to impact the effectiveness of ECPs, with LNG ECPs being negatively affected to a greater extent than UPA ECPs. A meta-analysis of oral EC studies demonstrated that the risk of pregnancy is one and one-half times greater in users with an overweight BMI (25–29.9 kg/m^2) and more than three times greater in users with an obese BMI (>30 kg/m^2), compared to nonoverweight users [47]. A meta-analysis by Festin et al. [48] pooled data from four oral EC studies and examined data from 6873 EC users. When compared to participants with BMI < 25 kg/m^2, participants with BMI > 30 kg/m^2 were eight times more likely to experience pregnancy after EC use. Despite the demonstrated increased risk of pregnancy, the overall pregnancy rate in the obese group was low, at only 2.03% [48]. A study of 1731 oral LNG EC users demonstrated pregnancy rates of 1.4% or less for participants weighing 75 kg or less compared to pregnancy rates of 6.4% and 5.7% among users weighing 75 to 85 kg and >85 kg, respectively [49].

While doubling the dose of LNG ECPs increases the maximum concentration of serum LNG in individuals with obesity to levels seen in individuals with normal BMI, it was not shown to decrease levels of follicular rupture within 5 days to levels seen in individuals with BMI < 25 kg/m^2 [50,51]. Although the Edelman 2022 study was not designed to evaluate oral LNG EC efficacy, the failure to decrease levels of follicular rupture in individuals with obesity to levels seen in individuals with overweight or normal BMI suggests lower efficacy of oral LNG EC in individuals with obesity, even with a higher dose of 3 mg LNG [51].

UPA ECPs are more effective than LNG ECPs in all users, including those with overweight and obese BMIs [2,16,22,24,26]. Patients with an overweight BMI have the same failure rate as patients with a normal BMI with the correct use of UPA for EC [47]. However, UPA ECP users with obesity are twice as likely to experience pregnancy compared to users with a normal BMI. It appears the upper limit of efficacy for LNG ECPs occurs at a bodyweight of 70 kg and the upper limit of efficacy for UPA ECPs occurs at a bodyweight of 85 kg, though it is unclear how the data from prior studies translates from patient weight to BMI [47]. *Based on this data, we recommend that clinicians counsel individuals that UPA ECPs, if available, are more effective than LNG ECPs in overweight and obese persons and those with bodyweight 70 kg or greater (GRADE 1C).*

2.3.3. Medications

As LNG and UPA are substrates of cytochrome P450 3A4 (and LNG also of P450 3A5), concurrent use with enzyme inducers, such as efavirenz, carbamazepine, oxcarbazepine, and phenytoin, is expected to lower the dose of the ECPs, which may decrease their effectiveness [52]. In women taking the former EC regimen of oral LNG 0.75 mg (two doses 12 hours apart) concurrent with efavirenz (a reverse transcriptase inhibitor commonly used in the treatment of HIV), the AUC12, Cmax, and Cmin of LNG were decreased by 56%, 41%, and 67%, respectively [53]. Similar reductions have been noted with carbamazepine, phenytoin, oxcarbazepine, and eslicarbazepine [52]. While the clinical significance of these reductions is unclear, in 2016 the European Medicines Agency (EMA) recommended to double the dose of LNG ECPs for patients taking CYP3A4 inducers in the preceding 4 weeks [52]. However, the effectiveness of double dosing LNG ECPs in this setting has not been evaluated, and it may be inadequate to address the effects of medications that induce CYP3A4 more strongly than efavirenz, such as rifampin and phenytoin [52]. Lamotrigine, a glucuronidation enzyme inducer, also reduces levels of LNG taken orally [52,53]. In contrast, coadministration of oral LNG with vigabatrin, levetirac-

etam, ticagrelor, solifanacin, and vortioxetine does not decrease LNG levels [52].

Only three studies evaluating medication interactions with oral UPA are available. While erythromycin and ketoconazole do not lower levels of UPA taken orally, rifampicin, an enzyme inducer, decreases mean UPA exposure more than 10-fold [54,55]. Similar but more modest interactions are predicted for carbamazepine, rifabutin, dabrafenib, and phenobarbital, while stronger interactions are predicted for phenytoin, enzalutamide, and mitotane [52,54,55]. Using modeling, predicted required dose increases for oral UPA when coadministered with a CYP3A enzyme inducer vary from 1.3-fold for the weakest inducer to 14.3-fold for the most potent inducers, rifampicin, and mitotane [52]. While current UPA ECP labeling recommends avoiding use in patients who have taken CYP3A4 inducers in the past 4 weeks, this interval may be insufficient for such medications with long half-lives, such as enzalutamide, phenobarbital, and mitotane [18,52].

While neither UPA nor oral LNG inhibits CYP450 enzyme activity, both may inhibit P-glycoprotein (P-gp) at emergency contraceptive doses, thereby elevating levels of P-gp substrates, such as digoxin, colchicine, and fexofenadine, resulting in potential morbidity related to supratherapeutic levels of such medications [18,56]. A case report of a supratherapeutic international normalized ratio not associated with hemorrhage, noted in a patient on warfarin taking two doses of 0.75 mg LNG for EC, may be illustrative of such interaction [57].

We recommend advising patients currently or recently taking cytochrome P450–3A4 and P450–3A5 inducers or glucuronidation enzyme inducers that ECPs may be less effective and that IUD placement for EC should be considered (GRADE 1C).

2.4. What are counseling considerations regarding repeated use of EC, use by an unknowingly pregnant individual, and use with other hormonal contraceptives?

2.4.1. Repeated use of EC in the same cycle

There are no specific safety concerns regarding the repeated or frequent use of LNG ECPs [12]. Additionally, there is no evidence for the increased incidence of ectopic pregnancy (relative to intrauterine pregnancy) with repeated LNG ECP use [58]. Further, weekly dosing of UPA has not been associated with serious side effects, although headache and nausea were reported in almost 70% of participants in one study [59]. While no reports of serious adverse events have been noted with the use of UPA ECPs, recent reports of rare but serious liver injury in women using lower daily dosing for the treatment of uterine fibroids calls for additional study of the safety of frequent UPA dosing [60]. In September 2020, the EMA concluded that UPA use for the treatment of uterine fibroids should no longer be marketed in the European Union due to eight case reports of serious liver injuries (four requiring transplantation) out of more than 765,000 patients included in postmarketing surveillance [61]. In such cases, the hepatotoxicity is thought to be an idiosyncratic drug-induced liver injury (DILI) potentially also impacted by UPA's high lipophilicity and long half-life, inhibition of breast cancer resistance protein in liver cells, and bile salt export pump inhibition [62]. Such reactions are related more to host factors than to toxic properties of the medication itself, and are thus less dose-dependent and more varied in latency, presentation, and course than intrinsic DILI (such as acetaminophen-associated DILI) [63]. In contrast, Yoon et al. [64] compared more than 20,000 patients taking UPA for fibroids to those taking gonadotropin releasing hormone agonists and did not find a difference in the incidence of severe or toxic liver disease between the groups. In that study the rate of severe liver disease and hepatic failure in patients using UPA was 0.04% and no liver transplantations were performed.

The daily dosing of 5 to 10 mg UPA is associated with complete ovulation inhibition in approximately 80% of individuals, as observed with the use of a contraceptive vaginal ring releasing 1.5 to 2.5 mg of UPA daily (unavailable in the United States) [59]. However, in a contraceptive study of women administered UPA 30 mg orally every five to seven days, ovulation was observed in more than 70% of cycles, likely explained by the half-life of UPA being only 32 hours [59]. Repeat dosing of UPA ECPs in the same cycle is not recommended by the manufacturer [18]. Given the potential morbidity of mistimed or unwanted pregnancy, and the fact that individuals may take ECPs at times in the cycle when they are not at significant risk of pregnancy, repeated dosing should not be withheld. Patients should be counseled that repeat dosing of UPA appears safe but the contraceptive effectiveness of multiple UPA doses within the same cycle remains unclear.

2.4.2. EC use by an unknowingly pregnant patient

For patients who take LNG ECPs while unknowingly pregnant, or who conceive as a result of LNG ECP failure, there is no concern for associated pregnancy-related morbidity. Meta-analyses have not demonstrated an association between embryonic exposure to contraceptive hormones and fetal malformations generally, or genital malformations specifically [65,66]. More limited but similarly reassuring data are available regarding inadvertent exposure to UPA in pregnancy. One case of optic nerve atrophy has been documented in a pregnancy with UPA exposure, a condition which was determined by an independent Data Safety Monitoring Board not to be attributable to UPA in utero exposure [67]. No other pregnancy or delivery complications have been reported in association with UPA ECP use. The miscarriage rate associated with UPA-exposed pregnancies (13.8%) is not higher than the 20% reported in the general population [67,68] . Similarly, the incidence of ectopic pregnancy (1.1%) is similar to that in the general population of pregnant individuals of 0.8% to 2% [67,69,70]. More pregnancies following ECP exposure end in abortion than in the general population, consistent with differences in pregnancy intention between the 2 populations [67]. Given such findings, pregnancy testing is unnecessary prior to ECP use, unless a patient is concerned about their pregnancy status for other reasons.

For patients seeking copper or LNG IUDs for EC who also report episodes of unprotected intercourse in the current cycle more than five days before planned IUD insertion, the potential presence of a preimplantation fertilized ovum should be considered. Several studies demonstrate that pregnancy is uncommon in such situations following IUD placement. In a study of same-day LNG IUD placement for routine contraception, 0.4% of patients who did not meet checklist criteria supported by the CDC for reasonable certainty of not being pregnant received a diagnosis of pregnancy in the weeks following IUD insertion [71]. In another study, one out of 40 patients (2.5%) who presented for EC and reported additional unprotected intercourse 6 to 14 days prior to IUD insertion had a positive pregnancy test within the subsequent 2 weeks [6]. A study of 134 patients who had a copper IUD placed 6 to 14 days after unprotected demonstrated 0 pregnancies two to four weeks after IUD placement [46].

Although uncommon, pregnancies in patients with an IUD have elevated risks of adverse pregnancy outcomes compared to patients who conceive without an IUD. Such elevated risks include miscarriage, preterm delivery, and septic abortion. These risks are decreased in patients who undergo IUD removal during the pregnancy but remain elevated relative to baseline risks without an IUD [72]. There is currently insufficient data to reach conclusions about any specific risks of an LNG IUD on a developing fetus [72]. Similar considerations pertain to patients who receive an IUD for EC with unprotected intercourse limited to the previous five days in whom the IUD fails, resulting in pregnancy. Given the risks of pregnancy

in the setting of an IUD, pregnancy testing should be performed prior to IUD insertion for EC and patients counseled regarding the risks of pregnancy in the case a preimplantation fertilized ovum is present at the time of IUD placement for EC or in the case of IUD EC failure.

2.4.3. Use with other hormonal contraceptives

Initiating regular contraceptive use immediately following ECPs increases uptake and continuation of the regular contraceptive method [73,74]. There is no mechanism by which LNG, a progestin, would decrease the effectiveness of subsequently initiated hormonal contraception. Similarly, initiation of regular hormonal contraception immediately following LNG ECP use will not decrease the effectiveness of LNG as an ECP. *We recommend routine hormonal contraception be initiated as soon as desired following LNG ECP use, with abstinence or a nonhormonal contraceptive method used as back-up for 7 days or until the next menstrual period/withdrawal bleed, whichever occurs first (GRADE 1A).*

UPA does not appear to decrease subsequent oral contraceptive pill efficacy. UPA had no significant effect on the contraceptive onset of a 75 mg desogestrel progestin-only pill, with regard to desogestrel's impact on cervical mucus or ovulation inhibition [75]. Administration of UPA mid-cycle, followed the next day by initiation of a daily 30 mcg EE/150 mcg LNG-containing combined hormonal contraceptive pill was associated with ovarian quiescence in most women by seven days, with a minority of women taking additional days (up to 14) to reach quiescence [76]. All women who ovulated did so after 11 days of combined oral contraceptive pill use [76]. No studies to date have investigated the potential for delayed effectiveness of routine contraceptive effects when UPA is closely followed by the use of nonoral hormonal contraceptives. After resuming or initiating regular contraception following ECP use, the Centers for Disease Control and Prevention Selected Practice Recommendations for Contraceptive use recommends abstinence or barrier method use for seven days, or until the next menses, whichever occurs first [36].

In contrast, the effectiveness of UPA in delaying ovulation for EC use is reduced by subsequent administration of hormonal contraceptive pills. When a combined oral contraceptive pill containing 30 mcg of EE and 150 mcg of LNG was administered 2 days following UPA, more subjects demonstrated evidence of ovulation (follicular rupture) within 5 days (27% vs 3%) [77]. Similarly, administration of 75 mg desogestrel the day following UPA is associated with evidence of ovulation within five days in 45% of subjects, compared to 3% of subjects who took only UPA [75]. The mean time to ovulation was 8 days in the UPA only group, compared to four days in the group taking UPA followed by desogestrel [75]. Consequently, extrapolation of decreased UPA effectiveness to coadministration with other progestin-only pills and nonoral routes of progestin administration should be done with caution [75].

Whether the effectiveness of UPA is similarly decreased when used following missed doses of routine short-term hormonal contraception followed by resumption of the routine contraception is unclear. Additionally, individuals who delay reinitiating their routine hormonal contraception following UPA use may be at elevated risk of ovulation and consequent pregnancy compared to those who resume hormonal contraception immediately following UPA use. In a study of women who missed combined oral contraceptive pill doses (as part of a 21/7 regimen of 30 mcg EE/150 mcg LNG) on days five, six, and seven, and took UPA the morning of day eight, those who resumed their combined oral contraceptive pill the same evening demonstrated decreased evidence of subsequent ovulation during that pill pack compared to those who waited five days to restart contraceptive pills [78]. No women who completed the study ovulated in the five days after taking UPA, regardless of when the contraceptive pill was restarted [84]. Given that ovarian activity is suppressed during combined oral contraceptive pill use and that time is required after missed pills for recovery of ovarian activity, restarting contraceptive pills soon after missing pills and taking UPA would be unlikely to result in ovulation [78,79]. Some may argue that individuals who miss only a few contraceptive pills are not indicated to use EC at all. However, given that an individual may intermittently miss doses throughout a cycle, providing a patient with a specific risk assessment for conception after missed doses is challenging [78].

Concerns that initiating routine hormonal contraception in the days following UPA use may decrease UPA's effectiveness must be weighed against the risk of subsequent pregnancy if routine contraception is not established or reestablished. This risk-benefit ratio is expected to vary by individual and situation based on the risk of pregnancy from the index exposure, risk of subsequent pregnancy in the short-term, contraceptive access, and individual preferences. *Following UPA ECPs, we recommend generally delaying initiation of routine hormonal contraception for five days and abstinence or a nonhormonal contraceptive method used as back-up for an additional seven days or until the next menstrual period/withdrawal bleed. However, the specific timing of routine hormonal contraceptive initiation should be individualized through shared decision-making (GRADE 1B).*

2.5. What follow-up and additional services should be offered to individuals seeking EC?

2.5.1. Urine pregnancy testing (at time of provision and at follow-up)

EC reduces the risk of pregnancy after unprotected intercourse but does not completely resolve this risk. EC is associated with pregnancy rates ranging from 0.09% to 2.6% [24,28,33]. If an EC user experiences menses within two weeks of EC use, they can be reassured of their nonpregnant status. If this does not occur, a pregnancy test is recommended three weeks after EC use. Additionally, pregnancy testing should be considered one month following LNG IUD placement for EC given the potential for menstrual changes with this method [28]. If pregnancy is detected, the patient should present for pregnancy localization and pregnancy options discussion. While pregnancy testing should be performed prior to IUD insertion for EC, ECPs should not be withheld or delayed for pregnancy testing. *We recommend against withholding or delaying ECPs for pregnancy testing (GRADE 1B). We recommend offering urine pregnancy testing for post-EC pregnancy assessment as needed (GRADE 1C).*

2.5.2. Sexually transmitted infection (STI) screening and treatment

In 2018, one in five adults in the United States had a STI [80]. Given the prevalence of STIs, people who report unprotected or under protected intercourse should be offered screening for STIs [81]. Active mucopurulent discharge and current chlamydia or gonorrhea infections are contraindications to IUD placement [36]. However, asymptomatic individuals with chlamydia or gonorrhea infection at the time of IUD placement may not be at elevated risk of pelvic inflammatory disease when such infections are recognized and appropriately treated compared to individuals undergoing IUD insertion in the absence of such infections [82]. Patients with incidentally positive tests noted following IUD insertion should be treated according to current CDC guidelines and the IUD may remain in place if desired [36]. The placement of an IUD for EC should not be withheld or delayed for STI screening in the absence of active mucopurulent discharge, regardless of the patient's STI risk. Empiric treatment for gonorrhea, chlamydia, and trichomoniasis should be given to persons reporting sexual assault. Such individuals should be offered Hepatitis B and HPV vaccinations based on their vaccination status [81]. HIV postexposure and preexposure prophylaxis should be considered within a framework

of shared decision-making [81]. *We recommend offering or referring persons requesting EC for sexually transmitted infection screening, postexposure prophylaxis, pre-exposure prophylaxis, and treatment as indicated (GRADE 1C).*

2.5.3. Intimate partner violence and human trafficking screening

People who experience intimate partner violence or who are being human trafficked are likely to experience unprotected or under protected intercourse [83,84]. People who present for EC should be screened for intimate partner violence and sex trafficking and provided local resources and referrals as desired. *We recommend screening persons who use EC for intimate partner violence and human trafficking as indicated (GRADE 1C).*

2.5.4. Ongoing contraception

Unprotected intercourse is common and EC users frequently have more than one episode of unprotected intercourse prior to presenting for EC [5,6]. Discussing or initiating ongoing contraception at the time of presentation for EC may help EC users meet their fertility goals. It is important to recognize that people are fluid in their reproductive intentions [85]. Acceptance of EC does not commit a person to avoiding pregnancy for any duration outside of the initial EC use. At EC encounters, health care providers should assess users for interest in ongoing contraception and provide contraception management or referrals as desired by the patient. *We recommend offering or referring persons who use EC for ongoing contraception as desired (GRADE 1C).*

2.6. How can clinicians support EC use in special populations?

2.6.1. Use by gender diverse individuals (particularly those taking testosterone)

Clinicians should educate all patients at risk for pregnancy, including gender diverse individuals, regarding EC and provide advance prescription of ECPs if desired. Although gender diverse patients may experience amenorrhea secondary to gonadotropin releasing hormone agonist or testosterone use, they remain at risk for pregnancy if having receptive intercourse with a sperm-producing partner. Such patients may be unaware of their pregnancy risk. In addition to the general risks of unintended pregnancy, in gender diverse individuals unintended pregnancy may also be associated with gender dysphoria and with fetal risks associated with in utero testosterone exposure. While there are no published studies regarding EC use in gender diverse populations, expert consensus based on other hormonal contraceptives does not prompt concern about the loss of efficacy of EC or testosterone when used concurrently [86]. As with all patients, clinicians should use a trauma-informed approach when counseling gender diverse individuals interested in an IUD [87].

2.6.2. Use while breastfeeding, lactating, or chest feeding

ECPs are an effective complement for individuals relying on the lactational amenorrhea method (LAM) for contraception. In a study of Egyptian women comparing standard LAM education to LAM and EC education with advanced provision of one pack of LNG ECPs, 44% of women in the EC group used the LNG ECPs, of which 88% did so correctly (when at least one requirement of LAM had expired and intercourse occurred before initiating a regular contraceptive method) [88]. Significantly more women in the EC group initiated regular contraception within or shortly after the first 6 months postpartum (30% vs 7.3%) and fewer pregnancies occurred in the EC group (0.8% vs 7.3%)[88]. There were no significant differences between groups in duration of lactation, pattern of breastfeeding, or resumption of menstruation [88]. The most common LNG side effect was nausea without vomiting, which occurred in approximately 30% of women [88]. *We recommend clinicians provide EC counseling and advanced prescription of ECPs to individuals relying on the lactational amenorrhea method (GRADE 1B).*

Similar to progestin-only regular contraceptives, LNG ECPs have not been shown to objectively affect the health or development of nursing infants or to subjectively impact the volume of breast milk produced [88,89]. After a single 1.5 mg dose of LNG, levels peak in breast milk after approximately four hours and reach a maximum concentration of approximately 4.1 to 10.7 ng/mL, with a mean terminal half-life of 26 hours [90]. The amount of LNG excreted in milk over the first 24 hours is 0.09% of the dose and decreases rapidly over time, with only 0.01% of the dose recovered in breast milk over the 49 to 72 hours interval [90]. The estimated mean amount of progestin absorbed by a nursing infant intaking 800 mL/day of breast milk is 1.6 mcg in the first 24 hours, 0.3 mcg in the second 24 hours, and 0.2 mcg in the third 24-hour interval [90]. *We recommend that clinicians counsel individuals that breastfeeding does not need to be disrupted because of LNG ECP use (GRADE 1A).*

The copper IUD does not pose concerns for breastfed infants. Insertion of a copper IUD does not impact lactation performance and does not result in elevated levels of copper in breast milk compared to individuals who did not receive a copper IUD [91,92]. Health care providers should be attentive to the overall small but increased risk of uterine perforation associated with IUD insertion in breastfeeding individuals compared to individuals who are not breastfeeding [92].

Little information is available on the use of UPA ECPs while breastfeeding. Currently, package labeling recommends avoiding use while breastfeeding, while the CDC Medical Eligibility Criteria for Contraceptive Use recommends expressing and discarding breast milk for 24 hours after dosing [18,36]. It is estimated that following a 30 mg dose, a fully breastfed infant would receive approximately 4.1 mcg/kg of UPA and its active metabolite over the first 24 hours and a total of 5.2 mcg/kg over five days. This exposure would result in an approximate adjusted dosage of 0.8% of the medication and active metabolite on the first day and a total of 1% of the maternal dose over a five-day period [93]. No studies have addressed infant outcomes in the setting of UPA ECP use and there are no published reports of associated harm. Given the established benefits of breastfeeding, the low level of infant exposure, and no evidence of harm, it is reasonable for individuals to continue breastfeeding without interruption if desired in the setting of shared decision-making.

2.7. What are the barriers to EC use?

2.7.1. IUDs

IUD insertions require an in-person visit with a trained provider. While many clinicians in obstetrics and gynecology are well-trained and comfortable with long-acting reversible contraception (LARC) provision, many other health care professionals are uncomfortable placing an IUD [94]. There is limited awareness of the copper IUD as an EC option and very few obstetrics and gynecology and primary care clinics offer the copper IUD as EC [95]. Additional efforts should be made to increase health care provider and office staff knowledge and training in IUD provision for EC.

To effectively place IUDs upon patient request, a clinic or institution must stock devices for same-day placement. Unfortunately, many clinics do not have a readily available stock of IUD devices and instead employ a two-visit IUD insertion approach modeled after outdated STI screening and pregnancy testing protocols or based on difficulties with device reimbursement [96]. Approximately half of the patients who must return for a subsequent visit for IUD placement do not return [97]. Additionally, IUD devices can cost upwards of $800-$900 for self-funded patients, with

additional charges associated with insertion and removal [98,99]. While the Affordable Care Act has resulted in many insurers covering the cost of IUD placement without co-pay for patients, the cost may still be a barrier for uninsured and underinsured patients [100]. Same-day copper and LNG 52 mg IUD insertions for patients with a negative urine pregnancy test are safe and associated with low pregnancy rates [45,46]. Clinics should develop same-day IUD insertion protocols that balance their ability to meet patient needs and clinic financial responsibilities. Professional organizations should continue to advocate for private and public funding of IUDs for EC and routine use.

2.7.2. ECPs

LNG ECPs have been approved for sale over-the-counter without age or gender restrictions since 2013. However, individuals trying to purchase the product in pharmacies can encounter a lack of availability, additional security measures (locked cabinets, locked exterior packaging), unnecessary requests for identification to enforce outdated age restrictions, and unaffordable cost ($40–50 at most pharmacies) [101,102]. Individuals seeking UPA ECPs encounter additional challenges due to the requirement for a prescription. Clinicians and pharmacists are frequently unfamiliar with UPA [103,104]. Additionally, many pharmacies do not routinely stock UPA and may provide inaccurate information regarding its mechanism of action or differences from LNG ECPs [105,106]. Further, the nuanced clinical guidance related to the initiation of routine hormonal contraception following UPA use may deter providers from offering it instead of LNG ECPs [36]. In addition to these barriers, nine states have policies that restrict access to ECPs by excluding ECPs from contraceptive coverage mandates or allowing pharmacists to refuse to provide it [107].

Pharmacists play a key role in timely EC access. Pharmacists are positioned to advocate for stocking UPA ECPs, ensuring that LNG ECPs are stocked and available over the counter without additional security measures, and educating pharmacy staff members about EC. An informational guide for pharmacy staff is available from the American Society for Emergency Contraception [108]. Several states currently allow pharmacists to dispense ECPs without a prescription, either through a collaborative practice agreement with a physician or through a state-approved protocol [109]. Telemedicine visits for the provision of EC counseling, prescription of ECPs, and facilitation of in-person visits for EC IUD placement may also decrease barriers to EC access for care in which clinician contact is required or helpful [110].

2.7.3. Populations most negatively impacted by barriers to EC access

Barriers to accessing EC may be amplified for individuals from marginalized communities, those living in rural areas, and young people. In parts of the country that are more geographically dispersed, individuals who need EC may be far from a pharmacy. Additionally, individuals from rural or isolated areas may experience confidentiality or privacy concerns related to familiarity with pharmacy staff and lack of alternatives if ECPs are not in stock or difficult to obtain where initially sought. According to the National Survey of Family Growth, from 2006 to 2017, women of reproductive age living in rural areas were significantly less likely to have used EC than those living in urban areas, with reported ever use of ECPs increased from six percent to 15% in rural areas compared with 11% to 27% in urban areas during this time-period [111]. While EC should be routinely offered following sexual assault involving a risk of pregnancy, this is often not the case in emergency departments, particularly for individuals seeking care within religiously affiliated hospital systems [81,112].

Young people also face unique challenges in accessing EC. The complicated regulatory history of LNG ECPs in the United States involved several different age restrictions over the years. Although these restrictions have not been in place since 2013 (2014 for generics), pharmacy staff may still ask for identification [101]. Additionally, young people may have confidentiality concerns when accessing EC through parents' health insurance and may lack transportation to a health care provider or pharmacy. Young people and others with limited financial resources may find EC cost prohibitive, and only 11 states currently have laws that require insurance plans to cover over-the-counter EC without a prescription [113].

Gender diverse individuals face additional barriers when seeking reproductive health care generally and EC specifically [114]. Clinicians may not recognize that transgender and gender nonbinary patients are at risk of pregnancy or may be reluctant to offer EC to patients on testosterone due to concerns about interactions. Additionally, clinicians may be uncomfortable offering IUD placement. Gender diverse individuals may also anticipate and experience unwanted questions, judgment, and stigma when attempting to purchase ECPs at a pharmacy [86].

2.8. Is there a role for ECPs as a primary contraceptive method?

In one study, almost 70% of abortion clients and 50% of family planning clients would definitely or probably be interested in a postcoital contraceptive pill as routine contraception [115]. Patients who reported recently engaging in unprotected intercourse, those reporting that obtaining a prescription for contraception in the past was "not very easy," and African American women (compared to non-Hispanic white women) expressing higher levels of interest [115]. Top reasons for interest included not needing to remember to take a daily pill, liking the idea of only taking hormones when needed, and having infrequent intercourse. In contrast, top reasons for lack of interest included desiring a more effective method, not wanting to remember to use a method pericoitally, and dislike of altered menstrual cycles [115]. Additional reasons for interest in a routine postcoital contraceptive pill include the ability to conceal use and lack of coital interruption (as compared to the use of a coitally-dependent nonhormonal method) [116].

The use of LNG ECPs as a solitary primary contraceptive method is associated with effectiveness that compares reasonably with coitally-dependent methods, such as barrier methods, withdrawal, and periodic abstinence, that have typical use failure rates on the order of 14% to 40% [117]. However, given that individuals in studies of LNG ECPs as a primary contraceptive method are usually selected based on relatively low intercourse frequency, direct comparison of method effectiveness is challenging [118]. Additionally, the use of ECPs as a supplement to nonhormonal methods, planned periodic abstinence, and withdrawal may increase overall contraceptive effectiveness [119]. No studies have specifically evaluated routine postcoital use of UPA ECPs and concerns about delaying ovulation to later in the cycle may limit its effectiveness for this purpose.

A 2014 Cochrane review calculated a pooled Pearl Index of 5.4 per 100 person-years (95% CI 4.1–7) for the postcoital use of 0.75 mg LNG [120]. A study that specifically included US individuals taking 0.75 mg LNG within 24 hours of intercourse who expected to have intercourse 1 to 4 days per month noted a higher Pearl Index of 22.4 (95% CI 4.6–65.4) [121]. In a more recent study evaluating use of LNG 1.5 mg within 24 hours of intercourse, the Pearl Index was noted to be 7.5 for solitary use in all users, and 11.0 for solitary use in women under 35 years old [122]. Oral LNG use pre-coitally may be more effective than postcoital use, as it may concurrently affect both cervical mucus and ovulation [120].

The main side effect reported in oral LNG EC studies is bleeding abnormalities, which have been associated with high discontinuation rates in some studies. Other common side effects include nausea, breast tenderness, weakness, dizziness, headache, abdomi-

nal bloating or pain, pelvic pain, decreased libido, depression, and vomiting [118,122]. There is no consistent evidence of a relationship between bleeding abnormalities and the frequency of pill intake or total dose of LNG [120]. The side effect of irregular bleeding may be problematic for individuals who wish to use ECPs in conjunction with natural family planning methods that rely on cycle regularity [123]. Despite high rates of reported bleeding abnormalities and other side effects, a significant majority of study participants express favorable views of the method [118,122]. The current cost, access, and packaging of LNG ECPs in the United States may make routine ECP use challenging or prohibitive.

We recommend offering regular pericoital use of LNG ECPs for individuals who desire this method either alone or as a supplement to nonhormonal coitus-dependent methods, such as periodic abstinence, barrier methods, or withdrawal (GRADE 1B).

3. Clinical recommendations

Please see Appendix 1 for a key to interpreting GRADE.

- We recommend that the LNG 52 mg IUD be offered as a first-line EC option, along with other EC methods (GRADE 1B).
- We recommend that clinicians counsel individuals considering EC on the following:
  - The copper IUD is more effective than ECPs (GRADE 1A).
  - UPA ECPs are more effective than LNG ECPs (GRADE 1A).
  - LNG and UPA ECPs prevent pregnancy through pre-ovulatory effects (GRADE 1A).
  - The LNG 52 mg IUD is noninferior to the copper IUD for EC within five days of unprotected intercourse (GRADE 1B).
- Based on this data, we recommend that clinicians counsel individuals that UPA ECPs, if available, are more effective than LNG ECPs in overweight and obese persons and those with bodyweight 70 kg or greater (GRADE 1C).
- We recommend advising patients currently or recently taking cytochrome P450–3A4 and P450–3A5 inducers or glucuronidation enzyme inducers that ECPs may be less effective and that IUD placement for EC should be considered (GRADE 1C).
- We recommend routine hormonal contraception be initiated as soon as desired following LNG ECP use, with abstinence or a nonhormonal contraceptive method used as back-up for seven days or until the next menstrual period/withdrawal bleed, whichever occurs first (GRADE 1A).
- Following UPA ECPs, we recommend generally delaying initiation of routine hormonal contraception for five days and abstinence or a nonhormonal contraceptive method used as back-up for an additional seven days or until the next menstrual period/withdrawal bleed. However, the specific timing of routine hormonal contraceptive initiation should be individualized through shared decision-making (GRADE 1B).
- We recommend against withholding or delaying ECPs for pregnancy testing (GRADE 1B).
- We recommend offering urine pregnancy testing for post-EC pregnancy assessment as needed (GRADE 1C).
- We recommend offering or referring persons requesting EC for sexually transmitted infection screening, postexposure prophylaxis, pre-exposure prophylaxis, and treatment as indicated (GRADE 1C).
- We recommend screening persons who use EC for intimate partner violence and human trafficking as indicated (GRADE 1C).
- We recommend offering or referring persons who use EC for ongoing contraception as desired (GRADE 1C).
- We recommend clinicians provide EC counseling and advanced prescription of ECPs to individuals relying on the lactational amenorrhea method (GRADE 1B).
- We recommend that clinicians counsel individuals that breastfeeding does not need to be disrupted because of LNG ECP use (GRADE 1A).
- We recommend offering regular pericoital use of LNG ECPs for individuals who desire this method either alone or as a supplement to nonhormonal coitus-dependent methods, such as periodic abstinence, barrier methods, or withdrawal (Grade 1B).

4. Recommendations for future research

- Effectiveness of the copper IUD compared to the 52 mg LNG IUS for EC.
- Effective dosing of LNG and UPA ECPs for individuals with elevated BMI or body weight.
- Effective dosing of LNG ECPs for individuals concurrently or recently using CYP3A4 inducers.
- Clinically relevant medication interactions with UPA ECPs**.**
- Effects of initiation or reinitiation of various methods of regular hormonal contraception on the effectiveness of UPA ECPs.
- Effects on ovulation of repeat dosing of UPA ECPs at different times during the same menstrual cycle.
- Effects of UPA on lactation and breastfeeding infants.
- Acceptability of EC methods to gender diverse individuals.

Sources

A series of clinical questions was developed by the authors and reviewed by the Society of Family Planning Clinical Affairs Committee. A search of the medical literature was performed using the PubMed program of the National Library of Medicine and the Cochrane Library of Clinical Trials from the beginning of the databases through April 9, 2022. Search terms included but were not limited to LNG, UPA, copper IUD, LNG IUD, sexually transmitted infection, breastfeeding, mechanism of action, safety, effectiveness, transgender, and gender diverse, in combination with EC, ECPs, postcoital contraception, and pericoital contraception. We then hand-searched the references of these manuscripts for additional relevant publications. We reviewed relevant product labels and statements from the American College of Obstetricians and Gynecologists and United States Centers for Disease Control and Prevention. A comprehensive systematic review was not performed.

Intended audience

This Clinical Recommendation is intended for Society of Family planning members, reproductive health service clinicians, reproductive health researchers, and policy makers.

Disclaimer

This publication is designed as a resource to assist clinicians in providing family planning care. It should not be considered inclusive of all proper treatments or serve as the standard of care. It is not intended to substitute for the independent professional judgment of the treating clinician. Variations, taking into account individual circumstances, may be appropriate. This publication reflects the best available evidence at the time of publication, recognizing that continued research or major changes in the practice environment may impact future recommendations and should be evaluated for incorporation into care. Any updates to this document can be found on https://www.societyfp.org/clinical-guidance/. The Society and its contributors provide the information contained in this publication "as is" and without any representations or warranties, express or implied, of any kind, whether of accuracy, reliability, or otherwise.

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Supplementary materials

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