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EMERGENCY CONTRACEPTIVE PILLS

Medical and Service Delivery Guidance

International Consortium *for* Emergency Contraception

FIGO International Federation of Gynecology and Obstetrics
the Global Voice for Women's Health

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The International Consortium for Emergency Contraception (ICEC) unites organizations and individuals committed to a common mission: to expand access to emergency contraception, with an emphasis on developing countries. For more information about ICEC, visit our website at www.emergencycontraception.org.

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Foreword

The mission of the International Consortium for Emergency Contraception (ICEC) is to expand access to emergency contraception (EC), with an emphasis on developing countries. The Consortium was founded in 1996 by seven international organizations: the Concept Foundation; International Planned Parenthood Federation (IPPF); the Pacific Institute for Women's Health; PATH; Pathfinder International; the Population Council; and the World Health Organization's (WHO) Special Programme of Research, Development and Research Training in Human Reproduction. It now brings together several dozen agencies and thousands of individuals in support of its mission. Despite more than 20 years of efforts to expand access to EC, this contraceptive method remains out of reach for many women. The Consortium first produced guidelines in 2000, based on guidelines initially created by Pathfinder, PATH, and IPPF. The guidelines were revised in 2004 and 2012. Given recent changes in accessibility and new research findings in the field of emergency contraception, a new update was necessary.

The Consortium has produced this medical and service delivery guidance about oral emergency contraceptive pills to assist family planning programs and providers in ensuring that the women they serve can use these regimens effectively and safely. This document reflects the latest available evidence and has been reviewed by internationally recognized reproductive health experts. Local programs are welcome to adapt it as needed to comply with national or other requirements.

The guidance does not discuss in depth the use of the copper-bearing intrauterine device (Cu-IUD) for emergency contraception. This device is the most effective emergency contraceptive option and should be offered to women when appropriate. Further information about this option is available on the ICEC website (www.emergencycontraception.org) and the Emergency Contraception website managed by Princeton University and the Association of Reproductive Health Professionals (www.not-2-late.com). In addition, the United Kingdom Faculty of Sexual & Reproductive Healthcare and the European Consortium for Emergency Contraception have published guidelines that offer recommendations on EC pills and the Cu-IUD.

We hope this updated guidance will help you in your work, whether you are a pharmacist or pharmacy worker, health provider, program manager, policy maker, or advocate. We welcome your participation in our community of practice, which is open to all those committed to the Consortium's mission of expanding access to emergency contraception; please feel free to contact us via our website at www.emergencycontraception.org.

Summary Service Protocol

Indications: Emergency contraceptive pills (ECPs) are indicated to prevent pregnancy after sexual intercourse if no contraceptive was used, if a contraceptive was used incorrectly, or if a contraceptive was used correctly but was immediately observed to have failed.

ECP regimens: The two primary ECP regimens, packaged and labeled specifically for emergency contraception (EC), are:

- 1 tablet of levonorgestrel (LNG) 1.5 mg (also presented as 2 tablets of LNG 0.75 mg each, which can safely be taken together)
- 1 tablet of ulipristal acetate (UPA) 30 mg

Other ECP regimens are:

- 1 tablet of mifepristone 10–25 mg (less widely available)
- The Yuzpe combined hormonal regimen: using certain types of regular birth control pills as EC

Regardless of the regimen used, ECPs should be taken as soon as possible, and no later than five days after sexual intercourse, to maximize use before ovulation occurs.

How ECPs work: The primary mechanism is disruption of ovulation. Other mechanisms have been postulated but are not well supported by data. No evidence supports the theory that ECPs interfere with the implantation of a fertilized egg. ECPs do not cause abortion of an existing pregnancy.

ECP effectiveness: The LNG regimen reduces pregnancy risk by at least half and possibly by as much as 80% to 90% for one act of unprotected intercourse. The UPA and mifepristone regimens are more effective than the LNG regimen. The Yuzpe regimen is the least effective.

Side effects: ECPs are safe, and there is no situation in which the risks of using any EC regimen outweigh the benefits. Side effects are minor and self-limiting and may include altered bleeding patterns, nausea, headache, abdominal pain, breast tenderness, dizziness, or fatigue.

Effects on pregnancy: ECPs are not harmful if inadvertently taken in pregnancy. If the woman became pregnant despite using ECPs, these will do no harm to her, her pregnancy, or the fetus.

Precautions and contraindications: ECPs have no medical contraindications. Women should not take ECPs if they are already pregnant because they will not work.

Clinical screening: No examinations or laboratory tests are needed before using ECPs.

Special issues:

- **Adolescents:** ECPs are safe for all women regardless of age and can be used by girls in beginning stages of puberty, before menarche.
- **Breastfeeding:** LNG ECPs can be used with no restrictions. If UPA ECPs are used, it is recommended to stop breastfeeding for one week.
- **Use of ECPs before sex:** ECPs could be an appropriate method for women with low coital frequency, but this warrants further study. If a woman has the opportunity to plan to use a contraceptive method before sex, a method other than ECPs, such as condoms or another barrier method, is recommended.
- **Use after more than one episode of unprotected sexual intercourse:** Women should use only one ECP treatment at a time regardless of the number of prior episodes of unprotected intercourse. If all episodes of unprotected intercourse were within the last 120 hours, using UPA ECPs is recommended. If all episodes took place within the last 72 hours, a woman can either use LNG or UPA ECPs.
- **Repeated use:** ECPs can be used as often as needed but do not need to be taken more than once every 24 hours if multiple episodes of unprotected intercourse occur within this timeframe. Using EC more than once in the same menstrual cycle is perfectly safe. Because UPA and LNG interact with one another, the same regimen that had already been used (whether LNG or UPA) should be repeated if EC is needed again within a five-day period.
- **Use of ECPs during the "non-fertile period":** Determining with certainty whether intercourse had occurred on a fertile or non-fertile cycle day is often not possible. Thus, women should not refrain from using ECPs due to an assumption that a particular episode of unprotected intercourse may have occurred on a potential non-fertile day.
- **Drug interactions:** Inducers of hepatic CYP450 enzymes may reduce the effectiveness of LNG and UPA ECPs. These include the HIV medicines efavirenz and ritonavir, certain medicines for tuberculosis and epilepsy, and herbal medicines containing St. John's wort. A woman using these drugs and in need of EC should be offered the Cu-IUD or, alternatively, a double dose of LNG (3 mg). In addition, the effectiveness of UPA ECPs could be reduced if progestogen was taken seven days prior or is taken within five days after UPA intake. Use of UPA ECPs is not recommended in women with severe asthma treated by oral glucocorticoid or in women with severe hepatic impairment.
- **Ectopic pregnancy:** No ECP regimen increases the risk that a pregnancy will be ectopic.
- **Obesity:** ECPs may be less effective among women with a body mass index (BMI) ≥30 kg/m^2 than among women with a BMI <25 kg/m^2. The Cu-IUD or the UPA regimen is recommended for obese-BMI women. Alternatively, a double dose of LNG can be considered. Women should never be denied access to ECPs due to higher weights or BMI.

Service delivery systems: All women, girls, and men should be informed about ECPs before the need arises. To ensure timely access, obtaining a package of ECPs or a prescription in advance of need should be considered.

Providing ECPs: With a variety of EC methods increasingly available, women should be presented with thorough counseling information so they can choose the best EC method for them each time EC is needed. After EC use, no follow up is required.

Starting or resuming regular contraceptives after ECPs use: Women must be informed that they are at an increased risk of pregnancy after using ECPs if further episodes of unprotected intercourse take place in the same cycle and that ECPs will not provide contraception for subsequent unprotected intercourse. After using ECPs, a woman should use another contraceptive method before she resumes sexual activity.

- If she used LNG ECPs or the Yuzpe method, a barrier method or abstinence is advised for one week. Combined or progestogen-only hormonal contraceptive methods (pills, patches, injection, implants, ring) can be safely started or resumed on the same day of LNG ECP intake.
- If UPA ECPs were used, a barrier method or abstinence is advised for two weeks. Combined or progestogen-only hormonal contraceptive methods (pills, patches, injection, implants, ring), except the LNG Intrauterine System (LNG-IUS), can be safely started five full days after using UPA ECPs.

If the user becomes pregnant: A woman who used ECPs may subsequently learn that she is pregnant (because she may have already been pregnant; because the ECPs may have failed; or because subsequent unprotected intercourse may have taken place after using ECPs). In any case, she should be aware that ECPs have no known adverse effects on a pregnancy.

1. INTRODUCTION

Despite the availability of highly effective methods of contraception, many pregnancies are mistimed or unintended. These pregnancies may carry a high risk of morbidity and mortality, particularly in settings where safe abortion is not accessible or where quality obstetric services are not available for those women continuing a pregnancy to term. Many of these unintended pregnancies can be avoided using emergency contraception.

Emergency contraception refers to contraceptive methods that can be used to prevent pregnancy after sexual intercourse. Timely access to EC methods and information is a right of all women and girls at risk of unintended pregnancy. EC methods should be routinely included in national family planning programs, and EC should be integrated into health care services for populations most at risk of exposure to unprotected sex, including post-sexual assault care and services for women and girls in emergency and humanitarian settings.[1]

2. INDICATIONS

Emergency contraceptive pills are drugs taken orally to prevent pregnancy after unprotected or inadequately protected sex. ECPs are sometimes referred to as "the morning after pill" or "postcoital oral contraceptives."

ECPs are indicated when:

- No contraceptive was used
- A contraceptive was used incorrectly
- A contraceptive was used correctly but was immediately observed to have failed

Examples of common situations in which ECPs may be needed by a woman who is using a routine contraceptive method are listed below:[2]

- The condom broke, slipped, or was used incorrectly
- Three or more combined oral contraceptive pills were consecutively missed
- More than three hours have elapsed since the usual time of intake of the levonorgestrel-only pill (minipill) or, in other words, more than 27 hours since the previous pill
- More than 12 hours have elapsed since the usual time of intake of the desogestrel-containing pill (0.75 mg) or, in other words, more than 36 hours since the previous pill
- The woman is more than two weeks late for the norethisterone enanthate (NET-EN) progestogen-only injection
- The woman is more than four weeks late for the depot-medroxyprogesterone acetate (DMPA) progestogen-only injection
- The woman is more than seven days late for the combined injectable contraceptive
- The diaphragm or cervical cap was dislodged, broken, torn, or removed early
- Withdrawal failed and ejaculation occurred in the vagina or on external genitalia
- A spermicide tablet or film failed to melt before intercourse

- The abstinence period was miscalculated or the couple failed to abstain or use a barrier method on the fertile days of the cycle when using fertility awareness-based methods
- The intrauterine contraceptive device (IUD) or a hormonal contraceptive implant was expelled
- The method used is out of its period of effectiveness, according to the manufacturer

Because of the difficulties in determining the risk of pregnancy in any particular situation and the serious consequences of a mistimed or unintended pregnancy, a woman who does not want to be pregnant should consider using EC after any episode of sexual intercourse during which contraceptive protection was not reasonably assured. ECPs are particularly indicated in cases of non-consensual sex (rape) when the woman was not protected by an effective contraceptive method.

3. ECP REGIMENS

There are four main oral emergency contraceptive regimens. This guidance focuses primarily on two of the four regimens: the one containing the progestin hormone levonorgestrel and the one containing the selective progesterone receptor modulator ulipristal acetate:

- Levonorgestrel (LNG) regimen: 1.5 mg LNG in a single pill or in 2 pills of 0.75 mg each
- Ulipristal acetate (UPA) regimen: 30 mg UPA in a single pill

Pill products based on the LNG regimen have been marketed for almost 20 years and are currently available in most countries in the world. The newest generation of ECPs, the UPA formula, was first registered in the European Union in 2009 and in the United States of America in 2010. UPA ECPs are now available in many countries.

Both regimens are marketed as dedicated products, specifically packaged and labeled for EC. The UPA ECPs are licensed for use up to 120 hours after unprotected intercourse.[3,4,5] The LNG ECP products are licensed for use up to 72 hours after unprotected intercourse. Off-label use of LNG beyond 72 hours was and is still common (especially before the appearance of UPA ECPs or in settings where UPA is not available), given that it appears to still be moderately effective up to 96 hours after unprotected intercourse.[6]

Two other ECP regimens have also been well studied, one containing the progesterone receptor modulator mifepristone and the other using a combination of estrogen and progestin hormones:

- Mifepristone regimen: 10–25 mg mifepristone as a single pill
- Combined hormonal (Yuzpe) regimen: one dose of 100 mcg ethinyl estradiol plus 0.5 mg LNG followed by a second identical dose 12 hours later

Mifepristone ECPs are available as dedicated ECP products in a few countries, including Armenia, China, Moldova, Russia, Ukraine, and Vietnam. This regimen is likely effective up to five days after unprotected intercourse. The Yuzpe combined hormonal regimen is

not currently marketed anywhere, but it can be made up from many brands of widely available oral contraceptive pills. This regimen may be useful in settings where none of the dedicated products are available. Some data suggest that the combined hormonal regimen is effective up to three days after sex and possibly up to five days.[7,8] Listings of ECP products and regimens by country are available at www.emergencycontraception.org and www.not-2-late.com.

4. MODE OF ACTION

The primary documented mechanism of action for both the LNG and UPA regimens is interference with the process of ovulation.[9,10,11,12] If taken before the pre-ovulatory luteinizing hormone surge has started, LNG can inhibit the surge, impeding follicular development and maturation and/or the release of the egg itself. UPA has been shown to prevent ovulation both before and after the surge has started, delaying follicular rupture for at least five days.[13,14,15] Ovulation is not prevented if either LNG or UPA is administered on the day of the luteinizing hormone peak.[16]

The LNG regimen has been shown not to prevent implantation of a fertilized egg into the uterus in several studies.[17,18,19] Earlier UPA research suggested minor endometrial changes in certain aspects of endometrial function and receptivity.[20,21] One study of mid-cycle administration of UPA suggests an effect on endometrial gene expression.[22] Two functional studies of human embryo implantation (with in-vitro implantation models) found that UPA at the dosage used for EC does not affect the human embryo implantation process.[23,24] In addition, a significantly higher percentage of pregnancies were prevented when LNG and UPA were given pre-ovulatory compared with post-ovulatory administration.[25,26,27] Despite any possible effect on endometrial receptivity or maturation, UPA has not been demonstrated to be effective as EC when administered after ovulation. This is also the case with LNG.

Additional postulated mechanisms include interference with corpus luteum function, thickening of the cervical mucus resulting in trapping of sperm, alterations in the tubal transport of sperm or egg, or inhibition of sperm function.[28]

If taken after implantation has occurred, the LNG and UPA regimens have no effect on an existing pregnancy and do not increase rates of miscarriage.[29,30,31,32,33,34]

5. EFFECTIVENESS

Twelve studies of the LNG regimen that included more than 13,500 women concluded that this regimen reduced a woman's risk of pregnancy after a single episode of intercourse by between 52% and 100%.[35,36,37,38,39,40,41,42,43,44,45,46] A rigorous analysis of data from two randomized trials demonstrated that the LNG regimen reduces the absolute risk of pregnancy after unprotected intercourse by at least 49% (95% confidence interval 17–69%).[47]

Some data suggest that the efficacy of the LNG regimen decreases with time since coitus.[48,49] However, a combined analysis of data from four large trials did not find a significant decline in efficacy of this regimen over the first four days after sex. In this analysis, the regimen appeared to have minimal or no efficacy if taken on day five.[50]

Since data are conflicting, the prudent recommendation is always to take the LNG dose as soon as possible after intercourse.

Several studies have found that both the efficacy and the side effects of the LNG regimen are equivalent whether the hormone is taken as a single 1.5 mg dose or as two doses of 0.75 mg each, either 12 or 24 hours apart.[51,52,53,54] However, since taking one single dose is simpler for the user than taking two doses 12 hours apart, it is currently recommended that, when using the two-tablet LNG ECP product, both tablets be taken at the same time.[55]

Two randomized trials have found that UPA is at least as effective as the LNG regimen when used within 72 hours after sex.[56,57] An analysis that combined data from these trials suggested that the UPA regimen is more effective through five days after sex.[58] No decline in efficacy of the UPA was apparent within five days after sex. However, since effectiveness may depend on delaying ovulation, it is prudent to take the dose of UPA as soon as possible after intercourse.

With any ECP regimen, the risk of pregnancy is substantially higher if the woman has subsequent unprotected intercourse in the same menstrual cycle than if she does not.

A number of factors may impact the efficacy of LNG and UPA ECPs. These include the woman's weight, BMI, and concomitant use of certain drugs (see Section 10).

The mifepristone regimen is more effective than the LNG regimen,[59,60] but it has never been directly compared to the UPA regimen. A systematic review indicated that doses of 25–50 mg mifepristone may be significantly more effective for EC than a dose of 10 mg.[61,62]

The combined hormonal regimen is the least effective of the four ECP regimens.[63,64]

Although ECPs are effective in reducing pregnancy risk after unprotected intercourse, increasing the availability of this method to populations has not been shown to reduce rates of unintended pregnancy or abortion.[65,66,67] The reason for this apparent discrepancy is likely, at least in part, because even with ready access to ECPs, women do not use them after every episode of unprotected intercourse.[68] Tackling the public health problem of unintended pregnancy requires a multi-dimensional approach of which provision of EC is only one aspect.

6. SIDE EFFECTS

ECPs are extraordinarily safe. No deaths or serious complications have been causally linked to any ECP regimen. According to the World Health Organization (WHO) Medical Eligibility Criteria for Contraceptive Use (MEC), fifth edition, there are no situations in which the risks of using LNG or UPA ECPs or the combined hormonal regimen outweigh the benefits.[69,70]

Side effects are medically minor and self-limiting but may be troublesome to some users. The combined hormonal regimen has the highest incidence of side effects. Because they are less likely to cause nausea and vomiting, WHO recommends the use of

dedicated LNG or UPA ECPs over the use of the combined hormonal regimen.[71,72] Side effects are described below.

6.1 Altered vaginal bleeding patterns

Most women who have used ECPs have their next menstrual period within seven days of the expected time. Menstruation has been reported to occur on average one day earlier than expected after use of the LNG regimen and two days later than expected after use of the UPA regimen. Approximately 24% of women in clinical trials of UPA reported a delay of more than seven days.[73] Some women experience irregular bleeding or spotting after taking LNG ECPs.[74,75] The proportion with this side effect varies among studies. Bleeding alterations due to ECPs are not dangerous and will resolve without treatment.

6.2 Nausea and vomiting

Nausea occurs in less than 20% of women using the LNG regimen[76,77] and in approximately 12% of women using the UPA regimen.[78,79] Vomiting occurs in less than 2% of women using ECP regimens.[80] Routine use of anti-emetics before taking ECPs is, therefore, not recommended.[81]

If vomiting occurs within two hours after taking a dose of the LNG regimen or the combined hormonal regimen, another dose should be taken as soon as possible. If vomiting occurs within three hours after taking a dose of UPA ECPs, the dose should be repeated as soon as possible.[82]

6.3 Other symptoms

Other symptoms that may occur in users of ECPs include headache, abdominal pain, breast tenderness, dizziness, or fatigue. These side effects usually do not occur more than a few days after treatment, and they generally resolve within 24 hours.[83]

7. EFFECTS ON PREGNANCY

Studies of women who became pregnant despite using the LNG regimen or who used it inadvertently after becoming pregnant indicate that this regimen does not harm either a pregnant woman or her fetus. It does not increase rates of miscarriage, ectopic pregnancy, low birth weight, congenital malformations, or pregnancy complications.[84,85] Postmarketing pharmacovigilance data collection for UPA ECPs also confirm the safety of this regimen.[86] LNG and UPA ECPs are not indicated for women with a known or suspected pregnancy; however, there is no known harm to the woman, the course of her pregnancy, or the fetus if ECPs are accidentally used.[87]

8. PRECAUTIONS AND CONTRAINDICATIONS

ECPs are not dangerous under any known circumstances or in women with any particular medical conditions. WHO's MEC, fifth edition, states that there are no medical restrictions to the use of LNG, UPA, or combined hormonal ECP regimens.[88] Recognized contraindications to oral contraceptives do not apply to ECPs. In particular, the following conditions are NOT contraindications to ECPs: young age, obesity, personal or family history of venous thromboembolism, prior or current breast cancer, prior ectopic pregnancy, breastfeeding, migraine headaches, cardiovascular disease, liver disease, diabetes, hypertension, and prior ECP use in the same menstrual cycle.

ECPs are not indicated for a woman who has a confirmed pregnancy because they will have no benefit. However, if an evaluation for pregnancy has not been performed or if pregnancy status is unclear, ECPs may be used as there is no evidence to suggest harm to a developing fetus.

9. CLINICAL SCREENING

Because ECPs are safe for all women and women can determine for themselves whether they have had unprotected or inadequately protected sex, no provider screening is needed before the use of ECPs. Clinical assessments (e.g., pregnancy tests, blood pressure measurements, laboratory tests, pelvic examination) are not necessary. ECPs are appropriate for over-the-counter, non-prescription provision.

10. SPECIAL ISSUES

Several issues commonly raised regarding ECPs are discussed below.

10.1 Use in adolescents

Adolescents' access to ECPs should not be limited by clinical or programmatic concerns. ECPs are safe for all women regardless of age. Adolescents do not suffer greater rates of side effects[89] and are able to comprehend the label and other instructions about how to use the method.[90]

EC should be incorporated into routine family planning guidance for adolescents, males and females, and families of adolescents with disabilities, regardless of current intentions of sexual behavior.[91]

WHO strongly recommends offering EC to girls who have been raped involving peno-vaginal penetration and who present within five days of the incident. This includes girls who have attained menarche as well as those who are in the beginning stages of puberty (as they may be ovulating even prior to the onset of menstruation). UPA and LNG are recommended as first-line treatment. If these are not available, the combined hormonal regimen may be offered.[92]

10.2 Breastfeeding

A woman who is less than six months postpartum, is exclusively breastfeeding, and has not had a menstrual period since delivery is unlikely to be ovulating and therefore is unlikely to need ECPs. However, a woman who does not meet all three criteria may be at risk for pregnancy.[93]

WHO's MEC states that the LNG regimen of ECPs is not contraindicated during lactation and that the UPA regimen can generally be used by breastfeeding women, but as a precautionary measure, she should not breastfeed for one week and instead express and discard her breast milk.[94]

10.3 Use of ECPs before sex

An earlier systematic review of pericoital use of hormonal contraception containing LNG suggested that it is safe and moderately effective. Pericoital use means that the method is taken immediately before or after each episode of intercourse, during one or more menstrual cycles.[95] A more recent study evaluated the efficacy, safety, and acceptability

of pericoital oral contraception with 1.5 mg of LNG, in which women were instructed to take one dose up to 24 hours before or after intercourse over the 6.5-month study. Findings suggest that such a method was moderately effective and was well accepted and tolerated by healthy women who reported having intercourse up to six times a month.[96]

However, using LNG this way, as a pericoital contraceptive, warrants further research. With further study, it may be an appropriate method for women with low coital frequency who are comfortable using a less effective contraceptive method and who are at low risk of sexually transmitted infections (STIs).

If a woman has the opportunity to plan to use a contraceptive method before sex, a method other than ECPs is recommended.

10.4 Use after more than one episode of unprotected intercourse

Women should try to use ECPs as quickly as possible after each episode of unprotected intercourse; waiting until a series of episodes has occurred is not recommended. Similarly, a woman should not refrain from taking ECPs simply because she has had multiple episodes of unprotected intercourse. She should be aware that the efficacy of the ECPs may be limited if the earliest episode of unprotected intercourse was more than four or five days prior. She should use only one ECP treatment at a time regardless of the number of prior unprotected acts. If all episodes of unprotected intercourse were within the last 120 hours, using UPA ECPs is recommended. If all episodes took place within the last 72 hours, she can either use LNG or UPA ECPs.[97]

10.5 Repeated use

Although ECPs are not intended for deliberate repeated use or use as a regular, routine contraceptive method, repeated use of ECPs is extremely safe. Compared with the potential health risks of pregnancy or unsafe abortion, taking ECPs to prevent unintended pregnancy is much safer. Women should be able to access and use ECPs as many times as they need. However, ongoing methods of contraception are more effective than ECPs, and only barrier methods, such as condoms, protect against HIV and STIs.

ECPs pose no risk of harmful overdose, and evidence suggests that these regimens do not become less effective when used repeatedly.[98] A recent study tested women using 1.5 mg of LNG up to six times a month and found no adverse effects and a pregnancy rate comparable to that of condoms.[99] Several older studies had previously suggested that the use of LNG ECPs as a regular, ongoing contraceptive method is safe.[100] These data provide reassurance that women may safely use the LNG regimen as many times or as often as needed. Some experts recommend that no more than one dose is needed in a 24-hour period.[101,102,103]

The repeated use of UPA ECPs (either every five or seven days, up to an eight-week period) has also been studied recently, and safety data indicate that it can be safely used more than once in the same cycle.[104] The efficacy of the UPA regime, however, may be reduced by recent or subsequent use of LNG.[105,106] Therefore, if a woman who has recently (in the past five days) used the LNG regimen has a subsequent need for EC, she

should use the LNG regimen again. If a woman who has recently used the UPA regimen has a subsequent need for EC, she should use the UPA regime again. In both cases, she can also consider having the Cu-IUD inserted. Repeated use of ECPs is safer than pregnancy.

10.6 Use of ECPs during the "non-fertile period"

Studies have shown that fertilization can result from sex only during a five- to seven-day interval prior to or the day of ovulation.[107] Theoretically, ECPs should not be needed if unprotected sex occurs at other times in the cycle, because the chance of pregnancy even without ECPs would be zero. However, in practice, determining whether a specific act occurred on a fertile or non-fertile cycle day is often not possible. Therefore, women should not refrain from using ECPs because of the assumption that a particular episode of unprotected intercourse occurred on a non-fertile day.

10.7 Drug interactions

In the past few years, more data about potential interactions of ECPs with other drugs have become available. No drug interaction poses any health or safety risk but some may impact the effectiveness of LNG and UPA ECPs.

LNG regimen:

- Inducers of hepatic CYP450 enzymes may reduce the effectiveness of LNG ECPs. These include the HIV medicines efavirenz and ritonavir, certain medicines for tuberculosis and epilepsy, and herbal medicines containing St. John's wort.[108] A woman using these drugs and in need of EC should be offered the Cu-IUD or, alternatively, a double dose of LNG (3 mg).[109]

UPA regimen:

- Inducers of hepatic CYP450 enzymes may also reduce the effectiveness of UPA ECPs. Women using these drugs should be offered the Cu-IUD. A double dose of UPA is not recommended.[110]
- UPA effectiveness could be reduced if progestogen was taken seven days prior to taking UPA or within five days after UPA intake.[111]
- Use in women with severe asthma treated by oral glucocorticoid is not recommended.[112]
- In the absence of specific studies, the Summary of Product Characteristics of the UPA ECP recommends not to use UPA in women with severe hepatic impairment.[113]
- Drugs that increase gastric pH (such as esomeprazole) may interfere with UPA, but the clinical significance of this interaction for UPA ECPs is unknown.[114]

Both LNG[115] and UPA[116] ECPs contain lactose monohydrate (UPA products in larger amounts than LNG). Women with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not use either LNG or UPA regimens.

10.8 Ectopic pregnancy

All contraceptive methods reduce the absolute risk of ectopic pregnancy by preventing pregnancy in general. A systematic review of world literature found that 1% of

pregnancies occurring after use of the LNG regimen and 0.6% of pregnancies occurring after use of the mifepristone regimen were ectopic. These figures are similar to the risk that pregnancies not exposed to ECPs will be ectopic. Thus, the review concluded that neither regimen increases the risk that a pregnancy will be ectopic.[117]

10.9 Obesity

Research conducted in the past few years seems to suggest that the effectiveness of LNG and UPA ECPs could be reduced in women with overweight and/or high BMI.[118,119] According to WHO's MEC, ECPs may be less effective among women with BMI ≥ 30 kg/m^2 than among women with BMI < 25 kg/m^2.[120]

Recent pharmacokinetic studies found that clinical obesity reduces the bioavailability of LNG but not UPA.[121,122,123] Given that the negative effect of obesity is greater on LNG's effectiveness than it is on UPA's, the Cu-IUD or the UPA regimen should be recommended as the first-line treatment for obese-BMI women. A double dose of LNG can also be considered if the Cu-IUD or UPA is not an option.[124] Women should never be denied access to EC due to higher weight or BMI.[125]

11. SERVICE DELIVERY SYSTEMS

Because of the short timeframe during which ECPs are effective, unique service delivery issues arise in ensuring that women can benefit maximally from ECPs.

11.1 Advance education

Every effort should be made to ensure that all women, girls, and men are informed about ECPs before the need arises. Key messages include:

- A woman who does not want to be pregnant should consider using ECPs any time she has sex that was not adequately protected by effective contraception.
- She should try to obtain and use EC as quickly as possible.
- ECPs will not provide protection for subsequent episodes of unprotected intercourse. A woman is at increased risk of pregnancy after using ECPs and should, therefore, abstain from intercourse or use effective contraception during the rest of her cycle.
- ECPs are not intended for ongoing, routine contraception but are safe if used repeatedly. More effective methods are recommended for women with frequent need.

In addition, every woman and girl should know where and how she can obtain ECPs in her community. To ensure that she will have ECPs available whenever she needs them, she may consider obtaining a package of ECPs or a prescription in advance.

Providers and programs may disseminate these messages in numerous ways, including:

- Routinely informing women about ECPs at all visits to clinics, pharmacies, or other facilities where health care is provided
- Informing abortion clients about ECPs
- Including information about ECPs on clinic or pharmacy websites and telephone answering machines

- Distributing information about ECPs with other contraceptive supplies or medications
- Including information about ECPs in health education programs in schools, youth centers, and other venues[126]
- Instituting mass media informational and advertising campaigns for ECP products and services

11.2 ECP provision settings

To facilitate access, ECPs should be readily available. Because no clinician screening or assessment is required and women and girls can decide on their own whether the treatment is needed, ECPs may appropriately be sold over the counter, as they are in most countries. However, if it is difficult to obtain ECPs because of a prescription requirement or for some other reason, providers and programs may use the following approaches to ensure that this treatment can be obtained and used quickly:

- Provide an advance prescription or supply
- Prescribe by telephone without seeing the woman
- Allow non-physician personnel, such as pharmacy staff, nurses, midwives, and community health workers, to provide ECPs
- Ensure that all personnel who provide care or counseling to women and girls presenting after sexual assault routinely offer them ECPs
- Distribute ECPs in non-clinical settings, such as schools, non-pharmacy commercial outlets, and social service offices

12. PROVIDING ECPS

Because many women who use ECPs will obtain them over the counter, input from a health professional may not be available. However, if a provider is present, the following guidance may be useful.

12.1 Selecting and providing the method

- The Cu-IUD is the most effective emergency contraceptive, and it offers the added benefit of ongoing contraception for at least 10 years. Therefore, consider offering this alternative to oral ECP regimens if it is readily available and the woman is medically eligible to receive it (see WHO's MEC, fifth edition, 2015). The Cu-IUD can be inserted within five days of unprotected intercourse. If necessary, and when the time of ovulation can be estimated, it can be inserted beyond five days after intercourse as long as the insertion does not occur more than five days after ovulation.[127]
- If the woman chooses to use oral ECPs and if both UPA and LNG ECP products are readily available, inform her that the UPA regimen may be more effective, particularly if four to five days have elapsed since the first unprotected intercourse.[128] However, if only one of these products is available, the client should consider using that product immediately rather than delaying treatment to obtain an alternate product.
- If the LNG regimen is selected and the particular product provided contains two tablets of 0.75 mg LNG, advise the woman to take both tablets at once rather than 12 hours apart as indicated on the package label. Taking the two tablets

together will not compromise efficacy or increase side effects, and it is more convenient and will avoid the possibility that a second tablet will be lost or forgotten.
- If possible, provide the desired ECPs and recommend that the woman swallow them immediately. Alternatively, provide a prescription and instructions about where in the community the woman can obtain the product.
- Clearly inform the women that the ECPs will not protect her from pregnancy if she has subsequent unprotected sex within the same cycle and that she should abstain from sex, use condoms, or initiate an ongoing contraceptive method right away if she used LNG ECP (see Section 13).
- Caution the user that EC does not protect against HIV and other STIs.
- Tell the client that if she does not have a menstrual period within three weeks after taking ECPs, she should consider the possibility that she may be pregnant and seek appropriate evaluation and care.

12.2 Optional additional services

Additional services are not necessary but should be provided if the client desires. These services may include:

- Provision of a regular contraceptive method (see Section 13)
- Pregnancy testing
- Testing, prophylaxis, or treatment for STIs. Inform the woman that tests will not necessarily diagnose very recent infections, particularly infections that she may have acquired during the most recent unprotected sex act. If that is a concern, recommend retesting after an appropriate time interval.

ECPs should not be withheld from clients who decline these additional services.

12.3 Follow-up

No scheduled follow-up is required after ECP use unless the client identifies a problem or question. However, she should be encouraged to seek follow-up care if she:

- Needs ongoing contraception or wishes to switch methods
- Has not had a menstrual period by three weeks after taking the ECPs, as this could be a sign of pregnancy
- Has irregular bleeding with lower abdominal pain more than a few days after taking ECPs, as these could be symptoms of an ectopic pregnancy
- Desires evaluation for STIs
- Needs management of issues related to rape
- Has any other health concerns.

13. STARTING OR RESUMING REGULAR CONTRACEPTIVES AFTER ECP USE

ECP intake increases the risk of pregnancy if further episodes of unprotected intercourse take place during the same cycle. ECPs do not provide contraception for subsequent unprotected intercourse. Therefore, after using ECPs, a woman should use another method before she resumes sexual activity.

Combined or progestin-only hormonal contraceptives (pills, patches, injection, implants, vaginal ring):
Recent research findings suggest that hormonal contraception can disrupt the effect of UPA ECPs up to five days after intake.[129,130] Therefore, the choice and timing of initiation of an ongoing hormonal contraceptive method should take into account which ECP regimen was used.

- If the LNG or the combined hormonal regimen was used, a barrier method or abstinence is advised for one week. All combined or progestogen-only hormonal contraceptive methods (pills, patches, injection, implants, ring) can be safely started or resumed on the same day of LNG ECP intake. The LNG Intrauterine System (LNG-IUS) can also be inserted as long as pregnancy can be ruled out.[131,132]
- If the UPA regimen was used, a barrier method or abstinence is advised for two weeks. Combined or progestogen-only hormonal contraceptive methods (pills, patches, injection, implants, ring), except the LNG-IUS, can be safely started five full days after using UPA EPCs (that is, the sixth day after the day of UPA ECPs intake).[133]

Condoms or other barrier methods:
Start using immediately at the next intercourse.

Cu-IUD:
The Cu-IUD, when inserted within five days after unprotected intercourse, will provide highly effective EC. Therefore, oral ECPs are not needed if this type of IUD is inserted in this time interval. If a woman wants the Cu-IUD more than five days after using ECPs, it may be inserted after the start of the next menstrual period.

Fertility awareness methods:
Initiate after the first normal menstrual period following ECP use. Note that the first bleeding episode after taking ECPs may not be a "normal" menstrual period. Use a barrier method until the first normal period.

Sterilization:
Perform the procedure after the start of the menstrual period following ECP administration. Use a barrier method until the sterilization is completed.

14. IF THE USER BECOMES PREGNANT

A woman who has used ECPs may subsequently learn that she is pregnant because the ECPs may have failed, because she may have already been pregnant before taking the ECPs, or because unprotected intercourse after taking the ECPs may have led to pregnancy. In any of these cases, she should be aware that ECPs have no known adverse effects on a pregnancy. Whether she chooses to continue the pregnancy or seek abortion, she should know that she does not need any special management because of exposure to ECPs.

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