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MINIREVIEWS

Emergency contraception: What is new?

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Abstract

Unintended pregnancy rates remain high throughout the World and increase the risk of poor maternal and infant outcomes. Most of unintended pregnancies occur in women who were not using contraception or who became pregnant despite the reported use of contraception. Women who have had recent unprotected intercourse including those who have had another form of contraception fail are potential candidates for this intervention. Currently used emergency contraceptive methods are pills that contain combined estrogen-progesterone, only progestin, antiprogestins and copper intrauterine devices. The most common form of this type of contraception is oral progestin-only pills (levonorgestrel). The most effective method is copper intrauterine devices followed by anti-progestins and oral progestin-only pills. The major pathogenesis of oral emergency contraceptives is the prevention or delay of ovulation. Although conception is possible on only a few days of the cycle, emergency contraception is offered when indicated without regard to the timing of the menstrual cycle because of uncertainty in the timing of the ovulation. Levonorgestrel and E/P regimes are most effective as soon as possible after unprotected sexual intercourse. A linear relationship has been shown between effectiveness and the time of dose. The effectiveness continues for 120 h, but it is recommended to be used within 72 h after intercourse. Intrauterine devices may prevent pregnancy when 5 d after ovulation.

Key words: Emergency contraception; Levonorgestrel; Mifepristone; Ovulation; Ulipristal acetate

Core tip: Emergency contraception methods have varying ranges of effectiveness depending on the method and timing of administration. The major pathogenesis of oral emergency contraceptives is the prevention or delay of ovulation or prevention of fertilisation. Combined and progestin-based emergency contraceptives should be used as soon as possible to enhance the efficacy. Emergency contraception offers a final chance to prevent pregnancy.

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INTRODUCTION

Emergency contraception is defined as contraceptive methods used after unprotected sexual intercourse or sexual assault and in cases with contraceptive failure. Currently used emergency contraceptive methods are pills that contain combined estrogen-progesterone, only progestin, antiprogestins and copper intrauterine devices.

The most common form of this type of contraception is progestin-only pills (levonorgestrel). The most effective method is copper intrauterine devices followed by anti-progestins and oral progestin-only pills. The major pathogenesis of oral emergency contraceptives are presumed to be a delay or prevention of ovulation. Levonorgestrel in particular is ineffective as emergency contraception after ovulation. The major role of copper-induced intrauterine devices in emergency contraception is the prevention of fertilization[1]. There is much evidence suggesting that implantation of the fertilized ovule cannot be prevented by emergency contraception.

The possibility of pregnancy after unprotected sexual intercourse changes between 12%-30% in a population of young couples in their mid-twenties depending on the day of the menstrual cycle[2]. While the possibility of pregnancy is higher on the day of ovulation, emergency contraception can be used at any time of the menstrual cycle. It is independent of the day of ovulation. The most widely used EC methods are summarised in Table 1.

Indications for possible emergency contraception fallow as[3]: When no contraceptive was used during sexual intercourse within the previous 120 h; When there is a contraceptive failure or incorrect use of a contraceptive within the previous 120 h, including: (1) condom breakage, slippage, or incorrect use; (2) three or more 30 to 35 mcg ethinyl estradiol pills have been missed (or two or more 20 to 25 mcg pills); (3) progestin-only pill (minipill) taken more than three hours late; (4) more than two weeks late for injection of depot-medroxyprogesterone acetate; (5) dislodgment, breakage, tearing, or early removal of a diaphragm or cervical cap; (6) dislodgment, delay in placing, or early removal of a contraceptive hormonal skin patch or vaginal ring; (7) failed coitus interruptus (*e.g.*, ejaculation in vagina or on external genitalia); (8) failure of a spermicide tablet or film to melt before sexual intercourse; (9) miscalculation of the periodic abstinence method or failure to abstain on fertile day of cycle; and (10) expulsion of intrauterine contraception.

Table 1 Summary of emergency contrception methods

Contraceptive methods	Mechanism of action	Effective time	Most common side effects
Contraceptive Pills (Yuzpe Regimen)	Inhibition or delay of ovulation	72 h recommended (Up to 120 h)	Same as COC
Progestin-only ECP	Inhibition or delay of ovulation	72 h recommended (Up to 120 h)	Nausea and vomiting Irregular bleeding
Ullipristal	Inhibition or delay of ovulation	Up to 120 h	Nausea and vomiting Abdominal pain
Copper induced IUD	Prevention of İmplantation	Up to 5 d (recommended)	Genital infection

ECP: Emergency contraceptive pills; IUD: Intrauterine devices; COC: Combined oral contraceptives.

COMBINED EMERGENCY CONTRACEPTIVE PILLS (YUZPE REGIMEN)

Many clinical studies have shown that ovulation can be prevented or delayed with emergency contraceptive pills that contain estrogen (E) and progesterone (P)[4,5]. After the first studies showing prevention of pregnancy with high dose of estrogen in 1974, Yuzpe *et al*[6] defined a low dose regime containing 200 mcg ethinyl estradiol and 1 mg levonorgestrel.

Some studies suggested that emergency contraceptive pills (ECP) prevent the implantation of the fertilized ovule by changing the endometrial receptivity in addition to the biochemical and histological changes in the endometrium after use of this regime. However, these suggestions were not confirmed in recent studies. Other possible mechanisms of ECP include changes to the function of the corpus luteum, thickening of cervical mucus, changes in tubal transport and prevention of fertilization[7-9].

Preven was approved for emergency contraception by Food and Drug Administration (FDA) in 1998 and was withdrawn in 2004. However, combined oral contraceptives (COC) that are not packed for emergency contraception can be used as 100 mcg ethinyl estradiol and 0.50 mg levonorgestrel with the same dose repeated in 12 h[10]. Levonorgestrel and E/P regimes are most effective after as soon as possible after unprotected sexual intercourse. There is a linear relationship between efficacy and the dose time. The efficacy continues for 120 h, but use within 72 h is recommended. Patients must be warned about this reduction in efficacy - especially after 96 h. In a meta-analysis of 3800 women, the success of the Yuzpe regime in the prevention of unwanted pregnancies was found to be 56%-89%[11]. However,

the Yuzpe regimen is not recommended because side effects are more common, and the efficacy of ECP is approximately half of the use of only levonorgestrel[12].

PROGESTIN-ONLY ECP

Early studies showed that levonorgestrel disrupts ovulation and the luteal functions. No effect on the endometrium was reported in these studies despite a study suggesting that the use of levonorgestrel glycodelin just before the luteinizing hormone (LH) surge changes the luteal phase secretory pattern. Levonorgestrel has no effect on the endometrial implantation of the embryo and endometrial receptivity markers[13-18]. The original prescription is the use of 0.75 mg oral levonorgestrel in the first 72 h with a repeated identical dose after 12 h. The same efficacy was reported with a 1.5 mg single dose in different studies. In addition to the studies supporting the same side effects for the two methods, most studies reported more headaches and breast sensitivity in the single dose regime[19,20]. In another study, 2 doses of 0.75 mg levonorgestrel repeated at 24 h had the same efficacy. Levonorgestrel is more effective than the Yuzpe regime in the prevention of pregnancy (RR = 0.51, 95%CI: 0.31-0.83) with fewer side effects (nausea RR = 0.43, 95%CI: 0.39-0.48; vomiting RR = 0.24, 95%CI: 0.18-0.31; headache RR = 0.83, 95%CI: 0.69-1.00; breast tenderness RR = 0.84, 95%CI: 0.69-1.01)[21].

ANTIPROGESTINS

Ullipristal and mifepristone are similar antiprogestins with similar chemical structures. The major mechanism is *via* prevention or delay of ovulation in addition to the effects on endometrium causing disruption of implantation[22].

MIFEPRISTONE

Mifepristone is a first-generation progesterone receptor modulator and is approved for use in many countries for first trimester abortion. In randomized studies, a dose of 5-600 mg mifepristone (RU-486) has the same or better efficacy in the prevention of pregnancy than oral emergency contraceptives (up to 99%-100%)[23-26].

The optimal dose is not clearly defined but may be 25-50 mg with no serious side effects. A delay in menstrual bleeding after the use of antiprogestins decreases doubts of pregnancy and anxiety[27,28]. The use of mifepristone in pill form is prevented for widespread use as emergency contraception. Mifepristone is only approved in Armenia, China, Russia and Vietnam as an emergency contraceptive.

ULLIPRISTAL

A selective progesterone receptor modulator with antiprogestin effects that can cause 5 d in delay of ovulation. There are studies showing that it can cause endometrial changes, however it remains controversial if it inhibits implantation. Ullipristal is used as a single dose of 30 mg. It is the most effective ECP in Europe and United States with an efficacy of 62%-85%[29-31]. Ullipristal is effective in the late follicular phase in which a rise in the level of LH has begun but no peak was achieved. In a meta-analysis comparing the efficiencies of levonorgestrel and ullipristal, the latter was shown to be higher at 0-24, 0-72 and 0-120 h after intercourse with no differences in side effect profiles[31].

COPPER-INDUCED INTRAUTERINE DEVICES

Implantation occurs 6-12 d following ovulation. Intrauterine devices may prevent pregnancy when applied 5 d after ovulation. Copper induced intrauterine devices (IUD) are the most effective emergency contraceptives with a major advantage for continuous contraceptive effect. In a multi-centre study with 1013 patients, its efficiency was 96.9% when used 120 h after intercourse[32]. The contraindications of applying an IUD at the same day of intercourse are acute cervicitis and other known medical contraindications. It should be applied 5 d after unprotected sexual intercourse, however there is limited data suggesting that the efficiency continues to 7 d[33].

OTHER INTRAUTERINE CONTRACEPTIVE METHODS

No data was found in the literature about the use of LNG-IUDs in emergency contraception. It was not recommended for this indication[34,35]. The LNG-IUDs can only be applied after the exclusion of pregnancy and only if the patient is 7 d or more into the menstruel cycle. If not, an additional contraceptive method or ECP for 7 d is recommended[35].

The frameless copper IUDs produced for adolescents and nullipar women (GyneFix® 330) have the same efficiency as ordinary copper IUDs in emergency contraception[36].

THE FACTORS CHANGING THE EFFICIENCY OF EMERGENCY CONTRACEPTIVES

Timing of treatment

Combined and progestin-based emergency contraceptives should be used as soon as possible (0-72 h) to enhance the efficacy[37]. Both drugs can be started up to 120 h after sex, but patients must be informed about the reduced activity after 96 h[38]. Ullipristal is the only approved oral agent for emergency contraception

from 72-120 h. Copper IUDs can be used for up to 5 d because of the post-fertilization effects. A systematic review reported the efficiency of IUDs up to 7 d, but there is limited data supporting this claim[39].

Body mass index

The efficiency of levonorgestrel ECP is decreased in obese women with an increase in unwanted pregnancies; however, no such effect was seen for ullipristal[39]. Because of these results, one commercial form of levonorgestrel added a warning of reduced efficiency in patients over 75 kg. After revision of the study, the European Medicines Agency described no reduction, and the warning was removed[40].

SAFETY

There is no physical examination or laboratory testing required before the use of oral progestin-based emergency contraceptives beyond the unnecessary pregnancy test unless there is no doubt of pregnancy due to symptoms or last menstruation date. No teratogenic effects on the foetus or side effects have been reported, however pregnancy must be excluded in cases using ullipristal or IUD.

Emergency contraception did not show any causal connection to death or serious complications. According to profit and loss rate data from the United States Medical Eligibility Criteria for Contraceptive Use (US MEC), no risk factors were reported to prevent the use of combined ECP and progestin-only pills[34,35]. ECP can be used in patients with lactation or a history of ectopic pregnancy, cardiovascular disease, migraine, and liver disease. ECPs can be used in patients contraindicated for combined oral contraceptives because of the short use time and lower total hormone dose[35]. Ullipristal acetate, progestin-only ECP, or copper-induced IUDs are preferred in women with changes in coagulation factors or a history of venous thromboembolism (VTE) or pulmonary embolism (PE). Repeated ECP use is safer than pregnancy even if there is no sufficient data for repeated ECP use. A warning to not repeat the dose in one menstrual cycle is included in the prospectus of ullipristal asetate[41].

CONTRAINDICATIONS

The contraindications for hormonal contraceptives cannot be adapted to women using emergency contraception. This is especially true in cases with cardiovascular diseases, thrombotic diseases, migraine, and liver disease. The advantages of use overpower the potential risks[42,43]. These guides do not include ullipristal. The contraindications for use of ullipristal are suspected pregnancy, uncontrolled asthma and liver diseases. The contraindications for IUD are uterine distortion, active pelvic infection, allergy to copper, and suspected pregnancy.

SIDE EFFECTS

Nausea-vomiting, abdominal pain, breast tenderness, headache, dizziness and weakness that regressed spontaneously in 24 h are the major side effects. Nausea and vomiting are seen in nearly half and 20% of the patients using combined ECP, respectively. Nausea and vomiting are less common in levonorgestrel than in combined ECP[12].

Some authors suggest a repeated dose in case of vomiting. This should be given 2 h later. In combined ECPs containing E/P, a repeated oral levonorgestrel and ullipristal dose is given at 1 h and 3 h after vomiting, respectively. Meclisine can be used to prevent nausea but it has no effect on dizziness. Vaginal administration is described, but the efficiency remains unclear. The application of the IUD is preferred instead.

ECPs containing levonorgestrel may shorten menstrual cycle when used in the early days of the cycle. ECPs have no effect on the duration of the cycle, but the duration of bleeding may extend to the next cycle. The duration of the menstrual cycle extends when used in periovulatory and postovulatory phases. Inter menstrual bleeding is seen in 15% of patients.

EFFECTS ON PREGNANCY

In a study of 332 pregnant women who used levonorgestrel in during the conception phase, there was no rise in birth defects[44]. ECPs do not increase the risk of extrauterine pregnancy in future pregnancies[45,46].

USE IN LACTATION

There is no restriction on the use of levonorgestrel or combined ECPs in lactating women[44]. In a study researching the pharmacokinetics of the use of 1.5 mg levonorgestrel for emergency contraception in lactating women, it is recommended to break from breastfeeding for 8 h during the excretion of levonorgestrel to breast milk. Feeding should restart in 24 h[47].

In a study comparing efficiencies of progestin-only oral contraceptives and progestin-only ECPs in lactating women, no difference was detected in maternal and foetal effects[48]. Seven days hiatus from breastfeeding is advised after a single dose of ullipristal. The milk must be collected and discarded during this time to continue to stimulate lactation[49].

DRUG INTERACTIONS

Drugs that induce liver enzymes may reduce the efficiency of levonorgestrel and ullipristal. Therefore, IUDs may be recommended for emergency contraception in patients using drugs inducing liver enzymes such as anti-epileptics and antiviral agents in the last 28 d[50]. In addition, ullipristal should not be

used with drugs increasing gastric pH.

PROCEEDING OR STARTING HORMONAL CONTRACEPTION

Because of the unknown duration of emergency contraceptive effects, it is unclear how to proceed with continuous contraception at the same menstrual cycle. The patient must be informed about using a safe contraceptive method[51]. According to pharmacokinetic studies and expert opinions, barrier methods and hormonal contraceptives may be started after application of emergency contraception. In the first seven days of hormonal contraceptives, an additional failsafe method must be used.

The use of long-term contraceptives is not recommended prior to exclusion of pregnancy. The efficiency of hormonal contraceptives may decrease in patients using ullipristal depending on the progesterone antagonistic effect. The FDA does not recommend the use of hormonal contraceptives within 5 d of ullipristal[52].

EXPERIMENTAL METHODS

Prostaglandin inhibitors

Cyclooxygenase enzyme (COX-1 and COX-2) inhibitors have female reproductive functions of oocyte maturation and ovulation. Many studies targeting this effect in emergency contraception are still underway. Studies have shown 15 mg of meloxicam with 1.5 mg levonorgestrel is more effective on follicular rupture in 5 d in patients with a follicular size over 15 mm than levonorgestrel only[53,54]. In addition, a 400 mg dose of celecoxib may delay or prevent luteal changes[55].

CONCLUSION

Emergency contraception is the last chance to prevent pregnancy after unprotected sexual intercourse or contraceptive failure. The efficiency increases by starting the medication as soon as possible. It is important to remember the rate of unsuccessful contraception and to exclude pregnancy especially in obese or drug-contraindicated patients. Of course, patients must be informed and encouraged to use regular and effective contraception.

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