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Emergency Contraception – An Overview

C. Berger*, E. Norlin*, P. G. L. Lalitkumar, K. Gemzell-Danielsson

The ability to control fertility through the use of effective and safe contraception is essential in preventive medicine. EC offers a second chance to prevent an unwanted pregnancy after the event of an UPSI, contraceptive failure or after rape. Health care providers should routinely and more frequently recognize and inform women about the risk of an unintended pregnancy and EC options to avoid this and women should be provided the correct information about the mechanism of action of various EC options. Lack of knowledge on the mechanisms of action obstructs wide spread access and use globally. Currently, the three most commonly licensed methods of EC are insertion of a Cu-IUD or the hormonal pills UPA 30 mg or LNG 1.5 mg. All EC methods are safe with almost no contraindications and minimal side effects. Considering that ovulation and the fertile window are difficult to assess, it is recommended that EC is administered after an UPSI, regardless of cycle day.

With an extremely low failure rate, the Cu-IUD is an attractive option for EC regardless of the woman's weight or concomitant medication and has the additional propensity to serve as a long-term contraceptive after insertion including if further acts of UPSI should take place in the same cycle. A Cu-IUD inserted within 5 days after ovulation, or when not known 5 days after UPSI, should be the first method of choice if available and suitable. The additional post-ovulatory effect makes the Cu-IUD a superior EC method.

Of the available hormonal EC treatments, UPA 30 mg should be the first choice being the most effective option with a wider window of effect than LNG. UPA has the ability to delay or inhibit ovulation beyond the life span of sperm even when given at an advanced follicular phase when the risk of pregnancy is high. In comparison, LNG has a narrower window of effect on ovulation with no effect after LH has started to rise, but LNG in a dose of 1.5 mg is recommended where UPA is not available. It is of great importance that any ECP is administered as soon as possible after an UPSI since the risk of nearing an anticipated ovulation increases if treatment is delayed, should the timing be pre-ovulatory.

There is no evidence of teratogenic effects of currently available EC methods, although data on UPA is still scarce.

It should be pointed out that an ECP is not as effective as regular contraception. There is an opportunity to introduce a long-term contraceptive method to a woman when she seeks EC, which preferably should be a non-user dependent option, such as a non-forgettable LARC. **J Reproduktionsmed Endokrinol_Online 2015; 12 (4): 260–7.**

Key words: emergency contraception, levonorgestrel, ulipristal acetate, mifepristone, Cu-IUD

List of abbreviations

BMI	Body Mass Index	FIGO	International Federation of Gynecology and Obstetrics
CEU	Clinical Efficacy Unit		
CHMP	Committee for Medicinal Products for Human Use	FSRH	Faculty of Sexual and Reproductive Health
Cu-IUD	Copper Intrauterine Device	ICEC	The International Consortium for Emergency Contraception
EC	Emergency Contraception	LARC	Long Acting Reversible Contraception
ECEC	The European Consortium for Emergency Contraception	LH	Luteinizing Hormone
ECP	Emergency Contraceptive Pill	LNG	Levonorgestrel
EE	Ethinylestradiol	OTC	Over the Counter
EMA	European Medical Association	POP	Progestogen-only Pill
EML	Essential Medicines List	PRM	Progesterone Receptor Modulator
ESHRE	European Society of Human Reproduction and Embryology	UPA	Ulipristal Acetate
		UPSI	Unprotected Sexual Intercourse

■ Introduction

Emergency contraception (EC) is a post-coital treatment to prevent pregnancy. Such drug or device thus offers a chance to avoid unwanted pregnancy after the event of unprotected sexual intercourse (UPSI), contraceptive failure or as treatment after rape [1].

In lay language EC is frequently referred to as “the morning after pill”. This can be misleading both regarding the route of administration, as well as the time window of effect. There are currently two categories of EC available; insertion of a copper intrauterine device (Cu-IUD) within 5 days after UPSI or intake of an oral hormonal pill (ECP) within 72–120 h after such an event.

EC is also often confused with medical abortion and termination of an already existing pregnancy. The myths and misconceptions surrounding EC contribute to confusion regarding mechanisms of action and increase difficulty of access to the treatment around the world. Also, where EC is available, there is a risk of incorrect use, misunderstanding of when EC could be an option to prevent an un-

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wanted pregnancy and additionally overestimation of the efficacy. These potential errors are not limited to women being treated, but are also associated with the health care providers treating them.

The objective of this review is to give an updated overview of currently available, evidence-based EC options, their mode of action and efficacy, contributing factors to EC failure as well as safety aspects and clinical recommendations.

■ EC Globally

A study by Ahmed et al concluded that if the unmet need for contraception were to be fulfilled worldwide maternal mortality would decrease by nearly a third [2]. Unsafe abortions contribute substantially to maternal morbidity and mortality globally [3]. Thus the avoidance of unwanted pregnancies with safe and effective contraceptive methods, including EC, is essential for the fundamental human right of sexual and reproductive health. The World Health Organization (WHO) has included EC on their Essential Medicines List (EML) and the International Federation of Gynecology and Obstetrics (FIGO) has declared that EC should be easily available and accessible at all times to all women [4]. The use of EC can prevent a substantial percentage of expected pregnancies [5].

Although efforts to increase availability of EC worldwide are continuously in progress, access is unequally spread and still limited, especially in low-income countries. Out of 196 countries worldwide there was at least one hormonal EC method available in 148 countries in 2014. However only 54% of countries provide EC in the public sector and 74% have a registered EC product distributed in the commercial sector. Of 111 countries with available EMLs, 57 list EC products as essential, 56 do not require a prescription from a doctor, and only 17 make EC available over the counter [4].

■ The Fertile Window and Pregnancy Risk

Whether a single act of UPSI can result in a pregnancy or not depends on when, during the menstrual cycle, it has taken place. The limited time during the cycle that this event can occur is known as the

fertile window [6–8]. Fertilization of an oocyte can take place within a maximum of 24 h after ovulation. However, the fertile window during which UPSI can result in a pregnancy is wider, as spermatozoa can survive in the female reproductive tract for up to 6 days after intercourse and there await the oocyte to be released [9]. If the conceptus reaches the uterus after transportation executed by smooth muscular contractions and the beating motion of cilia through the fallopian tube and is able to implant into the necessarily prepared receptive endometrium, a clinical pregnancy can occur [10, 11].

Occurrence of the fertile window varies in women according to the time of ovulation. Thus, it appears to be easily predictable for women with regular menstrual cycles. However, even for women who regard their cycles as being regular, ovulation has shown to be highly variable and unpredictable, with sporadic ovulations outside this time, resulting in a wide range of fertile days, and even more so for women with irregular cycles. In a study by Wilcox et al where the timing of ovulation was studied prospectively in 221 women and altogether 689 menstrual cycles, the fertile window occurred at the expected interval in only 30% of women [12]. Therefore, it is difficult to estimate, for most women, the probability of being in the fertile window and at risk of pregnancy at a given time.

Studies have shown that sexual intercourse is more likely to occur during the most fertile days in the menstrual cycle, even for women who are not trying to conceive, with increasing frequency during the follicular phase, a peak near ovulation and thereafter a rather steep decrease [13, 14]. Several hypotheses have been made to try and explain this pattern of increased intercourse frequency around ovulation including a cyclic increase in the woman's libido and/or sexual attractiveness at this time or, as in certain other species, that ovulation could possibly be accelerated and triggered by an act of intercourse [13]. Since it is difficult to determine the time of ovulation and because sexual intercourse and ovulation can occur dependently, EC treatment is recommended to be administered regardless of when in the cycle UPSI has taken place for women who do not wish to become pregnant [15].

■ EC Efficacy

It is difficult to determine the proportion of pregnancies prevented by EC. When trying to estimate the efficacy of different EC methods one has to consider the theoretical baseline risk or probability of pregnancy for that woman depending on when in the menstrual cycle the act of UPSI took place, as well as the interval between that event and treatment with EC [16]. For ethical reasons, clinical trials of EC efficacy have often been designed to compare different EC methods instead of randomized placebo controlled studies so the actual effectiveness with reduction in pregnancy risk is difficult to assess for each method. The proportion of pregnancies that can be prevented by currently available EC options has been estimated to be 57%–99%, depending on the method and when in the menstrual cycle it is used [17–21]. A recent study reanalyzed data from previous studies on the probability of conception after one act of UPSI taking into consideration that intercourse and ovulation do not occur independently and concluded that EC may be more effective than previously estimated [14]. However, rather than comparing how many pregnancies could be prevented by different methods to assumption based estimates of how many pregnancies might have occurred, a more accurate way of calculating EC efficacy is to compare failure rates in clinical trials among different options [15].

■ Brief EC History and Yuzpe

Postcoital methods to avoid an unwanted pregnancy have been described in literature since ancient times [22] but it was not until the 1960s that effective hormonal EC methods were developed. Initially, these regimens included high doses of estrogens, such as 5 mg of ethinylestradiol (EE) and commonly had a high incidence of side effects including nausea and vomiting [5]. One decade later Dr Yuzpe from Canada introduced a method combining 0.1 mg ethinylestradiol with 0.5 mg levonorgestrel (LNG) to be taken within 72 h of UPSI, followed by repeated administration 12 h later [23]. This so-called Yuzpe regimen was the standard hormonal EC method until mono-treatment with LNG or mifepristone was introduced in the 1990s. However, the method remains

on the WHO EML and is still used in countries where a more effective option is lacking. A similar effect can also be achieved by taking several tablets of a, widely available, combined oral contraceptive pill (COCP) to reach the equivalent dose [24].

■ Current EC Methods and Mechanisms of Action

Copper Intrauterine Device

The most effective method of EC is insertion of a Copper intrauterine device (Cu-IUD) within 5 days after ovulation. However, because ovulation can be difficult to predict, it is recommended to insert the Cu-IUD within 5 days of UPSI [25, 26]. This method has a failure rate of 0.09% and has an additional propensity to serve as an effective long-term contraception option if left in place [21, 26]. Insertion of an IUD has shown to be highly acceptable among parous as well as nulliparous women [25, 26].

When used for regular contraception, copper ions released from the Cu-IUD enhance the inflammatory response caused by the induced foreign body reaction. This reaction is toxic to gametes and has impact on viability, motility and fertilizing capacities of spermatozoa [27, 28]. It also interferes with the development of viable embryos [29, 30] and increases smooth muscle activity in the fallopian tubes [31] and uterus [32]. If a fertilized oocyte reaches the uterine cavity, the Cu-IUD prevents implantation by making the intrauterine milieu unreceptive [33]. As an EC, the contraceptive mechanism of a Cu-IUD depends on when in the cycle it is inserted. It may prevent fertilization when inserted before ovulation and will inhibit implantation, primarily by altering endometrial receptivity, if inserted after ovulation and before the implantation window. A recent study concluded that the Cu-IUD is highly effective for EC if in fact inserted at any time in the menstrual cycle given a negative urine pregnancy test prior to placement [34]. The post-fertilization effects of a Cu-IUD consist of preventing implantation at an endometrial level and not as an abortifacient [35].

Although being the most effective method of EC, health care providers often fail to inform and recommend insertion of a Cu-IUD and women are generally not

aware of the overall efficacy and long-term benefit of this method. Additionally, hormonal treatment is often considered as a more convenient method as it does not require access to insertion by a health care professional [36].

Hormonal EC Pills

Mifepristone

Since progesterone plays an essential biological role for human reproduction, progesterone receptor modulators (PRMs) have been acknowledged and studied regarding their anti-fertility properties. The most well known anti-progestin, mifepristone, when administered in a low- or mid-dose within 120 h after UPSI, is a highly effective method of EC [5]. The mechanism of action depends on when during the menstrual cycle the treatment is administered. If given pre-ovulatory mifepristone delays or blocks follicular development and ovulation [37]. Upon the administration of 10 mg mifepristone, ovulation is delayed but not eliminated, while a higher dose (200–600 mg) completely inhibits ovulation and a new follicle is often recruited [38, 39]. Mifepristone administered post-ovulatory, exerts a dose-dependent endometrial effect ranging from only minor impacts on endometrial maturation to preventing implantation [40–42]. Mifepristone is well established for use in termination of pregnancy when given in a single high dose of 200–600 mg in combination with a prostaglandin [43]. This association with abortion has limited mifepristone use as EC to a few countries for political reasons. Currently, mifepristone is marketed as EC in doses of 10 and 25 mg, however only in Armenia, China, Russia, Vietnam and Ukraine [4, 24, 44]. A recently published study compared the efficacy between a dose of 5 mg and 10 mg of mifepristone when used for EC, given up to 144 h after UPSI. There were 15/1,206 (1.2%) and 9/1,212 (0.7%) pregnancies in the 5 mg and 10 mg groups respectively, which was a significant difference with regards to the number of expected and observed pregnancies between the groups but no significant difference in the percentage of prevented pregnancies [45].

Levonorgestrel (LNG)

Levonorgestrel-ECP is the most widely available EC in the world and since introduction, until recently, it has been the

gold standard for hormonal EC. LNG-ECP is available in a majority of European countries over the counter (OTC) or in some cases, behind the counter, provided after a consultation with a pharmacist [46]. The recommended dose is 1.5 mg administered within 72 h after UPSI and has shown to be equally effective as original two doses of 0.75 mg with 12 h apart [19]. Clinical trials comparing LNG-only with the Yuzpe regimen concluded that LNG was more effective in preventing pregnancy and also had a significantly lower incidence of side effects than the Yuzpe regimen [5].

The efficacy of LNG decreases with increasing interval between UPSI and treatment and although it is being used up to 120 h after UPSI, there are significantly higher failure rates when administered after more than 72 h [5]. This is explained by the mode of action of LNG. When administered after the selection of the dominant follicle and before the LH surge, LNG inhibits or delays follicular growth. However, when taken after LH levels have started to rise, LNG cannot hinder a follicle rupture nor ovulation more often than placebo [37, 47]. Thus, if an UPSI and subsequent LNG treatment occur pre-ovulatory, the risk of an ovulation to occur increases as the interval between the events increases.

The effect on cervical and intrauterine mucus, as when used for regular contraception, is unlikely the mechanism of action when LNG is administered postcoitally, as viable spermatozoa can be retrieved in the female genital tract 24–28 h after administration [48]. LNG, in the doses used for EC, does not have an effect on sperm quantity, viability, adhesion to epithelium, distribution or acrosome reaction rate in vitro [49].

In vitro studies have shown a dose-dependent effect of LNG on muscular contractions in the fallopian tube, but have also shown the distribution of progesterone and estrogen receptors herein to be unaffected, in vivo, following administration of 1.5 mg LNG at the time of ovulation [50, 51].

Ulipristal Acetate (UPA)

The most recent contribution to hormonal EC is ulipristal acetate (UPA), a selective PRM, which was specifically developed for EC. It is administered as a sin-

gle dose of 30 mg and is approved in the European (2009) and USA (2010) markets. UPA was recently authorized by EMA to be accessible directly from pharmacies in all EU states without the need for a prescription from a doctor [52]. UPA is recommended as the first choice among oral hormonal alternatives when available, as it is the most effective option [20]. It has effect even when given at a very late pre-ovulatory state and acts by delaying or inhibiting ovulation beyond the life span of sperm. At a mean follicular diameter of 18 mm or more, UPA delayed ovulation by at least 5 days in 59% of women [53]. Brache et al demonstrated that UPA was superior to LNG in preventing ovulation at an advanced phase of follicular development in a series of pharmacodynamic studies comparing different oral EC regimens [47, 53, 54]. UPA administered before the onset of the LH surge inhibited 100% of follicular ruptures. When administered after the onset of the LH surge, but before the LH peak, UPA inhibited 78.6% of follicular ruptures. The ability of UPA to inhibit follicular rupture and ovulation also after LH has started to rise explains the higher efficacy. LNG contrastingly fails to affect ovulation after LH has begun rising. However, at the LH peak or thereafter, UPA can no longer prevent ovulation better than a placebo (8.3%) [54]. Thus, at the stage when the risk of conception is at its highest after the LH peaks at the time of ovulation none of the EC Pills are active.

UPA in concentrations relevant to plasma levels after oral intake as EC, prevents DNA-damage in spermatozoa and does not alter sperm function [55, 56]. Further, UPA exhibits a decrease in smooth muscular contractility and a dose-dependent suppressive effect on ciliary beating in the fallopian tube, which has also been demonstrated for mifepristone [57].

A meta-analysis based on the results of past clinical trials, concluded that UPA administration resulted in a statistically significant reduction in pregnancy rates after UPSI and prevented a larger number of pregnancies than LNG when taken up to 120 h after UPSI. Glasier et al also concluded that women who took UPA within 24 h after UPSI lowered the pregnancy risk by almost two thirds and halved the risk when taken within 72 h of UPSI compared to those who took LNG [20].

■ EC Effect on Endometrial Receptivity, Embryo Implantation and Pregnancy

Cu-IUD

Among the multiple mechanisms of action of the Cu-IUD in preventing pregnancy it also exerts several effects on the endometrium, which contributes to inhibition of implantation in the event that a fertilized ovum should reach the uterine cavity. The inflammatory foreign body reaction induced by the Cu-IUD is present in the uterus and fluids throughout the genital tract [58]. In addition Cutions can induce other biochemical changes in the endometrium, including altering specific enzyme activities and cell metabolism generally [59]. Copper in doses similar to those in a Cu-IUD has also shown to stimulate myometrial contractile activity *in vitro* and *in vivo* [32]. The cyclic endometrial development is not affected by a Cu-IUD used continuously, however integrin cell adhesion molecules of importance for endometrial receptivity and involved in embryo implantation can be altered by a Cu-IUD during the window of implantation [33]. The prevention of implantation rather than interruption was suggested in a study where chorionic activity in the late luteal phase was strongly reduced in women with Cu-IUDs compared with women with inert IUDs or no contraceptive use [60]. The post-ovulatory effects, including the effect on the endometrium makes the Cu-IUD near perfect in efficacy as EC. In the rare event of a pregnancy occurring with a Cu-IUD *in situ*, the device should promptly be removed due to risk of adverse pregnancy outcomes, like miscarriage or pre-term delivery, if left in place. There is no evidence of any teratogenic effect when the Cu-IUD is successfully removed [61].

Hormonal EC Pills

Pre- or post-ovulatory administration of LNG did not affect endometrial morphology or receptivity [37, 62, 63] and only minor effects on gene expression in the endometrium of no relevance to receptivity have been described when administered post-ovulatory [64]. A recent prospective cohort study of pregnancy outcome after LNG-ECP failure found no association between LNG exposure and congenital malformations or effect on physical growth or mental develop-

ment in children born from these pregnancies [65].

UPA has a dose-dependent effect on the endometrium and a high dose, or repeated doses, affects endometrial histology. However, low doses, such as concentrations used for EC, do not significantly delay endometrial maturation, compared to placebo, when administered post-ovulation, although minor changes are observed [66, 67].

A report from post-marketing surveillance recently concluded that there was no evidence of any teratogenic effects after UPA exposure [68]. However, the numbers of known pregnancies that have come to term after UPA exposure are small, most likely due termination a pregnancy after EC failure and the probability that uncomplicated pregnancies are seldom recognized as adverse events and therefore not reported [68].

3D *in vitro* endometrial co-culture model

Due to technical, ethical and legal reasons it is, to date, impossible to study the effect of EC treatment on human embryo implantation *in vivo*. However, a 3D *in vitro* endometrial, co-culture model, that mimics the receptive endometrium, has been developed, which allows for studies of the human embryo implantation process including progesterone regulated markers of endometrial receptivity [42, 69, 70]. Previous studies using this model have shown that LNG, in concentrations relevant for EC, has no effect on embryo viability or early human embryo implantation processes *in vitro* (Fig. 1) but, that exposure to a high concentration of mifepristone significantly alters the molecular profile of the construct and inhibits embryo attachment [42]. There are so far, no published data on the effect of exposure to very low dose mifepristone on embryo implantation when used for EC.

Due to the similarity in class of UPA to mifepristone and higher efficacy as EC compared to LNG, there have been concerns regarding a possible effect of UPA on the endometrium as well as embryo implantation. A recently published study provided new insights on the mechanism of action of UPA on human embryo implantation, using the described 3D-model (Fig. 1), demonstrating that UPA, in a concentration relevant for EC, caused

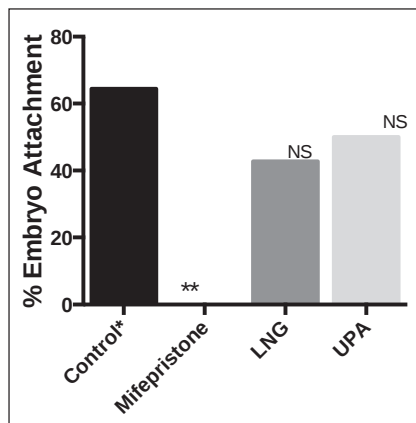


Figure 1. Pooled data from studies on in vitro model for human embryo implantation. Mod. according to: [42, 71]. No difference in human embryo implantation rate with LNG or UPA exposure, compared with the control. Treatment with mifepristone significantly inhibited embryo implantation rate. NS: non-significant.

only minor changes in the gene expression of six out of 17 genes studied. These minor changes were observed with no coinciding effects on neither functionality nor embryo viability, as there was no significant difference in the embryo attachment rate between the UPA treated group and the control group [71].

■ Risk Factors for EC Failure

Further UPSI after EC

Glasier et al compiled data from clinical studies of UPA and LNG to identify risk factors associated with EC failure. As expected, the cycle day of UPSI was significantly associated with pregnancy risk, with the highest risk being at the time of ovulation, independent of type of ECP. In consistency with the mechanism of action for both hormonal ECPs, not having post-fertilization effects to prevent pregnancy, further acts of UPSI after ECP intake was associated with a higher risk of pregnancy [72]. After intake of an oral EC follicular development and ovulation usually resume within a week, which puts women at risk of pregnancy if further acts of UPSI take place in the same cycle due to timing of a postponed ovulation. A Cochrane review with a meta-analysis showed that the pregnancy risk was almost three times higher for women who had further acts of UPSI in the same cycle as treatment with EC than for women who did not [5].

Weight/BMI

There has been a lot of debate over how weight and body mass index (BMI) in-

fluence the effect of EC pills. Clinical trial data suggests a greater decrease in contraceptive efficacy of LNG in overweight women compared to UPA [72]. In the analysis by Glasier et al 2011, treatment with LNG was no more effective than no treatment in women with BMI 26 or higher. UPA however was still effective at higher BMI levels with loss of effectiveness at BMI 35. When calculated by weight, the efficacy limit was 70 kg for LNG and 88 kg for UPA [72]. Although the effect of BMI on EC efficacy is of great clinical importance, the conducted trials were not initially designed to study this relationship. Limitations of the trial included a small number of overweight and obese women as well as the number of pregnancies in these groups were extremely small. Additionally, weight was often self-reported and possibly underestimated and thus, may have resulted in an overestimation of at what weight or BMI ECP efficacy begins to decline. However, following these findings, LNG-EC labels were changed and many women reported denial of EC due to their weight or BMI. Based on a review also including three large clinical WHO trials on LNG with no apparent impact of weight or BMI on the efficacy of LNG-EC, EMAs Committee for Medicinal Products for Human Use (CHMP) finally concluded that although increased BMI might decrease efficacy, the benefits ultimately outweigh the risks, and that women of all weights could continue using LNG or UPA for EC [19, 73–75].

■ Bridge to Long-term Contraception and Quick-Start

If a Cu-IUD has not been inserted for EC, it is of great importance to initiate a regular, long-term, contraceptive method to reduce the pregnancy risk after EC treatment. There is an ongoing discussion that EC could serve as a gateway to more effective long-term contraception. It is a valuable opportunity to introduce a woman to regular long-term contraception when she seeks EC and has no ongoing regular contraception as she is probably motivated to do so at this time. The sooner a woman starts, the sooner she will be protected. The term “quick-starting” refers to immediately initiating a regular method of contraception after EC use. In a pilot study from the UK, a high-

er proportion of women who were provided with a packet of progestogen only pill (POP) from the pharmacy when seeking LNG-EC were using a regular contraception after two months compared to women who only received the ECP [76].

There are, however, concerns about possible interactions between hormonal ECPs and regular oral contraceptives at the progesterone receptor site that would impair their contraceptive effect. Cameron et al recently conducted a randomized, placebo-controlled study to determine whether UPA intake affects the ability of a COCP to induce ovarian quiescence (article in press) [77]. The conclusion was that the most cautious advice to women is to use a barrier method for 14 days after quick-starting treatment with a COCP following UPA intake. For some women this period of time is required before the COCP has induced ovarian quiescence, although most women will have achieved it after 7 days [77]. This might also be true when quick-starting a COCP after the use of LNG for EC (or in cases when a COCP is initiated in mid-cycle even if not preceded by intake of an ECP) as it for some women who received placebo followed by quick-starting the COCP in this study, also took up to 14 days before achieving ovarian quiescence, suggesting that the use of a barrier method for 7 days, currently advised in these cases, might not be sufficient for all women either.

■ Side Effects and Safety

Side effects associated with estrogen containing hormonal methods such as Yuzpe include nausea and vomiting. Treatment with LNG, mifepristone or UPA primarily affects the subsequent menstruation but additional reported side effects are considered as mild self-limiting conditions, commonly occurring even generally without treatment [78]. On average, LNG shortens the cycle by 1–2 days while mifepristone or UPA on the other hand lengthen the cycle by 1–2 days. The duration of bleeding is not affected by given EC [20].

The side effects of Cu-IUD insertion as EC would be similar to those when inserted for long term contraception, so called interval insertion.

Drug interactions

There are no drug-interactions to consider when using a Cu-IUD for EC but the effect of an oral EC can be reduced if a woman uses liver enzyme-inducing drugs like some antiepileptic or antiretroviral drugs due to enhanced metabolism of the ECP. In a statement from the Clinical Efficacy Unit (CEU) within The Faculty of Sexual and Reproductive Healthcare (FSRH) in UK, women who use such drugs should be advised that a Cu-IUD is the preferred option when in need for an EC but it is also suggested that LNG may be given in a double dose (3 mg) outside product license although evidence for this regimen is lacking [79]. UPA is not recommended as EC for women who take liver enzyme-inducing drugs [80].

Contraindication for EC is an established pregnancy, and where the hormonal methods in the occurrence of a pregnancy will fail but not have adverse effects on pregnancy outcome, insertion of a Cu-IUD might cause disruption of an implanting embryo but if the device is removed in early pregnancy, not causing a miscarriage, no teratogenic effects have been seen [61].

Breastfeeding

It is safe to use LNG for lactating women but it is usually recommended to avoid breastfeeding for at least 8 h, thus avoiding the time when LNG is at maximal concentrations [81]. To date, there are no studies on UPA concentration in breast milk after intake. Lactating women who take UPA for EC are advised to discontinue breastfeeding for 36 h until more information is obtained [79]. A study measuring mifepristone concentration in breast milk after medical termination of pregnancies, using a high dose of mifepristone (200 mg) showed low levels of the compound in breast milk, concluding that there was no need to discontinue breastfeeding [82]. Therefore it is considered safe to do so also after mifepristone in low EC-doses, and the same should apply to UPA.

Ectopic Pregnancy

In a meta-analysis study with data from 136 studies of women treated with either mifepristone or LNG for EC, the rate of ectopic pregnancies after EC failure was 0.6% and 1% in the mifepristone and LNG group respectively, not exceeding

the rate in the general population [83]. It is generally accepted that because EC methods reduce the risk of pregnancy, they ultimately reduce the risk of ectopic pregnancy. In a recently published case-control study, women who participated in further acts of intercourse after EC use were found to be at a slightly higher risk of ectopic pregnancy. Furthermore, repeated use of LNG-EC within the same cycle was associated with increased risk of ectopic pregnancy [84]. However, these results are consistent with the overall increase in pregnancy with UPSI as the risk of unintended pregnancy including ectopic pregnancy was reduced after EC use compared to women who did not use any form of contraception at all [84].

EC Availability and Public Health

Disappointingly, although clinical studies demonstrate the efficacy of EC it has not yet been possible to see an effect on a public health level, in terms of reduction of abortion rates, even though a woman's individual risk of pregnancy is reduced after EC [85, 86]. In settings where EC is available OTC at pharmacies and the overall knowledge of EC would be considered as good, few women seeking abortion had tried to avoid the unwanted pregnancy with EC [87]. Many women seem to underestimate the risk of becoming pregnant when exposed to UPSI and do not recognize the need for EC, even in studies where participants were provided with advanced provision of an oral EC [88]. There is no evidence that advanced provision of ECP would increase rates of STI or lead to more risky sexual behavior with increased rates of unintended pregnancies or changes in regular contraceptive use [86].

Future perspectives

Since time interval between UPSI and treatment is an important factor for EC effectiveness, greater knowledge and acceptability worldwide, as well as availability and access for all women could offer means to decrease unwanted pregnancy rates and thereby increase public health at population level. Ideally EC should be supplied OTC where provision of more effective long-term contraceptive options, such as long-acting reversible contraception (LARC), can be offered simultaneously. Also, it is naturally

important that such interventions are evaluated.

There is a need to develop more effective EC methods, preferably with the option to use on demand pre- or postcoitally. For an EC to work optimally it should have effect throughout the entire menstrual cycle with effect on ovulation as well as post-ovulatory, such as the Cu-IUD involving an effect on the endometrium.

Conclusion and Clinical Recommendations

- All women presenting for EC within 120 h after UPSI should be offered a Cu-IUD if eligible since insertion of a Cu-IUD undoubtedly is the most effective EC – with no reduction in effectiveness over time and can be used for long-term contraception including further acts of UPSI in the same cycle.
- The mechanism of action of current ECPs is to interfere with the ovulatory process and postpone or inhibit ovulation but they do not inhibit embryo implantation.
- A single dose of UPA 30 mg within 120 h after UPSI is recommended as the first choice among oral ECPs due to its wider window of effect pre-ovulatory.
- If no more effective options are available, a single dose of LNG 1.5 mg as soon as possible within 72 h after UPSI is a well-tolerated option with no contraindications.
- After ECP use, further acts of UPSI should be avoided and quickstart initiation or resumption of regular contraception encouraged, with use of an additional barrier method for 14 days after UPA and at least 7 days after LNG.

Conflict of Interest

The authors declare no conflict of interest.

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