Review article

Emergency contraception — mechanisms of action

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Abstract

Concerns regarding the mechanisms of action of emergency contraception (EC) create major barriers to widespread use and could also lead to incorrect use of EC and overestimation of its effectiveness. While the copper intrauterine device (Cu-IUD) is the most effective method available for EC, the hormonal methods are frequently considered to be more convenient and acceptable. Today, the most commonly used method for hormonal EC is levonorgestrel (LNG). More recently, the progesterone receptor modulator ulipristal acetate (UPA) has been shown to be more effective than LNG to prevent an unwanted pregnancy. The main mechanism of action of both LNG and UPA for EC is delaying or inhibiting ovulation. However, UPA appears to have a direct inhibitory effect on follicular rupture which allows it to be effective even when administered shortly before ovulation, a time period when use of LNG is no longer effective.

The main mechanism of action of the Cu-IUD is to prevent fertilization through the effect of Cu ions on sperm function. In addition, if fertilization has already occurred, Cu ions influence the female reproductive tract and prevent endometrial receptivity.

Based on this review of the published literature, it can be concluded that existing methods used today for EC act mainly through inhibition of ovulation or prevention of fertilization. An additional effect on the endometrium as occurs for the Cu-IUD, but not for the hormonal alternatives, seems to increase the efficacy of the method.

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1. Introduction

Emergency contraception (EC) is defined as the use of any drug or device after an unprotected intercourse to prevent an unintended pregnancy [1]. EC offers a second chance to prevent pregnancy when contraception has failed or in the case of unprotected sexual intercourse. If properly used, the widespread use of EC holds the potential to reduce the number of induced abortions. Early methods of hormonal EC were based on existing oral contraceptive preparations, the so-called Yuzpe regimen [2]. Later on, it was shown that levonorgestrel (LNG) alone was more effective than the combined regimen [3]. With LNG, estrogenic side effects could also be reduced or eliminated. Ulipristal acetate (UPA) represents a recent innovation in EC, promising better efficacy than LNG due to a wider time window of action [4].

A single dose of 30 mg UPA has recently been approved in Europe and the United States for EC use up to 120 h of unprotected intercourse. Although less practical and accessible for many women, EC with a copper intrauterine device (Cu-IUD) also offers an immediate long-acting highly effective emergency contraceptive method.

The efficacy of EC pills (ECPs) has been questioned, and interventions to make EC more available have failed in reducing abortion rates [5–7]. However, it has also been recognized that EC is still underutilized worldwide. Introduction of ECPs in many countries has generated much controversy and litigation. One of the main barriers to the widespread use of EC around the world is the lack of knowledge on the mechanisms of action, especially with regard to the effect on the endometrium, endometrial function and embryo implantation [8]. Therefore, an increased knowledge about the mechanisms of action and safety of EC is essential for the development of new methods as well as for optimizing the use of those already available. This knowledge may also influence individual and cultural acceptability of EC use.

The objective of this review is to give an overview of the mechanisms of action of EC on female reproductive
functions. The review is an update of previous reviews [9–11]. Although other alternatives will be mentioned, the focus in the current article will be mainly on LNG, which is the most widely used EC method worldwide; UPA, the most recent option; and the Cu-IUD, which when used for EC also offers the possibility of long-lasting contraception.

2. EC methods

Several approaches to EC have been described [12], broadly classified as pills containing synthetic hormones and insertion of a Cu-IUD. Hormonal pills are often referred to as “postcoital pills” or “morning-after pills” in the media and in lay language. Methods used postcoitally have included diethyl stilbestrol, high doses of ethinylestradiol and LNG, danazol and mifepristone [2,13–16]. The hormonal methods are usually considered as more convenient than the insertion of a Cu-IUD which is otherwise the most effective method of EC. In the late 1970s, Yuzpe introduced a regimen consisting of 0.1 mg ethinylestradiol and 0.5 mg LNG, given once within 72 h after intercourse and repeated after an additional 12 h [2]. The Yuzpe regimen remained the standard hormonal EC method until the introduction of treatment with LNG only or mifepristone which was shown to be associated with less side effects and higher efficacy than the Yuzpe regimen [3,17]. Meta-analysis of mifepristone for EC demonstrated a dose-dependent efficacy [12]. Mifepristone in low doses (10, 25 or 50 mg) for EC is mainly used in China.

Recently, a new class of a second-generation selective progesterone receptor modulator UPA has been developed and approved for EC treatment. A single dose of 30 mg UPA for EC (ellaOne®, HRA-Pharma, Paris, France) was approved by European Medicines Agency (EMA) in May 2009 and by the US FDA in June 2010 (named Ella in the USA). The half-life after oral intake of UPA is 32 h. UPA bound up to 97%–99.5% to plasma proteins in the blood, and it is mainly metabolized by cytochrome P450 (CYP3A4). Following oral administration of a single 30-mg dose, UPA is rapidly absorbed, with peak plasma concentration occurring approximately 0.5–3 h after ingestion depending on whether the drug is taken during the fasting state or after a meal. Although specific drug–drug interaction studies have not been performed, it is possible that inducers of CYP3A4, e.g., rifampin, dexamethasone, St. John’s Wort and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine), may increase the metabolism of UPA and cause lowered plasma levels. Furthermore, inhibitors of CYP3A4, e.g., the HIV protease inhibitors, iraconazole, erythromycin and grapefruit juice, may inhibit the metabolism of UPA and cause increased plasma levels [18].

It has been stated that Hippocrates himself in ancient times has mentioned copper as a metal with influence on fertility. Postcoital insertion of a Cu-IUD within 5 days after unprotected intercourse is a highly effective method for emergency contraception [19–21]. However, the Cu-IUD is an underutilized method of EC. This is presumably partially due to the fact that contraceptive providers infrequently recommend the Cu-IUD as EC despite its additional benefit as a safe and effective method for long-term contraception [22] and because women generally are not aware of this being a highly effective method of EC [23].

3. Effectiveness and timing of EC treatment

Although the Cu-IUD is the most effective method of EC, the administration of oral hormonal pills is usually considered more convenient, with almost no medical contraindications. The absolute efficacy of ECPs remains undetermined and depends on the specific formulation, doses of regimen, time interval between unprotected intercourse and treatment, as well as the risk of conception. The proportion of pregnancies prevented by EC compared with the expected number without treatment has been reported to vary from 57% to >95% [3,17,24–29]. LNG is more effective than the Yuzpe regimen [3]. However, compared to both of them, a single dose of mifepristone (≥50 mg) has higher EC efficacy (LNG vs. mid-dose (25–50 mg) (15 trials, RR: 2.01; 95% CI: 1.27 to 3.17) or low-dose mifepristone (<25 mg) (9 trials, RR: 1.43; 95% CI: 1.02 to 2.01). [30].

In order to increase statistical power to detect any difference in efficacy between UPA and LNG, data from both randomized controlled trials that compared UPA and LNG for EC were combined in a meta-analysis [31]. This meta-analysis contained data on 3445 women and showed that for those treated with UPA, the risk of pregnancy was significantly reduced compared to those who received LNG. For women who were treated with UPA within 72 h after unprotected intercourse, the risk of pregnancy was almost half of those receiving LNG (odds ratio (OR) and 95% CI 0.58 (0.33–0.99, p=.046)). Furthermore, if EC was taken within 24 h after intercourse, the risk of pregnancy in women who received UPA was reduced by almost two thirds of those women receiving LNG (OR 0.35, 95% CI 0.11–0.93, p=.035).

It is only during a limited period in the menstrual cycle that conception is possible. This is due to the limited life span of spermatozoa in the female reproductive tract (120 h) as well as the oocyte length of survival after ovulation (12–24 h). The fertile window, when an unprotected intercourse or failed contraception can result in a pregnancy, thus extends from 5 days before ovulation up to 1 day after, with the highest rates of conception occurring within 2 days prior to ovulation [32]. Fertilization must occur within a maximal 24 h of ovulation, and probably much shorter, since after that time the oocyte deteriorates rapidly and fertilization then either fails or gives rise to a defective embryo. In contrast, spermatozoa can survive in the female reproductive tract for 5–6 days after intercourse [33]. Studies have shown that the frequency of sexual intercourse peaks during the time in the menstrual cycle where the probability of conception is at its
highest [34,35]. The discrepancy between the stage of menstrual cycle that women self-report and the dating based on endocrine data [36], as well as the findings that unprotected intercourse outside of the supposed fertile period also may result in pregnancy [37], makes it difficult to assess the time of ovulation and has led to the recommendation that EC should be administered regardless of cycle day after an act of unprotected sexual intercourse to prevent an unwanted pregnancy.

The possible mechanisms of action of an EC could include effects on sperm mobility, transport and function, follicular development, ovulation, fertilization, embryo development and transport, endometrial receptivity and implantation and corpus luteum function.

4. Effects on human sperm function

LNG does not influence sperm acrosome reaction [38,39]. It inhibits spermatozoa–oocyte fusion as well as decreases the curvilinear velocity of spermatozoa only at high concentration, and the contribution of these effects to EC is unlikely to be significant [38].

In vitro data indicate that LNG or mifepristone in doses relevant for EC has no direct effect on sperm function [38,40,41]. The observations described by Kesserü et al. [42] on LNG effects on cervical and intrauterine mucus are probably of importance when LNG is used as a regular contraceptive but unlikely to be the main mechanism of action of LNG used for EC since sperm can be retrieved from the fallopian tube within 5 min after insemination of semen in the vagina [42,43]. Furthermore, viable spermatozoa were found in the female genital tract 24–28 h after intake of LNG [44]. Recently, it was shown that LNG in a similar dose to that observed in serum following oral intake for EC had no [44]. Recently, it was shown that LNG in a similar dose to that observed in serum following oral intake for EC had no [44]. Recently, it was shown that LNG in a similar dose to that observed in serum following oral intake for EC had no [44]. Recently, it was shown that LNG in a similar dose to that observed in serum following oral intake for EC had no [44]. Recently, it was shown that LNG in a similar dose to that observed in serum following oral intake for EC had no [44]. Recently, it was shown that LNG in a similar dose to that observed in serum following oral intake for EC had no [44]. Recently, it was shown that LNG in a similar dose to that observed in serum following oral intake for EC had no [44]. Recently, it was shown that LNG in a similar dose to that observed in serum following oral intake for EC had no [44]. Recently, it was shown that LNG in a similar dose to that observed in serum following oral intake for EC had no [44].

Cu ions released from the Cu-IUD enhance the inflammatory response and reach concentrations in the luminal fluids of the genital tract that are toxic for spermatozoa [46]. This affects the function and viability of gametes and prevents fertilization [46]. In vitro studies have shown that copper, at concentrations similar to those released from Cu-IUDs, affects the motility, viability, acrosome reaction and fertilizing capacity of human spermatozoa, both in culture medium and in cervical mucus [47–49].

The diminished sperm penetration and impaired motility seen in spermatozoa in the cervical mucus from women using a Cu-IUD that were not seen in the mucus from women using a plastic IUD without copper indicate that these effects are primarily attributed to the copper in the mucus and not to a local foreign body reaction [50]. A markedly decreased number or absence of spermatozoa has been found near the site of fertilization in Cu-IUD users compared to non-IUD users [51].

5. Effects on follicular development and ovulation

LNG has been shown to affect follicular development after selection of the dominant follicle but before the rise in luteinizing hormone (LH) has begun. When LNG treatment was administered at days −2 or −3 before the LH peak, the LH peak was inhibited or delayed and blunted [52,53]. The effect on follicular development varied between delayed follicular development and arrested or persistent unruptured follicles. In contrast, treatment given when LH had already started to rise, on day LH −1 or on the day of the LH peak failed to inhibit ovulation [53,54]. Similar results were obtained in the rat and monkey where the closer to ovulation the treatment was given, the less was the effect [55]. Furthermore, treatment with LNG in the rat and monkey does not affect fertilization or implantation.

Administration of mifepristone during the preovulatory phase, after selection of the dominant follicle, either blocks or delays ovulation in a dose-dependent fashion. At doses of 10 mg, ovulation is delayed but not necessarily abolished [53]. At higher doses, 200–600 mg, ovulation is inhibited, and a new follicle is often recruited [56,57]. The follicle may also remain unruptured until the end of the cycle. When ovulation occurs, the following luteal phase seems to be normal with normal endometrial development and function, as judged by implantation rates [58,59]. At the pituitary level, mifepristone does not block the ‘rise’ in progesterone; it blocks the ability of progesterone to act on progesterone receptors (PRs) in the pituitary to facilitate the LH surge [60,61].

In a series of clinical trials, the effect of UPA at different follicular diameters and temporal relation to the LH peak and ovulation was studied [62,63]. When given prior to the LH rise, UPA inhibited 100% of follicular ruptures. When UPA was administered when the size of the leading follicle was ≥18 mm, follicular rupture failed to occur within 5 to 6 days following treatment in 44% to 59%. Even on the day of the LH peak, UPA could delay ovulation for 24 to 48 h after administration [62]. Taken together, these studies demonstrate that UPA may have a direct inhibitory effect on follicular rupture. This allows UPA to be effective even when administered before ovulation when LH has already started to rise, a time when LNG is no longer effective.

6. Effects on the fallopian tube and fertilization

Fertilization normally occurs in the ampulla of the fallopian tube within 24 h after ovulation. Between day 3 and 4 (approximately on cycle day 18 of an ideal 28-day cycle), the zygote migrates through the fallopian tube until it reaches the uterine cavity at the morula stage [64–66]. The tubal microenvironment is probably of great importance to ensure normal embryo development, and stage-specific expression of receptors for various growth factors has been
found on human embryos [67]. Too rapid or too slow tubal transport of the zygote could also be expected to cause desynchronization between the embryo and the fallopian tube, and/or the blastocyst and the endometrium. A spatially dependent expression of PRs has been shown in the human fallopian tube [67]. Higher levels of receptors are being expressed in the isthmic region than in the ampullar region on days after the LH peak +4 to +6. Progesterone has been shown to regulate tubal transport of the zygote in vitro. Both muscular contractions and cilia activity are involved in the transportation. Cilia from the human fallopian tube beat significantly slower after treatment with high doses of progesterone, an effect that could be reversed by mifepristone [68,69]. A dose-dependent effect on muscular contractions was observed following in vitro exposure to LNG and mifepristone [70]. Treatment with LNG (1.5 mg) on day LH peak +2 did not affect the distribution of progesterone or estrogen receptors in the human fallopian tube in vivo. In contrast, administration of 200 mg of mifepristone on day LH +2 peak resulted in increased expression of PRs in epithelial and stromal cells compared to untreated controls. There was also an effect on estrogen receptor levels, although it was less pronounced and restricted to the epithelial cells [67].

Data from 136 studies on LNG or mifepristone EC revealed that, in the studies of mifepristone, 3 of 494 (0.6%) pregnancies were ectopic; in the LNG studies, 3 of 307 (1%) were ectopic, a rate which does not exceed the rate in the general population. It was concluded that, since EC pills are effective in reducing the risk of pregnancy, their use will also reduce the risk of ectopic pregnancy [71].

When studied in vitro, exposure of human embryos to LNG at concentrations relevant for EC had no effect on embryo viability [72]. Exposure of mifepristone to rat embryos did not affect embryo development or their ability to implant [73]. In a rat pituitary cell culture system mifepristone inhibited GnRH-induced LH and FSH secretion in a dose-dependent manner, without affecting basal gonadotropin release [74]. In humans, 100 mg of mifepristone 1 h before induction of ovulation with injection of 5000 IU of human chorion gonadotropin (hCG) did not interfere with gonadotropin-induced oocyte maturation and fertilization [75]. Laparoscopy (for tubal sterilization) was performed 34 h after hCG injection, and all follicles with a diameter of at least 15 mm were aspirated, and collected oocytes were submitted to in vitro fertilization (IVF). The number of retrieved oocytes, the rate of fertilization and the cleavage rate did not differ between the mifepristone-treated group and untreated controls [75].

An increased concentration of copper is found in uterine and tubal fluid from women using Cu-IUDs [76], and copper is markedly accumulated throughout the epithelium in the fallopian tubes, implying that tubal fluid mixes with uterine fluid and intrauterine substances, thus having the ability to exert extraglandular effects. Copper also increases the smooth muscle activity in the fallopian tube [77,78]. These findings indicate that the Cu-IUD has effects beyond the uterine cavity.

Recovery of oocytes from the fallopian tubes to a lesser extent in women using Cu-IUD than in controls, as well as low recovery of oocyte in the uterus of these women, suggests action of the Cu-IUD before the oocyte reaches the uterine cavity, likely also including destruction of fertilized oocytes [51]. If any embryos are formed in the presence of an IUD, it happens at a much lower rate than in non-IUD users [79]. The presence of a Cu-IUD thus decreases the rate of fertilization and lowers the chances of survival of any embryo that may be formed before it reaches the uterus, which suggests that the major postfertilization effect is destruction of the early embryo in the fallopian tube, in the same way that the major prefertilization effect is likely to be destruction of sperm and ova.

7. Effect on endometrial receptivity and embryo implantation

Successful implantation is the end result of a complex molecular interaction between the hormone-primed uterus and a mature blastocyst. The estimated rate of implantation in natural cycles is 15% to 30% [80]. Uterine receptivity is defined as “the temporally and spatially unique set of circumstances within the endometrium that allows for successful implantation of the embryo” [81]. The features of uterine receptivity include histological changes in which the endometrium becomes more vascular and edematous, the endometrial glands display enhanced secretory activity and the pinopodes develop on the luminal surface of the epithelium [82]. In addition, multiple signals synchronize development of the blastocyst and the preparation of the uterus.

A considerable number of factors have been suggested as markers of endometrial receptivity. Treatment with LNG (1.5 mg) on day LH −2 did not affect endometrial morphology or any studied markers of receptivity during the midluteal phase at the expected time of endometrial receptivity and implantation [83,84]. The same results were observed with vaginal administration of 1.5 mg LNG or repeat oral doses (0.75 mg×4 po) [85]. Recently, it was shown that postovulatory administration of LNG caused minimal changes in gene expression profiling during the receptive period [86]. Neither the magnitude nor the nature or direction of the changes endorses the hypothesis that LNG interferes with endometrial receptivity.

The dose-dependent endometrial effects of mifepristone administered postovulation have been investigated in several studies. Once-a-month treatment with a single dose of 200 mg mifepristone on day LH peak +2 has been shown to be an effective contraceptive method [87–90]. Early luteal phase treatment of mifepristone causes pronounced changes in endometrial development and function [91–94] despite unchanged menstrual rhythm and serum levels of estradiol.
and progesterone [95]. While treatment with 5 mg mifepristone once a week or 0.5 mg daily administered for three cycles did not inhibit ovulation, the endometrial development was retarded or desynchronized [96,97]. An increase in PR levels, as well as impaired secretory activity, was observed. Both regimens were shown to be insufficient to prevent implantation [98,99]. When a single dose of 10 mg mifepristone was administered on day LH peak +2, the observed minor effect on the endometrium showed individual variation [52]. Consistent with this finding, repeat administration of 10 mg mifepristone once a week was not effective to prevent pregnancy [100].

Significant advances in the understanding of embryo implantation have been made by using animal models, especially mice and nonhuman primates. However, the results from animal studies cannot be extrapolated unconditionally to humans as the process of human implantation may be unique. For ethical and legal reasons, the implantation of a blastocyst in the human endometrium cannot be studied in vivo. Therefore, the molecular and cellular events that mediate human embryo implantation remain largely unknown. In the absence of in vivo implantation sites, an in vitro model mimicking the different stages of human embryo implantation that occur in vivo during the first few days of pregnancy has recently been developed [72]. To allow studies on human embryo implantation, a three-dimensional endometrial construct comprising endometrial stromal cells in collagen matrix with a surface of epithelial cells was developed. The in vitro study shows that the molecular profile of this three-dimensional endometrial construct is similar to the receptive endometrium in vivo [101]. Consistent with the in vivo effects, exposure to a high concentration of mifepristone caused significant changes in the in vitro luminal epithelium and resulted in inhibition of blastocyst attachment [72]. In a rat pituitary cell culture system mifepristone inhibited GnRH-induced LH and FSH secretion in a dose-dependent manner, without affecting basal gonadotropin release [74]. In contrast, LNG had no effect on blastocyst viability or hatching and did not prevent blastocyst attachment and early implantation [72] (Fig. 1).

The effect of UPA on the endometrium has also been demonstrated to be dose dependent [102]. Treatment with 10 to 100 mg UPA resulted in inhibition of down-regulation of PRs, reduced endometrial thickness and delayed histological maturation with the highest dose, while the effect of lower doses equivalent to the 30 mg used for EC was similar to that of placebo [102].

Copper in doses similar to those in a Cu-IUD has been shown to stimulate myometrial contractile activity, both in vitro and in vivo, in animal models as well as in women, an effect which has been suggested to contribute to the contraceptive effect [103].

The endometrial morphology in women using a Cu-IUD was investigated during 1 year, and the results showed that presence of a Cu-IUD in the uterine cavity did not interfere with the development of the endometrium during the menstrual cycle but, following continuous use, there was a gradual increase in leukocytes in the glandular lumina, indicating an inflammatory reaction. A Cu-IUD thus induces a foreign body reaction, and the cellular and humoral components from this response can be retrieved in fluid from the uterus. Cu ions can enhance the inflammatory response with increased numbers of leukocytes and also alter the metabolism of endometrial cells. This inflammatory reaction present in the fluids throughout the genital tract is toxic for gametes, preventing formation of viable embryos [104]. Furthermore, copper can alter molecules like cytokines, but presumably also integrins, in the endometrial lining and thereby consequently act on the implantation site, inhibiting implantation in the event that a blastocyst does reach the uterus [105]. Early signs of implantation have been investigated by measuring biochemical markers in serum during a menstrual cycle, comparing women with medicated IUDs, such as a Cu-IUD, and those with an inert IUD as well as controls. The results showed a strongly reduced incidence of implantation signs in women with the Cu-IUD, indicating its prevention rather than interruption of implantation [106].

8. Effects on corpus luteum function and pregnancy

A meta-analysis of 12 available prospective studies did not find any statistically significant association between oral contraceptive use in early pregnancy and fetal malformation [107]. An adverse effect of LNG on embryo implantation and pregnancy seems unlikely since gestagens are commonly administered to facilitate implantation following assisted reproduction such as IVF. Postovulatory use of 1.5 mg LNG in women who become pregnant did not cause any changes in
the immunoreactivity of various steroid receptors or proliferation in first-trimester decidua and chorionic villi when compared to unexposed controls. A recent prospective cohort study confirmed that there was no association between the exposure to LNG after failed or mistimed EC use and the risk of major congenital malformation, pregnancy complications or any other adverse pregnancy outcomes [108].

So far, only a very small number of pregnancies have been exposed to UPA. In an agreement between the EMA and the market authorization holder, HRA Pharma, a registry has been created to collect data on any pregnancy exposed to UPA, such as an unrecognized pregnancy before EC intake or following treatment failure.

To date, it is unknown whether UPA is excreted in human breast milk. However, since UPA is a lipophilic compound, this is at least theoretically possible. Therefore, until more data become available, breastfeeding women who require EC and who take UPA are advised not to breastfeed for 36 h following UPA intake [4]. Following high-dose mifepristone, breastfeeding is not contraindicated based on mifepristone concentration in breast milk [109]. For LNG, the corresponding recommendation is to avoid breastfeeding for at least 8 h but not more than 24 h after LNG intake [110].

If pregnancy occurs with a Cu-IUD in place, the IUD should be removed as soon as possible. If the removal is done without inducing contractions and miscarriage, there does not seem to be any adverse effect on the continuing pregnancy [111].

9. Discussion

Although the main mechanism of action of both LNG and UPA is preventing follicular rupture and ovulation, the ‘window of effect’ for LNG EC is rather narrow. It begins after selection of the dominant follicle, but ends before LH begins to rise. LNG, if taken at the time when LH has already started to rise, cannot prevent ovulation and has no effect on the endometrium or other postovulatory events [52,85]. Consequently, it is ineffective to prevent pregnancy. This is also supported by clinical data on women exposed to unprotected intercourse at the time of ovulation. In a study including women at the time they requested EC, LNG was effective to prevent pregnancy if taken prior to the LH peak, while it had no effect when intercourse occurred on day LH −1 to 0 and LNG was taken on day LH +2 based on endocrine data [36]. Therefore, due to its limited window of action, although LNG is well tolerated and easily accessible, there is still a need to develop more effective EC methods. In contrast to LNG, UPA has been demonstrated to have a direct inhibitory effect on follicular rupture. This allows UPA to be effective even when administered shortly before ovulation, when the LH surge has already started to rise, a time period when use of LNG is no longer effective.

The main mechanism of action of the Cu-IUD is to prevent fertilization due to the effect of Cu ions on sperm viability and function. However, the effects on the oocyte and endometrium may contribute to its high efficacy and prevent pregnancy also if the unprotected intercourse takes place at the time when ovulation has already occurred [112]. The mechanism of action is likely partially different when the Cu-IUD is inserted postcoitally compared to preventing pregnancy when used as a regular ongoing contraceptive.

Knowledge on the mechanisms of action of EC is also important for their correct use. While the Cu-IUD offers immediate long-acting effective contraception, the duration of effect of the hormonal methods is limited. Since the main action of LNG and UPA is to delay ovulation without any effect on the endometrium, follicular development and ovulation usually resume within a week following its use. Thus, further acts of unprotected sex should be avoided in order to avoid unwanted pregnancy.

To prevent an unwanted pregnancy after unprotected intercourse at any time during the menstrual cycle, insertion of a Cu-IUD should be offered for EC and continuing long-term contraception if possible. Among the hormonal methods, a single dose of 30 mg UPA should be recommended for use as soon as possible and no later than 120 h (5 days) after intercourse. Further acts of unprotected intercourse after ECP use should be avoided to prevent the risk of having a delayed follicular rupture and ovulation. Regular contraception should be resumed/started as soon as possible after EC use. Backup contraception should be used for the initial 14 days. If UPA is not available, LNG EC offers a well-tolerated, and in many places easily accessible, alternative.

Taken together, there is still a need to develop more effective EC methods. To ensure the highest efficacy and to cover the entire window of fertility, the ideal agents for EC also need to target the endometrium and should be possible to use on demand pre- or postcoitally.

10. Conclusion

In conclusion, EC with a single dose of 1.5 mg LNG or 30 mg UPA acts through inhibition of or postponing ovulation but does not prevent fertilization or implantation and has no adverse effect on a pregnancy. The window of action of UPA seems wider than that for LNG since it may, in addition, prevent an ovulation after LH has started to rise. The main mechanism of action of Cu-IUD when used for regular contraception is prevention of fertilization. In addition and in contrast to the hormonal methods, Cu-IUD also has an effect on the uterine fluid/ endometrium which is likely to contribute to the high contraceptive efficacy when used for EC. Increased knowledge of the mechanism of action could hopefully increase the acceptability and, thus, availability of EC to offer women a chance to prevent an unwanted pregnancy.
Acknowledgment

KGD has served on Medical Advisory Boards of HRA-Pharma and Bayer on matters related to emergency contraception.

References

[10] KGD has served on Medical Advisory Boards of HRA-Pharma and Bayer on matters related to emergency contraception.


