ELSEVIER

Contraception xx (2012) xxx–xxx

Contraception

Review article

Emergency contraception — mechanisms of action

Kristina Gemzell-Danielsson*, Cecilia Berger, P.G.L. Lalitkumar

Department of Women's and Children's Health, Division of Obstetrics and Gynecology, Karolinska Institutet/ Karolinska University Hospital, S-171 76 Stockholm, Sweden

Received 8 July 2012; accepted 20 August 2012

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.

Keywords: Emergency contraception; Cu-IUD; Endometrial function; Implantation; Levonorgestrel; Ovulation; Mifepristone; Ulipristal acetate

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

* Corresponding author. Tel.: +46 851779539.
E-mail address: kristina.gemzell@ki.se (K. Gemzell-Danielsson).

0010-7824/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.contraception.2012.08.021

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, itraconazole, 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 effect on the number of motile spermatozoa recovered from the human fallopian tubes in vitro, their adhesion to the tubal epithelium, distribution or acrosome reaction rate [45].

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 contractility 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 extrauterine 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).

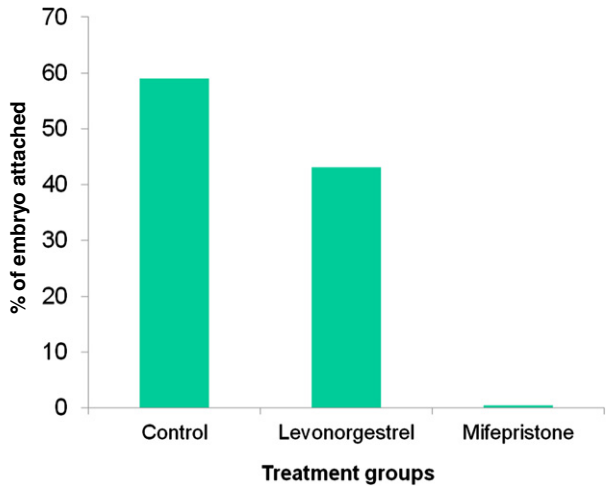

Fig. 1. In vitro model for human embryo implantation shows that treatment of the endometrial cell culture with LNG (10^{-5}M) showed no significant reduction in embryo attachment rate compared with the control group in which only the vehicle was added. No embryo was attached in the group of cultures treated with a high dose of mifepristone (10^{-5}M). This study shows that LNG has no effect on endometrial recptivity. Modified from Ref. [72].

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

[1] Consensus statement of emergency contraception. Consortium for Emergency Contraception Contraception 1995;52:211–3.
[2] Yuzpe AA, Lance WJ. Ethinylestradiol and DL-norgestrel as a potential contraceptive. Fertil Steril 1977;28:932–6.
[3] World Health Organization. Task Force on Post-ovulatory Methods for Fertility Regulation. Randomized controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Lancet 1998;352:428–33.
[4] Gemzell-Danielsson K, Meng CX. Emergency contraception: potential role of ulipristal acetate. Int J Womens Health 2010;9(2): 53–61.
[5] Cameron ST, Gordon R, Glasier A. The effect on use of making emergency contraception available free of charge. Contraception 2012:22464407 [PMID].
[6] Polis CB, Schaffer K, Blanchard K, Glasier A, Harper CC, Grimes DA. Advance provision of emergency contraception for pregnancy prevention. Cochrane Database Syst Rev 2007;2:CD005497 Review.
[7] Raymond EG, Trussell J, Polis CB. Population effect of increased access to emergency contraceptive pills: a systematic review. Obstet Gynecol 2007;109:181–8.
[8] Gemzell-Danielsson K, Marions L. Mechanisms of action of mifepristone and levonorgestrel when used for emergency contraception. Hum Reprod 2004;10:341–8.
[9] Gemzell-Danielsson K. Mechanism of action of emergency contraception. Contraception 2010;82:404–9.
[10] Cremer M, Masch R. Emergency contraception: past, present and future. Minerva Ginecol 2010;62:361–71.
[11] Blumenthal PD, Voedisch A, Gemzell-Danielsson K. Strategies to prevent unintended pregnancy: increasing use of long-acting reversible contraception. Hum Reprod Update 2011;17:121–37.
[12] Cheng L, Gülmezoglu AM, Piaggio G, Ezcurra E, VanLook PF. Interventions for emergency contraception. Cochrane Database Syst Rev 2008;16:CD001324.
[13] Morris JM, Van Wagenen G. Compounds interfering with ovum implantation and development. 3. The role of estrogens. Am J Obstet Gynecol 1966;15(96):804–15.
[14] Glasier A, Thong KJ, Dewar M, Mackie M, Baird D. Mifepristone (RU 486) compared with high-dose estrogen and progesterone for emergency postcoital contraception. N Engl J Med 1992;327: 1041–4.
[15] Webb AM, Russell J, Elstein M. Comparison of Yuzpe regimen, danazol and mifepristone (RU486) in oral postcoital contraception. Br Med J 1992;305:927–31.
[16] Lippes J, Tatum HJ, Maulik D, Sielezny M. Postcoital copper IUDs. Adv Plan Parent 1979;14:87–94.
[17] World Health Organization Task Force on Post-ovulatory Methods for Fertility Regulation. Comparison of three single doses of mifepristone as emergency contraception: a randomised trial. Lancet 1999;353:697–702.
[18] Blithe DL, Nieman LK, Blye RP, Stratton P, Passaro M. Development of the selective progesterone receptor modulator CDB-2914 for clinical indications. Steroids 2003;68:1013–7.
[19] IUD most effective post-coital contraception. [No authors listed]. Contracept Technol Update 1995;16:78–80.
[20] Wu S, Godfrey EM, Wojdyla D, et al. Copper T380A intrauterine device for emergency contraception: a prospective, multicentre, cohort clinical trial. BJOG 2010;117:1205–10.
[21] Zhou L, Xiao B. Emergency contraception with Multiload Cu-375 SL IUD: a multicenter clinical trial. Contraception 2001;64:107–12.
[22] Harper CC, Speidel JJ, Drey EA, Trussell J, Blum M, Darney PD. Copper intrauterine device for emergency contraception: clinical practice among contraceptive providers. Obstet Gynecol 2012;119: 220–6.
[23] Wright RL, Frost CJ, Turok DK. A qualitative exploration of emergency contraception users' willingness to select the copper IUD. Contraception 2012;85:32–5.
[24] Ho PC, Kwan MS. A prospective randomized comparison of levonorgestrel with the Yuzpe regimen in post-coital contraception. Hum Reprod 1993;8:389–92.
[25] Arowojolu AO, Okewole IA, Adekunle AO. Comparative evaluation of the effectivene1ss and safety of two regimens of levonorgestrel for emergency contraception in Nigerians. Contraception 2002;66: 269–73.
[26] von Hertzen H, Piaggio G, Ding J, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. Lancet 2002;360:1803–10.
[27] Xiao BL, Von Hertzen H, Zhao H, Piaggio G. A randomized double-blind comparison of two single doses of mifepristone for emergency contraception. Hum Reprod 2002;17:3084–9.
[28] Hamoda H, Ashok PW, Stalder C, Flett GM, Kennedy E, Templeton A. A randomized trial of mifepristone (10 mg) and levonorgestrel for emergency contraception. Obstet Gynecol 2004;104:1307–13.
[29] Ngai SW, Fan S, Li S, et al. A randomized trial to compare 24 h versus 12 h double dose regimen of levonorgestrel for emergency contraception. Hum Reprod 2005;20:307–11.
[30] Ashok PW, Stalder C, Wagaarachchi PT, Flett GM, Melvin L, Templeton A. A randomised study comparing a low dose of mifepristone and the Yuzpe regimen for emergency contraception. BJOG 2002;109:553–60.
[31] Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet 2010;375:555–62.
[32] Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. NEJM 1995;333: 1517–21.
[33] Gould JE, Overstreet JW, Hanson FW. Assessment of human sperm function after recovery from the female reproductive tract. Biol Reprod 1984;31:888–94.
[34] Wilcox AJ, Baird DD, Dunson DB, McConnaughey DR, Kesner JS, Weinberg CR. On the frequency of intercourse around ovulation: evidence for biological influences. Hum Reprod 2004;19:1539–43.
[35] Trussell J, Rodríguez G, Ellertson C. New estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception 1998;57:363–9.
[36] Novikova N, Weisberg E, Stanczyk FZ, Croxatto HB, Fraser IS. Effectiveness of levonorgestrel emergency contraception given before or after ovulation–a pilot study. Contraception 2007;75:112–8.
[37] Wilcox AJ, Dunson D, Baird DD. The "fertile window" in the menstrual cycle: day specific estimates from a prospective study. BMJ 2000;18(321):1259–62.
[38] Yeung WSB, Chiu PCN, Wang CHYQ, Yao YQ, Ho PC. The effects of levonorgestrel on various sperm functions. Contraception 2002;66:453–7.
[39] do Nascimento JA, Seppala M, Perdigão A, et al. In vivo assessment of the human sperm acrosome reaction and the expression of glycodelin-A in human endometrium after levonorgestrel-emergency contraceptive pill administration. Hum Reprod 2007;22:2190–5.
[40] Bahamondes L, Nascimento JAA, Munuce MJ, Fazano F, Faundes A. The in vitro effect of levonorgestrel on the acrosome reaction of human spermatozoa from fertile men. Contraception 2003;68:55–9.
[41] Uhler ML, Leung A, Chan SY, Wang C. Direct effects of progesterone and antiprogesterone on human sperm hyperactivated motility and acrosome reaction. Fertil Steril 1992;58:1191–8.

[42] Kesserü E, Camacho-Ortega P, Laudahn G, Schopflin G. In vitro action of progestogens on sperm migration in human cervical mucus. Fertil Steril 1975;26:57–61.
[43] Garmendia F, Westphal N, Parada J. The hormonal and peripheral effects of dl-norgestrel in postcoital contraception. Contraception 1974;10:411–24.
[44] Kunz G, Beil D, Deininger H, Wildt L, Leyendecker G. The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hystero-salpingoscintigraphy. Hum Reprod 1996;11:627–32.
[45] Hermanny A, Bahamondes MV, Fazano F, et al. In vitro assessment of some sperm function following exposure to levonorgestrel in human fallopian tubes. Reprod Biol Endocrinol 2012;10:8.
[46] Ortiz ME, Croxatto HB, Bardin CW. Mechanisms of action of intrauterine devices. Obstet Gynecol Surv 1996;51:S42–51.
[47] Roblero L, Guadarrama A, Lopez T, Zegers-Hochschild F. Effect of copper ion on the motility, viability, acrosome reaction and fertilizing capacity of human spermatozoa in vitro. Reprod Fertil Dev 1996;8:871–4.
[48] Ullmann G, Hammerstein J. Inhibition of sperm motility in vitro by copper wire. Contraception 1972;6:71–6.
[49] Kesserü E, Camacho-Ortega P. Influence of metals on in vitro sperm migration in the human cervical mucus. Contraception 1972;6: 231–40.
[50] Hefnawi F, Kandil O, Askalani H, Serour G. Influence of the copper IUD and the Lippes loop on sperm migration in the human cervical mucus. Contraception 1975;11:541–7.
[51] Ortiz ME, Croxatto HB. Copper-T intrauterine device and levonorgestrel intrauterine system: biological bases of their mechanism of action. Contraception 2007;75:S16–30.
[52] Marions L, Hultenby K, Lindell I, Sun X, Stabi B, Gemzell Danielsson K. Emergency contraception with mifepristone and levonorgestrel: mechanism of action. Obstet Gynecol 2002;100:65–71.
[53] Marions L, Cekan C, Bygdeman M, Gemzell Danielsson K. Preovulatory treatment with mifepristone and levonorgestrel impairs luteal function. Contraception 2004;69:373–7.
[54] Hapangama DK, Glasier AF, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. Contraception 2001;63:123–9.
[55] Müller AL, Llados CM, Croxatto HB. Postcoital treatment with levonorgestrel does not disrupt postfertilization events in the rat. Contraception 2003;67:415–9.
[56] Spitz IM, Croxatto HB, Salvatierra AM, Heikinheimo O. Response to intermittent RU486 in women. Fertil Steril 1993;59:971–5.
[57] Liu JH, Garzo G, Morris S, Stuenkel C, Ulmann A, Yen SS. Disruption of follicular maturation and delay of ovulation after administration of the antiprogesterone RU486. J Clin Endocrinol Metab 1987;65:1135–40.
[58] Shoupe D, Mishell Jr DR, Page MA, Madkour H, Spitz IM, Lobo RA. Effects of the antiprogesterone RU 486 in normal women. II. Administration in the late follicular phase. Am J Obstet Gynecol 1987;157:1421–6.
[59] Swahn ML, Johannisson E, Daniore V, de la Torre B, Bygdeman M. The effect of RU 486 administered during the proliferative and secretory phase of the cycle on the bleeding pattern, hormonal parameters and the endometrium. Hum Reprod 1988; 3:915–21.
[60] Ghosh D, Kumar PG, Sengupta J. Early luteal phase administration of mifepristone inhibits preimplantation embryo development and viability in the rhesus monkey. Hum Reprod 1997;12:575–82.
[61] Batista MC, Cartledge TP, Zellmer AW, Nieman LK, Merriam GR, Loriaux DL. Evidence for a critical role of progesterone in the regulation of the midcycle gonadotropin surge and ovulation. J Clin Endocrinol Metab 1992;74:565–70.
[62] Brache V, Cochon L, Jesam C, et al. Immediate pre-ovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture. Hum Reprod 2010;25:2256–63.
[63] Stratton P, Hartog B, Hajizadeh N, et al. A single mid-follicular dose of CDB-2914, a new antiprogestin, inhibits folliculogenesis and endometrial differentiation in normally cycling women. Hum Reprod 2000;15:1092–9.
[64] Adams CE. J A study of fertilization in the rabbit: the effect of post-coital ligation of the fallopian tube or uterine horn. Endocrinol 1956;13:296–308.
[65] Croxatto HB, Díaz S, Fuentealba B, Croxatto HD, Carrillo D, Fabres C. Studies on the duration of egg transport in the human oviduct. I. The time interval between ovulation and egg recovery from the uterus in normal women. Fertil Steril 1972;23:447–58.
[66] Norwitz ER, Schust DJ, Fisher SJ. Implantation and the survival of early pregnancy. N Engl J Med 2001;345:1400–8.
[67] Smotrich DB, Stillman RJ, Widra EA, et al. Immunocytochemical localization of growth factors and their receptors in the human pre-embryos and Fallopian tubes. Hum Reprod 1996;11:184–90.
[68] Christow A, Sun X, Gemzell-Danielsson K. Effect of mifepristone and levonorgestrel on expression of steroid receptors in the human Fallopian tube. Mol Hum Reprod 2002;8:333–40.
[69] Mahmood T, Saridogan E, Smutna S, Habib AM, Djahanbakhch O. The effect of ovarian steroids on epithelial ciliary beat frequency in the human Fallopian tube. Hum Reprod 1998;13:2991–4.
[70] Wånggren K, Stavreus-Evers A, Olsson C, Andersson E, Gemzell-Danielsson K. Regulation of muscular contractions in the human Fallopian tube through prostaglandins and progestagens. Hum Reprod 2008;23:2359–68.
[71] Cleland K, Raymond E, Trussell J, Cheng L, Zhu H. Ectopic pregnancy and emergency contraceptive pills: a systematic review. Obstet Gynecol 2010;115:1263–6.
[72] Lalitkumar PGL, Lalitkumar S, Meng CX, et al. Mifepristone but not levonorgestrel inhibits human blastocyst attachment to an in vitro endometrial three-dimensional cell culture model. Hum Reprod 2007;22:3031–7.
[73] Psychoyos A, Prapas I. Inhibition of egg development and implantation in rats after post-coital administration of the progesterone antagonist RU 486. J Reprod Fertil 1987;80:487–91.
[74] Wolf JP, Danforth DR, Ulmann A, Baulieu EE, Hodgen GD. Contraceptive potential of RU486 by ovulation inhibition II. Supression of pituitary gonadotropin secretion in vitro. Contraception 1989;40:185–93.
[75] Messinis IE, Templeton A. The effect of the antiprogestin mifepristone (RU486) on maturation and in-vitro fertilization of human oocytes. Br J Obstet Gynaecol 1988;95:592–5.
[76] Larsson B, Hamberger L. The concentration of copper in human uterine secretion during four years after insertion of a copper-containing intrauterine device. Fertil Steril 1977;28:624–6.
[77] Wollen AL, Sandvei R, Skare A, Justesen NP. The localization and concentration of copper in the fallopian tube in women with or without an intrauterine contraceptive device. Acta Obstet Gynecol Scand 1994;73:195–9.
[78] Larsson B, Ljung B, Hamberger L. The influence of copper on the in vitro motility of the human Fallopian tube. Am J Obstet Gynecol 1976;125:682–90.
[79] Alvarez F, Brache V, Fernandez E. New insights on the mode of action of intrauterine contraceptive devices in women. Fertil Steril 1988;49:768–73.
[80] Miller JF, Williamson E, Glue J, Gordon YB, Grudzinskas JG, Sykes A. Fetal loss after implantation. A prospective study. Lancet 1980;13(2):554–6.
[81] Tabibzadeh S, Shea W, Lessey BA, Broome J. From endometrial receptivity to infertility. Semin Reprod Endocrinol 1999;17:197–203.
[82] Giudice LC. Potential biochemical markers of uterine receptivity. Hum Reprod 1999;14(Suppl 2):3–6.
[83] Palomino WA, Kohen P, Devoto L. A single midcycle dose of levonorgestrel similar to emergency contraceptive does not alter the expression of the L-selectin ligand or molecular markers of endometrial receptivity. Fertil Steril 2010;94:1589–94.

[84] Durand M, del Carmen Cravioto M, Raymond EG, et al. The mechanism of action of short-term levonorgestrel administration in emergency contraception. Contraception 2001;64:227–34.
[85] Meng CX, Marions L, Byström B, Gemzell-Danielsson K. Effects of oral and vaginal administration of levonorgestrel emergency contraception on markers of endometrial receptivity. Hum Reprod 2010;25:874–83.
[86] Vargas MF, Tapia-Pizarro AA, Henríquez SP, et al. Effect of single post-ovulatory administration of levonorgestrel on gene expression profile during the receptive period of the human endometrium. J Mol Endocrinol 2012;48:25–36.
[87] Swahn ML, Gemzell K, Bygdeman M. Contraception with mifepristone. Letter to the Editor. Lancet 1991;338:942–3.
[88] Gemzell Danielsson K, Swahn ML, Svalander P, Bygdeman M. Early luteal phase treatment with RU486 for fertility regulation. Hum Reprod 1993;8:870–3.
[89] GemzellDanielsson K, Svalander P, Swahn ML, Johannisson E, Bygdeman M. Effects of a single-postovulatory dose of RU486 on endometrial maturation in the implantation phase. Hum Reprod 1994;9:2398–404.
[90] Hapangama DK, Brown A, Glasier AF, Baird DT. Feasibility of administering mifepristone as a once a month contraceptive pill. Hum Reprod 2001;16:1145–50.
[91] Gemzell-Danielsson K, Swahn M, Bygdeman M. The effect of various doses of mifepristone on endometrial leukaemia inhibitory factor expression in the midluteal phase — an immunohistochemical study. Hum Reprod 1997;12:1293–7.
[92] Marions L, Gemzell Danielsson K, Swahn M, Bygdeman M. The effect of antiprogestin on integrin expression in human endometrium: an immunohistochemical study. Hum Reprod 1998;4:491–5.
[93] Slayden OD, Nayak NR, Burton KA, et al. Progesterone antagonists increase androgen receptor expression in the rhesus macaque and human endometrium. J Clin Endocrinol Metab 2001;86:2668–79.
[94] Cameron ST, Critchley HO, Buckley CH, Kelly RW, Baird DT. Effect of two antiprogestins (mifepristone and onapristone) on endometrial factors of potential importance for implantation. Fertil Steril 1997;67:1046–53.
[95] Gemzell Danielsson K, Hamberg M. The effect of antiprogestin (RU 486) and prostaglandin biosynthesis inhibitor (naproxen) on uterine fluid prostaglandin F2a concentration. Hum Reprod 1994;9:1626–30.
[96] Swahn ML, Bygdeman M, Xing S, Cekan S, Masironi B, Johannisson E. The effect of RU 486 administered during the early luteal phase on bleeding pattern, hormonal parameters and endometrium. Hum Reprod 1990;5:402–8.
[97] Gemzell Danielsson K, Westlund P, Swahn ML, Bygdeman M, Seppala M. Effect of low weekly doses of mifepristone on ovarian function and endometrial development. Hum Reprod 1996;11:256–64.
[98] Marions L, Gemzell Danielsson K, Swahn ML, Bygdeman M. Contraceptive efficacy of low doses of mifepristone. Fertil Steril 1998;70:813–6.
[99] Marions L, Viski S, Danielsson KG, et al. Contraceptive efficacy of daily administration of 0.5 mg mifepristone. Hum Reprod 1999;14: 2788–90.
[100] Godfrey EM, Mawson JT, Stanwood NL, Fielding SL, Schaff EA. Low-dose mifepristone for contraception: a weekly versus planned postcoital randomized pilot study. Contraception 2004; 70:41–6.
[101] Meng CX, Andersson KL, Bentin-Ley U, Gemzell-Danielsson K, Lalitkumar PG. Effect of levonorgestrel and mifepristone on endometrial receptivity markers in a three-dimensional human endometrial cell culture model. Fertil Steril 2009;91:256–64.
[102] Stratton P, Beth Hartog B, Hajizadeh N, et al. Endometrial effects of a single early-luteal dose of the selective progesterone receptor modulator CDB-2914. Hum Reprod 2000;15:1092–9.
[103] Laundański T, Kobylec E. Akerlund M influence of copper ions on uterine activity. Contraception 1981;24:195–202.
[104] Hagenfeldt K, Johannisson E, Brenner P. Intrauterine contraception with the copper-T device. 3. Effect upon endometrial, morphology. Contraception 1972;6:207–18.
[105] Savaris R, Zettler CG, Ferrari AN. Expression of 4B1 and vB3 integrins in the endometrium of women using the T200 copper intrauterine device. Fertil Steril 2000;74:1102–7.
[106] Videla-Rivero L, Etchepareborda JJ, Kesseru E. Early chorionic activity in women bearing inert IUD, copper IUD and levonorgestrel-releasing IUD. Contraception 1987;36:217–26.
[107] Bracken MB. Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. Obstet Gynecol 1990;76:552–7.
[108] Zhang L, Chen J, Wang Y, Ren F, Yu W, Cheng L. Pregnancy outcome after levonorgestrel-only emergency contraception failure: a prospective cohort study. Hum Reprod 2009;24:1605–11.
[109] Sääv I, Fiala C, Hämäläinen JM, Heikinheimo O, Gemzell-Danielsson K. Medical abortion in lactating women — low levels of mifepristone in breast milk. Acta Obstet Gynecol Scand 2010;89: 618–22.
[110] Gainer E, Massai R, Lillo S, et al. Levonorgestrel pharmacokinetics in plasma and milk of lactating women who take 1.5 mg for emergency contraception. Hum Reprod 2007;22:1578–84.
[111] Brahmi D, Steenland MW, Renner RM, Gaffield ME, Curtis KM. Pregnancy outcomes with an IUD in situ: a systematic review. Contraception 2012;85:131–9.
[112] Stanford JB, Mikolajczyk RT. Mechanisms of action of intrauterine devices: update and estimation of postfertilization effects. Am J Obstet Gynecol 2002;187:1699–708.