ISGE STATEMENT ON EMERGENCY CONTRACEPTION

Mechanisms of action of oral emergency contraception

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Abstract

This review gives an overview of the mechanisms of action of oral emergency contraception pills (ECPs), focusing on the levonorgestrel (LNG) and ulipristal acetate (UPA) containing ECPs. In vivo and in vitro studies have addressed the effect of EC on various possible targets. Based on these studies as well as on clinical trials it is clear that the efficacy of ECPs to prevent an unintended pregnancy depends on their mechanism of action as well as on their use in relation to the fertile window. While the main effect of both available ECPs is to prevent or delay ovulation the window of action for UPA is wider than that of LNG. This provides the biological explanation for the difference observed in clinical trials and the higher efficacy of UPA. Neither LNG nor UPA impairs endometrial receptivity or embryo implantation. Correct knowledge on the mechanism of action of ECPs is important to avoid overestimating their effectiveness and to advise women on correct use.

Introduction

Emergency contraception (EC) is defined as a method used after an unprotected intercourse to prevent pregnancy. Effective postcoital contraception can have many advantages over regular contraceptive methods and is frequently highly accepted by women. Already the author and gynecologist, Soranos of Ephesus, 98–138 AD, described a postcoital method and in his text book on gynecology he stated that “the woman ought, in the moment during coitus when the man ejaculates his sperm, to hold her breath, draw her body back a little so that the semen cannot penetrate into the os uteri, then immediately get up and sit down with bent knees, and in this position, provoke sneezes. She should then wipe out the vagina carefully or drink cold water in addition” [1]. The mechanism of action of the cold water is hard to explain. Clearly, the lack of contraceptive efficacy of vaginal douching and shaking off the sperms makes the use more of a wishful thinking. Also today’s methods of EC are surrounded by myths regarding their mechanisms of action and wishful thinking when it comes to contraceptive efficacy and impact on preventing unintended pregnancy. The difference and impact of mechanisms of action is reflected in the difference in contraceptive efficacy. Here the mechanisms of action of the two most commonly used ECPs, with LNG and UPA, will be discussed.

Options for emergency contraception

Following large randomized controlled trials conducted by the WHO, the levonorgestrel containing emergency contraceptive pill (LNG-EC) replaced the Yuzpe regimen as the standard ECP due to higher efficacy and lower rate of side effects [2,3]. The use of the Yuzpe regimen consisting of EE (100µg) + LNG (0.5 mg) twice, 12 h apart, is now limited to use where there is no access to other options. LNG-EC is administered as a 1.5 mg single dose (which has replaced 0.75 mg, twice, 12 h apart). Since 2009 the progesterone receptor modulator ulipristal acetate (UPA) is available for EC (30 mg tablet in a single dose) in Europe and more recently in the US and in Asia. UPA-EC is recommended as the first choice of ECP, where available, due to its higher efficacy and similar low rate of side effects compared with LNG-EC. The use of mifepristone for EC in doses of 10 mg or more is limited to China. The most effective EC method which also provides continuous highly effective contraception is the copper intrauterine device (Cu-IUD) [4]. However, access to this is frequently limited due to barriers such as lack of trained health care providers and poor availability.

Potential targets for EC and the window of fertility

Since sperms can survive up to 5 days (120 h) and the oocyte is viable and fertilization is possible for 12–24 h after ovulation, the window of conception is about 6 days wide, starting on cycle day LH = 5 and ending on cycle day LH +1. The probability of conception in relation to the day of ovulation was described by Wilcox et al., who could show that the highest number of conceptions occurred following intercourse on the two days preceding ovulation and the day of ovulation. Of relevance for EC use is also the finding by the same group, that even women with regular cycles frequently ovulated outside of the expected window [5]. It may also be relevant to point out that intercourse post ovulation, does not result in pregnancy. This fact is frequently misunderstood as an effect of EC in preventing implantation. Possible targets for EC includes sperm transport and function, follicular development, ovulation, fertilization, embryo development and transport, endometrial receptivity, implantation and the corpus luteum. However, to be highly effective and based on the fertile window, a method used for EC also needs to act beyond...
reaction of capacitated human spermatozoa in vitro

Furthermore, although progesterone triggers acrosome reaction, an antagonist action of UPA is unlikely [16]. UPA contained medium, in a concentration corresponding to the plasma levels seen after UPA-EC intake (∼100–200 ng/ml), did not modify the signal transduction of tyrosine phosphorylation involved in sperm capacitation and spontaneous acrosomal reaction, which was not significantly different from spermatozoa exposed to control medium. Furthermore, UPA did not prevent human follicular fluid (hFF)-induced acrosomal reaction. Thus, UPA showed no agonist effect (no induction of acrosomal reaction). Since progesterone in hFF is essential for acrosomal reaction induction, and UPA did not prevent the hFF-induced acrosomal reaction, an antagonist action of UPA is unlikely [16].

A beneficial effect of low levels of oxidative stress on sperm-oocyte fusion has previously been described. Incubation of motile spermatozoa under capacitating conditions in control medium resulted in significantly increased percentage of fragmented DNA. In the presence of UPA, DNA fragmentation decreased significantly in a dose-dependent manner. In EC concentrations UPA also counteracted the effect of induced oxidative stress and prevented DNA fragmentation while no effect was seen on sperm vitality, lipid peroxidation or induced-acrosome reaction [17].

Cervical mucus viscosity

While a well-known contraceptive action of regular contraception with gestagen is an increased viscosity of the cervical mucus, this effect is not seen until 9 h following postcoital use of LNG and therefore unlikely to be a main action of EC [18].

Follicular development and ovulation

Studies in premenopausal, healthy women with proven fertility with daily monitoring of hormonal levels and follicular growth have shown that LNG-EC interrupts development of the dominant follicle if given before the onset of the LH peak. Depending on the timing of treatment, variable effects are seen on follicular growth with delayed development, inhibited growth or a persistent unruptured follicle. If given after the onset of the LH peak, LNG is ineffective to inhibit ovulation [19,20].

UPA given in mid-follicular phase inhibits or delays folliculogenesis and steroidogenesis depending on the time of administration in relation to the LH peak. In contrast to LNG, UPA given at LH onset or after LH has started to rise will also result in inhibition of follicular rupture. If given at a follicular diameter of 18 mm or more ovulation is delayed by five days in 59% of women [21]. In contrast, by the time the leading follicle reaches 15–17 mm, follicular rupture was prevented within 5 days no more often after LNG administration than after placebo administration [22]. If given at or after LH has peaked, UPA cannot prevent ovulation [21]. In mice, the direct action of UPA on progesterone receptor A is responsible for the inhibition of follicular rupture induced by UPA [23] (Figure 2).

Effects on the fallopian tube and endometrium

Progesterone regulates tubal transport in vitro through effects on muscular contractions and cilia activity. Cilia from the human fallopian tube beat slower after treatment with high doses of progesterone, an effect that can be reversed by mifepristone. A dose-dependent effect of LNG and mifepristone was shown on muscular contractility in vitro with no effects of doses relevant for EC [24]. This is in line with data from 136 studies on mifepristone or LNG use in humans with 0.6% and 1% of pregnancies, respectively, being ectopic – not exceeding the rate in the general population [25].

To study the effects of post-ovulatory exposure to EC on endometrial receptivity, an in vivo model was developed (Figure 2). Neither endometrial histology nor suggested markers of endometrial receptivity were significantly affected by LNG-EC administered on cycle day LH+2. The same results were observed with vaginal or repeat oral doses of LNG (0.75 mg × 4 p.o., or 1.5 mg p.v) [19,26]. In line with these results, post-ovulatory LNG caused minimal changes in gene expression during the receptive period. Neither the magnitude nor the nature or direction of the changes endorses the hypothesis that LNG interferes with
endometrial receptivity [27]. UPA can be used in early-luteal phase to show dose-dependent effects with no significant endometrial effects observed following exposure to doses relevant for EC [28].

To be able to study the effect of EC on human implantation, an in vitro three-dimensional implantation model has been developed. In this model, it has been demonstrated that LNG or UPA at EC concentrations have no effect on the human embryos or endometrial receptivity and cannot impair or prevent implantation [29]. Furthermore, LNG has shown to have no effects on pregnancy or the newborn [26,30,31]. The same is true for the more limited observational data available for UPA exposure during pregnancy (Data on file HRA-Pharma).

Discussion and conclusion

Taken together, the contraceptive effect of LNG or UPA used for EC is due to the effect on ovarian function (inhibited or postponed ovulation). In contrast to LNG, UPA has a wider window of action with an effect also after LH has started to increase why UPA is more effective in postponing ovulation. Neither LNG nor UPA in the doses used for EC have any clinically significant effects on the endometrium in vivo and does not inhibit embryo implantation in vitro. While UPA is more effective than LNG to postpone ovulation, the lack of effect post ovulation makes it less effective than the Cu-IUD. Furthermore, the return of ovulation and lack of effect on the endometrium of the ECPs leaves the woman without protection in case of further acts of unprotected intercourse.

Knowledge about the efficacy and mechanisms of action of EC is crucial for correct clinical recommendations and use. Frequently misunderstanding of the action of ECPs leads to overestimating their contraceptive efficacy. An ideal ECP should be safe and effective, highly accepted, easy to use and available without prescription to allow use as soon as possible and within 120 hours of unprotected intercourse. To increase the efficacy of ECPs, their action would need to be improved and to involve an effect on endometrial receptivity.

Declaration of interest

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References