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Review article

Mechanism of action of emergency contraception

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Abstract

A major barrier to the widespread acceptability and use of emergency contraception (EC) are concerns regarding the mechanisms of action of EC methods. Today, levonorgestrel (LNG) in a single dose of 1.5 mg taken within 120 h of an unprotected intercourse is the most widely used EC method worldwide. It has been demonstrated that LNG-EC acts through an effect on follicular development to delay or inhibit ovulation but has no effect once luteinizing hormone has started to increase. Thereafter, LNG-EC cannot prevent ovulation and it does not prevent fertilization or affect the human fallopian tube. LNG-EC has no effect on endometrial development or function. In an in vitro model, it was demonstrated that LNG did not interfere with blastocyst function or implantation.

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

1. Introduction

Emergency contraception (EC) is defined as the use of any drug or device used after an unprotected intercourse to prevent an unwanted pregnancy. Despite the availability of highly effective methods of contraception, a substantial proportion of pregnancies remains unplanned and results in an induced abortion [1]. More than half of unintended pregnancies — an estimated 45.5 million worldwide — are resolved by induced abortion each year [2]. Many women who experience an unplanned pregnancy have become pregnant as a result of either lack of contraceptive use due to various reasons or contraceptive failure. It has been estimated that millions of unwanted pregnancies could be avoided if effective postcoital EC methods were widely accessible [3]. Although this has been questioned and interventions to make EC available has failed in reducing abortion rates [4], it has also been recognized that the use of EC is still underutilized worldwide. A major barrier to the widespread acceptability and use of EC is concern regarding the mechanisms of action of EC methods. Although a number of available contraceptive methods are effective when used for EC, the knowledge of the mechanism underlying the contraceptive effects remains incomplete [5]. The objective of this review is to give an overview of the effect of EC on female reproductive functions. The focus will be mainly on levonorgestrel (LNG) which is the most widely used EC method worldwide although other alternatives will also be discussed.

2. EC methods

One of the earliest recommendations on EC use can be found in the first textbook on Obstetrics and Gynecology authored by the gynecologist Soranos of Ephesos (98–138 AD). 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" [6]. Since then, methods used postcoitally have included stilbestrol, ethinyl estradiol and LNG, danazol and mifepristone [7–10] or insertion of a copper intrauterine device (IUD) [11]. The hormonal methods are usually considered as more convenient than the insertion of a copper IUD which is otherwise the most effective method. In the late 1970s, Yuzpe and Lance introduced a regimen consisting of 0.1 mg ethinylestradiol and 0.5 mg LNG, given within 72 h

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of the intercourse and repeated after 12 h [8]. The Yuzpe regimen remained the standard hormonal EC method until the introduction of treatment with LNG only or mifepristone which were shown to be associated with less side effects and higher efficacy than the Yuzpe regimen [12,13]. Today, LNG is the gold standard for oral EC. LNG is to be administered within 72 h (can be extended to 120 h) of an unprotected intercourse, 1.5 mg either as a single dose (preferable) or in two doses of 0.75 mg LNG 12 h apart [14]. This regimen is estimated to reduce the risk of pregnancy by 57–93% [15,16]. Pregnancy rates did not differ between mifepristone and LNG treatment in divided or single doses when taken within 5 days of unprotected intercourse (1.5%). Side effects were mild and similar between treatment groups. However, the potential of mifepristone for EC is limited due to social and political reasons. Mifepristone in low doses (10, 25 or 50 mg) for EC is only available in China.

Recently, a new class of a second generation progesterone receptor modulator Ulipristal acetate (UPA) has been developed and approved for EC treatment. UPA-EC has been shown to be associated with a lower pregnancy rate compared to LNG-EC when used up to 120 h after an unprotected intercourse [17]. UPA is a progesterone receptor modulator that is a derivative of 19-norprogesterone and was developed to have enhanced specificity for the progesterone receptor (PR). The pharmacodynamic properties of UPA in humans reflect the mixed progesterone agonistic/antagonistic profile of the molecule [18].

3. The fertile window

It is only during a limited period during the menstrual cycle that unprotected intercourse may result in a pregnancy [19]. The high-risk fertile phase extends from 5 days before ovulation to the day of ovulation. Fertilization must occur within 12–24 h of ovulation, 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 [20]. Thus, possible targets for EC are:

- Sperm function
- Follicle maturation and ovulation
- Fertilization, zygote development and transport in the fallopian tube
- Endometrial receptivity and embryo implantation
- Corpus luteum function

In assessing the efficacy of EC, the variability of ovulation has to be taken into account. Furthermore, a major discrepancy between women's self-report of stage of the cycle and the dating calculation based on endocrine data was shown in a clinical trial on the effectiveness of EC [21]. Studies have also shown that the frequency of intercourse in the menstrual cycle peaks during the fertile window [22], rendering it likely that in a population of women administered EC, a significant proportion are at least at some risk of pregnancy. Therefore, EC should be recommended at any time during the cycle after any act of unprotected intercourse or contraceptive accident.

4. Effects on human sperm function

In vitro data indicate that LNG in doses relevant for EC have no direct effect on sperm function [23,24]. The observations described by Kesserü et al. [25,26] 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 sperms can be retrieved from the fallopian tube within minutes after insemination [26,27]. Furthermore, it was recently reported that viable spermatozoa were found in the female genital tract 24–28 h after intake of LNG [28].

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 administrated at days LH-2 or LH-3, the LH peak was inhibited or delayed and blunted [29,30] (Fig. 1). The effect on follicular development varied between the 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 [31,32]. Similar results were obtained in the rat and monkey where the closer to ovulation the treatment was given, the less was the effect [20]. 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 1–10 mg, ovulation is delayed but not necessarily abolished

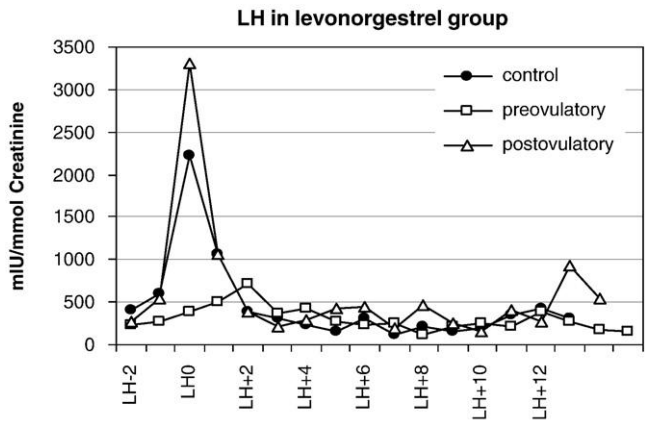

Fig. 1. LH in control and following preovulatory (LH-2) and postovulatory (LH+2) treatment with 1.5 mg levonorgestrel.

[29,33]. At higher doses, 200–600 mg, a new follicle is often recruited [34,35]. 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 [36,37]. At the pituitary level, mifepristone does not block the "rise" in progesterone, it blocks the ability of progesterone to act on PR in the pituitary to facilitate the LH surge [38,39].

6. Effects on the fallopian tube

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 [40]. Too rapid or too slow tubal transport could also be expected to cause desynchronization between the embryo and the tube and/or the blastocyst and the endometrium. A spatially dependent expression of PRs has been shown in the human fallopian tube [41]. Higher levels of receptors are being expressed in the isthmic region than the ampullar region of the tube on days LH+4 to +6. Progesterone has been shown to regulate tubal transport in vitro. Cilia from the human fallopian tube beat significantly slower after treatment with high doses of progesterone, an effect that could be reversed by mifepristone [42,43]. Treatment with LNG (1.5 mg) on day LH+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 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 less pronounced and restricted to the epithelial cells [41].

Exposure of mifepristone to monkey embryos did not affect embryo development or their ability to implant [44]. To investigate if mifepristone interferes with gonadotrophin-induced oocyte maturation and fertilization in humans, clomiphene was given for 5 days for stimulation of follicular growth to 40 volunteers [45]. On Day 16, 20 women received 100 mg mifepristone 1 h before induction of ovulation with injection of 5000 IU of Human Chorionic Gonadothopin (hCG). Laparoscopy (for tubal sterilization) was performed 34 h after hCG and all follicles with a diameter of .15 mm were aspirated, and collected oocytes were submitted to in vitro fertilization (IVF). The 20 women not receiving mifepristone served as a control group. The number of retrieved oocytes, the rate of fertilization and the cleavage rate did not differ between the mifepristone-treated group and the controls.

7. Endometrial receptivity and embryo implantation

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 mid-luteal phase at the expected time of endometrial receptivity and implantation [46].

The dose-dependent endometrial effects of mifepristone administered postovulatory has been investigated in several studies. Once-a-month treatment with a single dose of 200 mg mifepristone on day LH +2 has been shown to be an effective contraceptive method [47–50]. Early luteal phase treatment causes pronounced changes in endometrial development and function [51–55]. The normal menstrual rhythm remained undisturbed and serum levels of estradiol and progesterone were essentially unchanged [56]. Treatment with 5 mg mifepristone once a week or 0.5 mg daily was administered for three cycles; ovulation was not inhibited but endometrial development was retarded or desynchronized [57,58] An increase in PR levels was observed as well as impaired secretory activity. Both regimens were shown to significantly impair fertility although not sufficient for contraceptive use [59,60]. When a single dose of 10 mg mifepristone was administered on day LH +2, the observed effect on the endometrium showed individual variation but only minor effects on the endometrium [29]. Consistent with this finding, repeat administration of 10 mg mifepristone once a week was not effective to prevent pregnancy [61].

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 [62,63] (Fig. 2). Our in vitro study shows that the molecular profile of this three-dimensional endometrial construct is similar to the receptive endometrium in vivo. Exposure to a high concentration of mifepristone caused significant changes in the in vitro luminal epithelium and resulted in inhibition of blastocyst attachment. In contrast, LNG had no effect on blastocyst viability or hatching and did not prevent blastocyst attachment and early implantation (Fig. 3).

8. Corpus luteum function and pregnancy

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. 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 [64].

9. UPA for EC

In a series of clinical trials, the effect of UPA at different follicular diameters and in relation to the LH peak and ovulation was studied [65]. When given prior to the

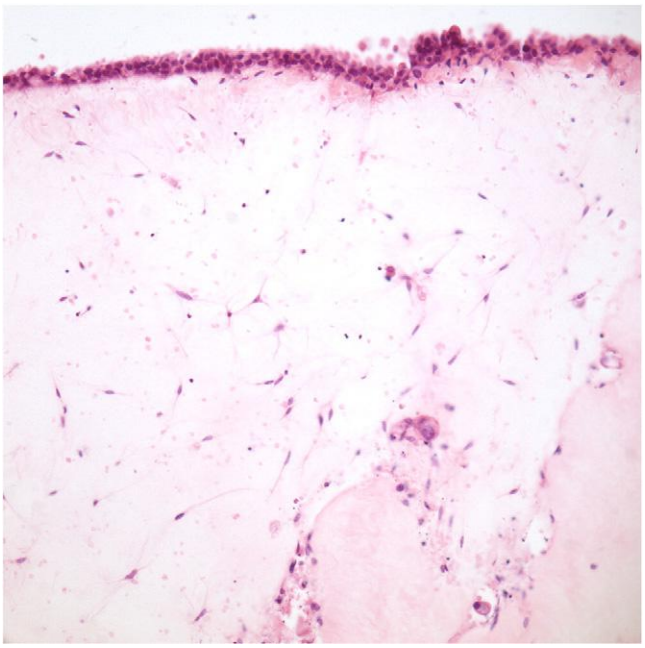

Fig. 2. Section of the three-dimensional endometrial construct showing stromal and epithelial cells.

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 5–6 days following treatment in 44–59%. Even on the day of the LH peak, UPA could delay ovulation for 24–48 h after administration [65]. 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 immediately before ovulation when LH has already started to rise, a time when LNG is no longer effective.

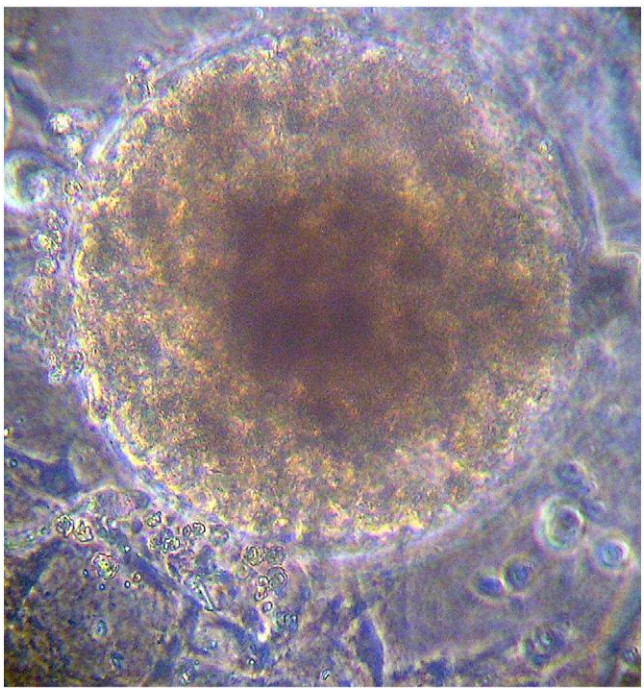

Fig. 3. A human blastocyst implanting into the endometrium in vitro.

The effect of UPA on the endometrium has also been demonstrated to be dose-dependent. Treatment with 10–100 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 were similar to that of placebo [66].

10. Discussion

Taken together, 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 post-ovulatory events. 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 [21]. In a clinical trial on LNG-EC, women were recruited at the time they presented with a request for EC and the effectiveness of Emergency Contraceptive Pills (ECP) when taken before and after ovulation was determined. A blood sample was taken immediately prior to ingestion of LNG 1.5 mg in a single dose for estimation of serum LH, estradiol and progesterone levels to calculate the day of ovulation. Three women became pregnant despite taking the ECP (pregnancy rate, 3.0%). All three women who became pregnant had unprotected intercourse between one day prior to and on the day of ovulation and took the ECP on day ovulation +2, based on the endocrine data. Among 17 women who had intercourse in the fertile period of the cycle and took the ECP after ovulation occurred (on Days +1 to +2), three or four pregnancies could have been expected and three were observed. Among 34 women who had intercourse on Days −5 to −2 of the fertile period and took ECP before or on the day of ovulation, four pregnancies could have been expected, but none were observed. 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. To ensure the highest efficacy and to cover the entire window of fertility, the ideal agents for EC also need to target the endometrium.

11. Conclusion

In conclusion, EC with a single dose of 1.5 mg of LNG acts through inhibition or postponing ovulation but does not prevent fertilization or implantation and has no adverse effect on a pregnancy. 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 and thus reduce the number of induced abortions.

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