Mechanism of Action of Emergency Contraceptive Pills

ECPs do not cause abortion[1] or harm an established pregnancy. Pregnancy begins with implantation according to medical authorities such as the US FDA, the National Institutes of Health[2] and ACOG.[3]

Ulipristal Acetate (UPA)

One study has demonstrated that UPA can delay ovulation.[4] In this study, 34 women were treated when the size of the leading follicle was at least 18 mm. Each woman contributed one cycle treated with placebo and another with UPA. Follicular rupture failed to occur within 5 days following UPA treatment in 20 (59%) subjects while normal ovulation was observed in all women within 5 days after placebo intake. Follicular rupture failed to occur within 5 days after treatment with UPA in all women treated before onset of the LH surge, in 79% of women treated after the onset of the LH surge but before the LH peak, and in 8% of women treated after the LH peak. Another study found that UPA altered the endometrium, but whether this change would inhibit implantation is unknown.[5]

Progestin-only Emergency Contraceptive Pills

Early treatment with ECPs containing only the progestin levonorgestrel has been shown to impair the ovulatory process and luteal function.[6,7,8,9,10] No effect on the endometrium was found in two studies,[7,8] but in another study levonorgestrel taken before the LH surge altered the luteal phase secretory pattern of glycodelin in serum and the endometrium.[11] However, this finding was not confirmed in two later studies explicitly designed to assess endometrial glycodelin expression.[12,13] The second of these studies also found no effect on other endometrial receptivity biomarkers or progesterone receptors. Levonorgestrel does not impair the attachment of human embryos to in vitro endometrial constructs and has no effect on the expression of endometrial receptivity markers.[14,15] In a study conducted more than 30 years ago, levonorgestrel was found to interfere with sperm migration and function at all levels of the genital tract;[16] however, another study designed to assess this issue found that 1500 mcg levonorgestrel had no effect on the quality of cervical mucus or on the penetration of spermatozoa in the uterine cavity,[12] and a recent study found an effect on sperm function only with much higher levels of levonorgestrel than are used for emergency contraception.[17]

The reduced efficacy with a delay in treatment, even when use is adjusted for cycle day of unprotected intercourse,[18] suggests that interference with implantation is likely not an important effect of ECPs. If ECPs did prevent all implantations, then delays in use should not reduce their efficacy as long as they are used before implantation.[19] Results of a simulation model demonstrated that the levonorgestrel regimen could not be effective on average when started after 96 hours without a post-fertilization effect, because with increasing delay, a greater proportion of women would be too near to ovulation.[20]

Studies in the rat and the Cebus monkey demonstrate that levonorgestrel administered in doses that inhibit ovulation has no post-fertilization effect that impairs fertility.[21,22,23] However, the extent to which these results can be extrapolated to women is unknown.

Croxatto and colleagues have argued that most, if not all, of the contraceptive effect of levonorgestrel only ECPs can be explained by inhibited or dysfunctional ovulation, based on the existing animal and human studies, including two human studies comparing observed and expected pregnancies when levonorgestrel-only ECPs were administered before and after

ovulation. In the first study, no pregnancies were observed when levonorgestrel-only ECPs were taken before the day of ovulation (in contrast to the 4 pregnancies that would have been expected without use of ECPs), whereas 3 pregnancies occurred when ECPs were taken after the day of ovulation (versus 3.5 expected pregnancies).[24] In a follow-up study no pregnancies were observed when levonorgestrel-only ECPs were taken before the day of ovulation (in contrast to the 13 pregnancies that would have been expected without use of ECPs, whereas when ECPs were taken on or after the day of ovulation, 6 pregnancies occurred (*versus* 7 expected pregnancies).[25] While some find the existing human and animal studies adequate to conclude that levonorgestrel ECPs have no post-fertilization effect,[26] others may always feel that this question has not been unequivocally answered. The best available evidence indicates that levonorgestrel ECPs prevent pregnancy by mechanisms that do not involve interference with post-fertilization events.[19]

Combined Emergency Contraceptive Pills

Several clinical studies have shown that combined ECPs containing the estrogen ethinyl estradiol and the progestin levonorgestrel can inhibit or delay ovulation.[27,28,29,30] This mechanism of action may explain the effectiveness of combined ECPs when used during the first half of the menstrual cycle, before ovulation has occurred. Some studies have shown histologic or biochemical alterations in the endometrium after treatment with the regimen, leading to the conclusion that combined ECPs may act by impairing endometrial receptivity to subsequent implantation of a fertilized egg[28,31,32,33] However, other more recent studies have found no such effects on the endometrium.[27,34,35] Additional possible mechanisms include interference with corpus luteum function; thickening of the cervical mucus resulting in trapping of sperm; alterations in the tubal transport of sperm, egg, or embryo; and direct inhibition of fertilization.[21,36,37,38] No clinical data exist regarding the last three of these possibilities. Nevertheless, statistical evidence on the effectiveness of combined ECPs suggests that that if the regimen is as effective as was initially claimed, it must have a mechanism of action other than delaying or preventing ovulation.[39] However, as it now appears that the effectiveness of combined ECPs was initially overestimated, there is less concern that ECPs do more than delay or prevent ovulation.[40] Nevertheless, the important point is that effectiveness and mechanism of action are not independent.[20] For example, a regimen without a post-fertilization effect could not be 100% effective in typical populations, which inevitably include some women who take ECPs after fertilization has already occurred.

To make an informed choice, women must know that ECPs—like all regular hormonal contraceptives such as the birth control pill, the implant Implanon, the vaginal ring NuvaRing, the Evra patch, and the injectable Depo-Provera,[41] and even breastfeeding[42,43,44,45]— prevent pregnancy primarily by delaying or inhibiting ovulation and inhibiting fertilization, but may at times inhibit implantation of a fertilized egg in the endometrium. At the same time, however, all women should be informed that the best available evidence is consistent with the hypothesis that levonorgestrel and ulipristal acetate ECPs' ability to prevent pregnancy can be fully accounted for by mechanisms that do not involve interference with post-fertilization events. That is the information we provide on the Emergency Contraception Website (not-2-late.com) and the Emergency Contraception Hotline (1-888-NOT-2-LATE).

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