

Mechanism of Action of Emergency Contraceptive Pills

Several clinical studies have shown that combined emergency contraceptive pills (ECPs) containing the estrogen ethinyl estradiol and the progestin levonorgestrel can inhibit or delay ovulation.^{1,2,3,4} This mechanism of action may explain combined ECP effectiveness 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 implantation of a fertilized egg.^{2,5,6,7} However, other more recent studies have found no such effects on the endometrium.^{1,8,9} 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.^{10,11,12,13} No clinical data exist regarding the last three of these possibilities. Nevertheless, statistical evidence on the effectiveness of combined ECPs suggests that if the regimen is as effective as claimed, it must have a mechanism of action other than delaying or preventing ovulation.¹⁴ However, if the effectiveness of combined ECPs was overestimated, which it seems to have been in that study, the results would be less persuasive.¹⁵ Nevertheless, the important point is that effectiveness and mechanism of action are not independent, a point emphasized in later work.¹⁶ For example, a regimen without a post-fertilization effect could not be 100% effective in typical populations, which will inevitably include some women who take it after fertilization has already occurred.

Early treatment with ECPs containing only the progestin levonorgestrel has been shown to impair the ovulatory process and luteal function;^{17,18,19,20,21,22} no effect on the endometrium was found in two studies,^{18,19} but in another study levonorgestrel taken before the LH surge altered the luteal phase secretory pattern of glycodelin in serum and the endometrium.²³ However, this finding was not confirmed in a later study explicitly designed to assess endometrial glycodelin expression.²⁴ 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;²⁵ however, a recent study designed to assess this issue found that 1.5 mg levonorgestrel had no effect on the quality of cervical mucus or on the penetration of spermatozoa in the uterine cavity.

The reduced efficacy with a delay in treatment, even when use is adjusted for cycle day of unprotected intercourse,²⁶ suggests that interference with implantation is likely not an inevitable 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.²⁷

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.^{13,28,29} Whether these results can be extrapolated to women is unknown. Based on those animal studies and on their own studies in women (including one in which no pregnancies were observed when levonorgestrel-only ECPs were taken before the day of ovulation whereas 4-5 would have been expected and three pregnancies were observed when ECPs were taken after ovulation when 3-4 would have been expected³⁰), Croxatto and colleagues have argued that most, if not all, of the contraceptive effect of both combined and levonorgestrel only ECPs can be explained by inhibited or dysfunctional ovulation. Based on their studies on human and animals, some are tempted to conclude that there is definitely no post-fertilization effect.³¹ It is unlikely that this question can ever be unequivocally answered, and we therefore cannot conclude that ECPs never prevent pregnancy after fertilization. Even if there were an accurate test for fertilization, a

finding that some fertilized eggs do not subsequently implant after ECPs are taken would not mean that ECPs can work after fertilization, since many, if not most, fertilized eggs naturally do not subsequently implant. Nevertheless, even if in some cases ECPs work by inhibiting subsequent implantation of a fertilized egg, these probably would be outnumbered by other cases in which fertilization of an egg that would not have subsequently implanted naturally is prevented because ECPs inhibited ovulation. Therefore, on balance, ECPs probably reduce the incidence of fertilized eggs that do not subsequently implant.

ECPs do not interrupt an established pregnancy, defined by medical authorities such as the United States Food and Drug Administration/National Institutes of Health³² and the American College of Obstetricians and Gynecologists³³ as beginning with implantation. Therefore, ECPs are not abortifacient.

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,³⁴ and even breastfeeding^{35,36,37,38}—may prevent pregnancy by delaying or inhibiting ovulation, inhibiting fertilization, or inhibiting subsequent implantation of a fertilized egg. At the same time, however, all women should be informed that the best available evidence is consistent with the hypothesis that Plan B's 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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References

- ¹ Swahn ML, Westlund P, Johannisson E, Bygdeman M. Effect of post-coital contraceptive methods on the endometrium and the menstrual cycle. *Acta Obstet Gynecol Scand* 1996;**75**:738-744.
- ² Ling WY, Robichaud A, Zayid I, Wrixon W, MacLeod SC. Mode of action of dl-norgestrel and ethinylestradiol combination in postcoital contraception. *Fertil Steril* 1979;**32**:297-302.
- ³ Rowlands S, Kubba AA, Guillebaud J, Bounds W. A possible mechanism of action of danazol and an ethinylestradiol/norgestrel combination used as postcoital contraceptive agents. *Contraception* 1986;**33**:539-545.
- ⁴ Croxatto HB, Fuentalba B, Brache V, Salvatierra AM, Alvarez F, Massai R, Cochon L, Faundes A. Effects of the Yuzpe regimen, given during the follicular phase, on ovarian function. *Contraception* 2002;**65**:121-128.

- 5 Kubba AA, White JO, Guillebaud J, Elder MG. The biochemistry of human endometrium after two regimens of postcoital contraception: a dl-norgestrel/ethinylestradiol combination or danazol. *Fertil Steril* 1986;**45**:512-516.
- 6 Ling WY, Wrixon W, Zayid I, Acorn T, Popat R, Wilson E. Mode of action of dl-norgestrel and ethinylestradiol combination in postcoital contraception. II. Effect of postovulatory administration on ovarian function and endometrium. *Fertil Steril* 1983;**39**:292-297.
- 7 Yuzpe AA, Thurlow HJ, Ramzy I, Leyshon JI. Post coital contraception—a pilot study. *J Reprod Med* 1974; **13**:53-58.
- 8 Taskin O, Brown RW, Young DC, Poindexter AN, Wiehle RD. High doses of oral contraceptives do not alter endometrial $\alpha 1$ and $\alpha v\beta 3$ integrins in the late implantation window. *Fertil Steril* 1994;**61**:850-855.
- 9 Raymond EG, Lovely LP, Chen-Mok M, Seppälä M, Kurman RJ, Lessey BA. Effect of the Yuzpe regimen of emergency contraception on markers of endometrial receptivity. *Hum Reprod* 2000;**15**:2351-5.
- 10 Glasier A. Emergency postcoital contraception. *N Engl J Med* 1997;**337**:1058-1064.
- 11 Ling WY, Wrixon W, Acorn T, Wilson E, Collins J. Mode of action of dl-norgestrel and ethinylestradiol combination in postcoital contraception. III. Effect of preovulatory administration following the luteinizing hormone surge on ovarian steroidogenesis. *Fertil Steril* 1983;**40**:631-636.
- 12 Croxatto HB, Devoto L, Durand M, Ezcurra E, Larrea F, Nagle C, Ortiz ME, Vantman D, Vega M, von Hertzen H. Mechanism of action of hormonal preparations used for emergency contraception: a review of the literature. *Contraception* 2001;**63**:111-121.
- 13 Croxatto HB, Ortiz ME, Müller AL. Mechanisms of action of emergency contraception. *Steroids* 2003;**68**:1095-1098.
- 14 Trussell J, Raymond EG. Statistical evidence concerning the mechanism of action of the Yuzpe regimen of emergency contraception. *Obstet Gynecol* 1999;**93**:872-876.
- 15 Trussell J, Ellertson C, von Hertzen H, Bigrigg A, Webb A, Evans M, Ferden S, Leadbetter C. Estimating the effectiveness of emergency contraceptive pills. *Contraception* 2003;**67**:259-265.
- 16 Mikolajczyk RT, Stanford JB. Levonorgestrel emergency contraception: a joint analysis of effectiveness and mechanism of action. *Fertil Steril* 2007;**88**:565-71.
- 17 Hapangama D, Glasier AF, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. *Contraception* 2001;**63**:123-129.
- 18 Durand M, del Carmen Cravioto M, Raymond EG, Durán-Sánchez O, De la Luz Cruz-Hinojosa L, Castell-Rodríguez A, Schiavon R, Larrea F. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception. *Contraception* 2001;**64**:227-234.
- 19 Marions L, Hultenby K, Lindell I, Sun X, Ståbi B, Gemzell Danielsson K. Emergency contraception with mifepristone and levonorgestrel: mechanism of action. *Obstet Gynecol* 2002;**100**:65-71.
- 20 Marions L, Cekan SZ, Bygdeman M, Gemzell-Danielsson K. Effect of emergency contraception with levonorgestrel or mifepristone on ovarian function. *Contraception* 2004;**69**:373-377.
- 21 Croxatto HB, Brache V, Pavez M, Cochon L, Forcelledo ML, Alvarez F, Massai R, Faundes A, Salvatierra AM. Pituitary-ovarian function following the standard levonorgestrel

- emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. *Contraception* 2004;**70**:442-50.
- 22 Okewole IA, Arowojolu AO, Odusoga OL, Oloyede OA, Adeleye OA, Salu J, Dada OA. Effect of single administration of levonorgestrel on the menstrual cycle. *Contraception* 2007;**75**:372-7.
- 23 Durand M, S pala M, del Carmen Cravioto M, Koistinen H, Koistinen R, Gonz lez-Macedo J, Larrea F. Late follicular phase administration of levonorgestrel as an emergency contraceptive changes the secretory pattern of glycodeclin in serum and endometrium during the luteal phase of the menstrual cycle. *Contraception* 2005;**71**:451-457.
- 24 do Nascimento JA, Seppala M, Perdigo A, Espejo-Arce X, Munuce MJ, Hautala L, Koistinen R, Andrade L, Bahamondes L. In vivo assessment of the human sperm acrosome reaction and the expression of glycodeclin-A in human endometrium after levonorgestrel-emergency contraceptive pill administration. *Hum Reprod* 2007;**22**:2190-5.
- 25 Kesser  E, Garmendia F, Westphal N, Parada J. The hormonal and peripheral effects of d-norgestrel in postcoital contraception. *Contraception* 1974;**10**:411-24.
- 26 Piaggio G, von Hertzen H, Grimes DA, Van Look PFA. Timing of emergency contraception with levonorgestrel or the Yuzpe regimen. *Lancet* 1999;**353**:721.
- 27 Davidoff F, Trussell J. Plan B and the politics of doubt. *J Am Med Assoc* 2006;**296**:1775-8.
- 28 M ller AL, Llados CM, Croxatto HB. Postcoital treatment with levonorgestrel does not disrupt postfertilization events in the rat. *Contraception* 2003;**67**:415-419.
- 29 Ortiz ME, Ortiz RE, Fuentes MA, Parraguez VH, Croxatto HB. Postcoital administration of levonorgestrel does not interfere with post-fertilization events in the new-world monkey *Cebus apella*. *Hum Reprod* 2004;**19**:1352-1356.
- 30 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**: 112-118.
- 31 Anonymous. Emergency contraception’s mode of action clarified. *Popul Briefs* 2005;**11**:3 Available at www.popcouncil.org/pdfs/popbriefs/pbmay05.pdf (accessed March 23, 2006).
- 32 OPRR Reports: Protection of Human Subjects. Code of Federal Regulations 45CFR 46, March 8, 1983.
- 33 Hughes EC (ed), Committee on Terminology, The American College of Obstetricians and Gynecologists, *Obstetric-Gynecologic Terminology*. Philadelphia PA: F.A. Davis Company, 1972.
- 34 *Statement on Contraceptive Methods*. Washington DC: American College of Obstetricians and Gynecologists, July 1998.
- 35 D az S, C rdenas H, Brandeis A, Miranda P, Salvatierra AM, Croxatto HB. Relative contributions of anovulation and luteal phase defect to the reduced pregnancy rate of breastfeeding women. *Fertil Steril* 1992;**58**:498-503.
- 36 Lewis PR, Brown JB, Renfree MB, Short RV. The resumption of ovulation and menstruation in a well-nourished population of women breastfeeding for an extended period of time. *Fertil Steril* 1991;**55**:529-536.
- 37 Brown JB, Harisson P, Smith MA. A study of returning fertility after childbirth and during lactation by measurement of urinary oestrogen and pregnanediol excretion and cervical mucus production. *J Biosoc Science* 1985;**9**(Suppl):5-23.

- ³⁸ Gray RH, Campbell OM, Apelo R, Eslami SS, Zacur H, Ramos RM, Gehret JC, Lobbok MH. Risk of ovulation during lactation. *Lancet* 1990;**335**:25-9.