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Contraception 74 (2006) 87–89

Contraception

Editorial

Mechanism of action of emergency contraceptive pills

Like breastfeeding and other forms of hormonal contraception, emergency contraception pills (ECPs) can prevent pregnancy by delaying or inhibiting ovulation. Some of these methods have other established mechanisms of action, and it is possible that all may act after fertilization. The preponderance of research, however, shows that ECPs do not have a major postfertilization mechanism of action. As social conservatives wage a scientifically inaccurate campaign wrongly portraying ECPs as abortifacient, some reproductive rights advocates have responded by asserting that ECPs have no postfertilization effect whatsoever. Healthcare practitioners and their patients alike should be fully informed of the proven and potential mechanisms of action to help increase both knowledge and widespread use of ECPs to prevent unintended pregnancies.

Several clinical studies have shown that combined ECPs containing the estrogen ethinyl estradiol and the progestin levonorgestrel can inhibit or delay ovulation [1–4]. This is an important mechanism of action and 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 [2,5–7]. 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 [10–13]. No clinical data exist regarding the last three of these possibilities. Nevertheless, statistical evidence regarding the effectiveness of combined ECPs suggests that there must be a mechanism of action in addition to delaying or preventing ovulation [14]. However, the effectiveness of combined ECPs was probably overestimated in that study, in which case this suggestion would be less persuasive [15].

Early treatment with ECPs containing only the progestin levonorgestrel has been shown to impair the ovulatory process and luteal function [16–20]; no effect on the endometrium was found in two studies [17,18], but in another study, levonorgestrel taken before the LH surge altered the luteal phase secretory pattern of glycodelin in serum and the endometrium [21]. Treatment with ECPs containing only levonorgestrel during the periovulatory phase may fail to inhibit ovulation but, nevertheless, reduce the length of the luteal phase and total luteal phase LH concentrations; this observation suggests a postfertilization contraceptive effect [16]. Levonorgestrel also interferes with sperm migration and function at all levels of the genital tract [22]. Studies in the rat and the *Cebus* monkey demonstrate that levonorgestrel administered in doses that inhibit ovulation has no postfertilization effect that impairs fertility [13,23,24]. Whether these results can be extrapolated to women is unknown.

Croxatto et al. [12,13] 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 no postfertilization effect [25]. 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 implant after ECPs are taken would not mean that ECPs can work after fertilization, since many if not most fertilized eggs naturally do not implant. Nevertheless, even if in some cases ECPs work by inhibiting implantation of a fertilized egg, these probably would be outnumbered by other cases where fertilization of an egg that would not have implanted naturally is prevented because ECPs inhibited ovulation. Therefore, on balance, ECPs probably reduce the incidence of fertilized eggs that do not implant. ECPs do not interrupt an established pregnancy, defined by medical authorities such as the United States Food and Drug Administration/National Institutes of Health [26] and the American College of Obstetricians and Gynecologists [27] as beginning with implantation. Therefore, ECPs are not abortifacient.

Making ECPs widely available is one of the most important steps that can be taken to reduce the unacceptable incidence of unintended pregnancy in the United States [28]. There are 3.0 million unintended pregnancies each year in the United States; half of all pregnancies are

0010-7824/$ – see front matter
doi:10.1016/j.contraception.2006.03.028

unintended, and half of all women aged 15–44 years have had an unintended pregnancy [29,30]. Widespread use of ECPs could halve the number of unintended pregnancies and the consequent need for abortion [28]. Yet, only 6% of women at risk of unintentional pregnancy in the United States have ever used ECPs, primarily because awareness of emergency contraception is so low [31]. To avail themselves of this important contraceptive option, therefore, women must be informed that ordinary birth control pills can be taken in higher than usual doses after unprotected intercourse to prevent pregnancy. To make an informed choice, women must know that ECPs — like all regular hormonal contraceptives such as the birth control pill, the progestin-containing implant and the injectable depot medroxyprogesterone acetate [32], and even breastfeeding [33] — may prevent pregnancy by delaying or inhibiting ovulation, inhibiting fertilization, or inhibiting implantation of a fertilized egg in the endometrium. This information is provided on the Emergency Contraception Web site (www.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;75:738–44.
[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;33:539–45.
[4] Croxatto HB, Fuentalba B, Brache V, et al. Effects of the Yuzpe regimen, given during the follicular phase, on ovarian function. Contraception 2002;65:121–8.
[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;45:512–6.
[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;39:292–7.
[7] Yuzpe AA, Thurlow HJ, Ramzy I, Leyshon JI. Post coital contraception — a pilot study. J Reprod Med 1974;13:53–8.
[8] Taskin O, Brown RW, Young DC, Poindexter AN, Wiehle RD. High doses of oral contraceptives do not alter endometrial α1 and $\alpha v\beta 3$ integrins in the late implantation window. Fertil Steril 1994;61:850–5.
[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;337:1058–64.
[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;40:631–6.
[12] Croxatto HB, Devoto L, Durand M, et al. Mechanism of action of hormonal preparations used for emergency contraception: a review of the literature. Contraception 2001;63:111–21.
[13] Croxatto HB, Ortiz ME, Müller AL. Mechanisms of action of emergency contraception. Steroids 2003;68:1095–8.
[14] Trussell J, Raymond EG. Statistical evidence concerning the mechanism of action of the Yuzpe regimen of emergency contraception. Obstet Gynecol 1999;93:872–6.
[15] Trussell J, Ellertson C, von Hertzen H, et al. Estimating the effectiveness of emergency contraceptive pills. Contraception 2003;67:259–65.
[16] Hapangama D, Glasier AF, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. Contraception 2001;63:123–9.
[17] Durand M, del Carmen Cravioto M, Raymond EG, et al. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception. Contraception 2001;64:227–34.
[18] 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.
[19] Marions L, Cekan SZ, Bygdeman M, Gemzell-Danielsson K. Effect of emergency contraception with levonorgestrel or mifepristone on ovarian function. Contraception 2004;69:373–7.
[20] Croxatto HB, Brache V, Pavez M, et al. 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.
[21] Durand M, Sépala M, del Carmen Cravioto M, et al. Late follicular phase administration of levonorgestrel as an emergency contraceptive changes the secretory pattern of glycodelin in serum and endometrium during the luteal phase of the menstrual cycle. Contraception 2005;71:451–7.
[22] Kesseru E, Garmendia F, Westphal N, Parada J. The hormonal and peripheral effects of d-norgestrel in postcoital contraception. Contraception 1974;10:411–24.
[23] Müller AL, Llados CM, Croxatto HB. Postcoital treatment with levonorgestrel does not disrupt post-fertilization events in the rat. Contraception 2003;67:415–9.
[24] 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;19:1352–6.
[25] Anonymous. Emergency contraception's mode of action clarified. Popul Briefs 2005;11:3 Available at http://www.popcouncil.org/pdfs/popbriefs/pbmay05.pdf [accessed March 23, 2006].
[26] OPRR Reports: Protection of human subjects. Code of Federal Regulations 45CFR 46, March 8, 1983.
[27] Hughes EC, editor. Committee on Terminology, The American College of Obstetricians and Gynecologists, Obstetric-Gynecologic Terminology. Philadelphia (Pa): F.A. Davis Company; 1972.
[28] Trussell J, Stewart F, Guest F, Hatcher RA. Emergency contraceptive pills: a simple proposal to reduce unintended pregnancies. Fam Plann Perspect 1992;24:269–73.
[29] Henshaw SK. Unintended pregnancy in the United States. Fam Plann Perspect 1998;30:24-9, 46.

[30] Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. Perspect Sex Reprod Health 2006;38:90–6.
[31] The Kaiser Family Foundation. Women's health care providers experiences with emergency contraception, June 28, 2003. Available at URL: http://www.kff.org/womenshealth/3343-index.cftn [accessed July 28, 2004].
[32] Statement on contraceptive methods. Washington (DC): American College of Obstetricians and Gynecologists; 1998.
[33] Díaz S, Cárdenas 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.