Published in final edited form as:

Contraception. 2013 November ; 88(5): 585–586. doi:10.1016/j.contraception.2013.08.007.

What Do We Need to Know about Emergency Contraception?

Kristina Gemzell-Danielsson and

Department of Women's and Children's Health, Division of Obstetrics and Gynecology,
Karolinska Institutet, Karolinska University Hospital, 171 76 Stockholm, Sweden

James Trussell, PhD

Office of Population Research, Princeton University, Princeton, NJ 08540, USA, The Hull York
Medical School, University of Hull, Hull HU6 7RX, England

In this issue of *Contraception* Brache *et al.* report pooled data from three randomized trials on the efficacy of emergency contraception (EC) pill regimens to prevent ovulation.¹ The efficacy of EC methods depends on several factors including how and when they are being used and their mechanisms of action. An ideal EC method should be safe and acceptable, easy to use (by the woman), readily available, effective when used at least up to 120h after the unprotected intercourse (the time period corresponding to the life span of sperm), and have mechanisms of action that makes it effective during the entire fertile window.

Additional effects such as dual protection would also be desirable. Today no existing method fulfills all these criteria. Among the available methods the copper intrauterine device (Cu-IUD) is the most effective, with a failure rate of 1 per 1,000 insertions.² The mechanisms of action include the effect of the copper ions on sperm function and prevention of fertilization. In addition copper ions render the endometrium non receptive and prevent embryo implantation.³ In contrast the EC pills have more limited mechanisms of action and thus lower efficacy. However, for practical reasons, the EC pills are more widely used. Until recently the levonorgestrel (LNG)-EC used to be the first choice and so far it is the only EC available over the counter (OTC).

Ulipristal acetate (UPA) is the first selective progesterone receptor modulator (SPRM) approved for emergency contraception (ellaOne[®] or Ella[®]). Compared with LNG, UPA has shown better efficacy, because of a wider time window of use. A meta-analysis of studies containing data on 3,445 women on the efficacy of LNG *versus* UPA showed that for those women treated with UPA the risk of pregnancy was significantly reduced compared to those who received LNG.⁴ For women who were treated with UPA within 72 hours of unprotected intercourse, the risk of pregnancy was almost half that of those receiving LNG. Furthermore, if EC was taken within 24 hours of intercourse, the risk of pregnancy in women who received UPA was reduced by almost two-thirds compared with that for women receiving LNG. Both UPA and LNG have been shown to be able to delay ovulation, although the

© 2013 Elsevier Inc. All rights reserved.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

effective time window for LNG is rather narrow. It begins after selection of the dominant follicle, but ends before Luteinising Hormone (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, and is thus ineffective at preventing pregnancy.^{5,6,7,8} This finding is also supported by clinical data.^{9,10} As for LNG the main mechanism of action for UPA is prevention of ovulation. However, that UPA is more effective than LNG in preventing ovulation has been shown by Brache *et al.*¹¹ When UPA was administered when the size of the leading follicle was 18mm (ovulation imminent), follicular rupture failed to occur within 5 days following treatment in 59% of women. 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.¹²

In the present analysis Brache and coworkers pooled data from three pharmacodynamic studies to compare the ability of three separate regimens and a placebo to prevent ovulation for five days after treatment when the leading follicular diameter was 18mm: 48 LNG (1.5 mg) cycles, 31 LNG (1.5 mg) +meloxicam (15 mg) cycles, 34 UPA (30 mg) cycles, and 50 placebo cycles.¹ UPA was superior to LNG and placebo. LNG was no more effective than placebo. Adding meloxicam to LNG significantly increased the effectiveness of LNG alone; LNG+meloxicam and UPA were statistically equivalently effective. UPA was effective even when administered on the day of the LH surge. No method was effective when administered on the day of the LH peak.

Knowledge about the efficacy and mechanisms of action of EC is crucial for correct clinical recommendations and use. Ignoring the evidence and overestimating the effect of UPA or LNG on the endometrium will also overestimate the efficacy of the EC pills. At the same time to improve efficacy new regimens need to act also beyond the LH peak during the entire window of fertility. Efforts should be made to make Cu-IUD available for EC as well as making the most effective EC pill UPA available and affordable OTC. Since the main action of UPA for EC is to delay ovulation, it is important that further acts of unprotected sex in the same cycle should be avoided in order to avoid pregnancy at the time of postponed ovulation. Given the finding that pregnancy after EC is more likely amongst women who go on to have other episodes of sex in the same cycle as EC has been given,¹³ clinical recommendations to help women to start effective methods of contraception immediately after EC (so called ‘quick start’ or ‘bridging’) are needed. UPA becomes completely ineffective when BMI reaches 35 (versus 26 for LNG). Use of a Cu-IUD would avoid both the need to start effective contraception after EC pill administration and the effect of BMI on EC pill efficacy.

References

1. Brache V, Cochon L, Deniaud M, Croxatto HB. Ulipristal acetate prevents ovulation more effectively than levonorgestrel: analysis of pooled data from three randomized trials of emergency contraception regimens. *Contraception*.
2. Cleland K, Zhu H, Goldstruck N, Cheng L, Trussell J. The efficacy of IUDs for emergency contraception: a systematic review of 35 years of experience. *Hum Reprod*. 2012; 27:1994–2000. [PubMed: 22570193]

3. Gemzell-Danielsson K, Berger C, Lalitkumar PGL. Emergency contraception - mechanisms of action. *Contraception*. 2013; 87:300–8. [PubMed: 23114735]
4. Glasier AF, Cameron ST, Fine PM, Logan SJ, Casale W, Van Horn J, Sogor L, Blithe DL, Scherrer B, Mathe H, Jaspert A, Ulmann A, Gainer E. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. *Lancet*. 2010; 375:555–62. [PubMed: 20116841]
5. 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. [PubMed: 12100805]
6. Hapangama D, Glasier AF, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. *Contraception*. 2001; 63:123–9. [PubMed: 11368983]
7. Lalitkumar PG, Lalitkumar S, Meng CX, Stavreus-Evers A, Hambiliki F, Bentin-Ley U, Gemzell-Danielsson K. Mifepristone, but not levonorgestrel, inhibits human blastocyst attachment to an in vitro endometrial three-dimensional cell culture model. *Human Reprod*. 2007; 22:3031–7.
8. Meng CX, Andersson KL, Bentin-Ley U, Gemzell-Danielsson K, Lalitkumar PG. Effect of levonorgestrel and mifepristone on endometrial receptivity markers in a three-dimensional human endometrial cell culture model. *Fertil Steril*. 2009; 91:256–64. [PubMed: 18206148]
9. Novikova N, Weisberg E, Stanczyk FZ, Croxatto HB, Fraser IS. Effectiveness of levonorgestrel emergency contraception given before or after ovulation—a pilot study. *Contraception*. 2006; 74:349–50. [PubMed: 16982238]
10. Noé G, Croxatto HB, Salvatierra AM, Reyes V, Villarroel C, Muñoz C, Morales G, Retamales A. Contraceptive efficacy of emergency contraception with levonorgestrel given before or after ovulation. *Contraception*. 2011; 84:486–92. [PubMed: 22018122]
11. Brache V, Cochon L, Jesam C, Maldonado R, Salvatierra AM, Levy DP, Gainer E, Croxatto HB. Immediate preovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture. *Hum Reprod*. 2010; 25:2256–63. [PubMed: 20634186]
12. 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. [PubMed: 15541405]
13. Glasier A, Cameron ST, Blithe D, Scherrer B, Mathe H, Levy D, Gainer E, Ulmann A. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. *Contraception*. 2011; 84:363–7. [PubMed: 21920190]