



March 2012

## MECHANISM OF ACTION

### How do levonorgestrel-only emergency contraceptive pills (LNG ECPs) prevent pregnancy?

#### Levonorgestrel-only emergency contraceptive pills:

- Interfere with the process of ovulation;
- May possibly prevent the sperm and the egg from meeting.

### The evidence shows that LNG ECPs:

#### Impair ovulation:

- A number of studies provide strong direct evidence that LNG ECPs prevent or delay ovulation. If taken before ovulation, LNG ECPs inhibit the pre-ovulatory luteinizing hormone (LH) surge, impeding follicular development and maturation and/or the release of the egg itself.<sup>1,2,3,4,5,6,7,8</sup>

**This is the primary mechanism of action for LNG ECPs.**

#### Do not inhibit implantation:

- Two studies have estimated effectiveness of LNG ECPs by confirming the cycle day by hormonal analysis (other studies used women's self-reported cycle date). In these studies, no pregnancies occurred in the women who took ECPs before ovulation, while pregnancies occurred only in women who took ECPs on or after the day of ovulation, providing evidence that ECPs were unable to prevent implantation.<sup>9,10</sup>
- A number of studies have evaluated whether ECPs produce changes in the histological and biochemical characteristics of the endometrium. Most studies show that LNG ECPs have no such effect on the endometrium, indicating that they have no mechanism to prevent implantation.<sup>1,2,11,12,13</sup> One of these studies found that following administration of double the standard dose of LNG, there are only minor or no alterations in endometrial receptivity.<sup>12</sup> One study found a single altered endometrial parameter only when LNG was administered prior to the LH surge, at a time when ECPs inhibit ovulation.<sup>14</sup>
- One study showed that levonorgestrel did not prevent the attachment of human embryos to a simulated (in vitro) endometrial environment.<sup>15</sup>
- Animal studies demonstrated that LNG ECPs did not prevent implantation of the fertilized egg in the endometrium.<sup>16,17</sup>

#### May affect sperm:

- Contradictory results exist regarding whether LNG taken post-coitally and in doses used for EC affects sperm function.
- Early studies suggested that LNG ECPs interfere with sperm motility by thickening cervical mucus.<sup>18,19</sup> However, two in vitro studies found that LNG in doses used for EC has no direct effect on sperm function.<sup>20,21</sup> Recent in vivo studies found no effect of LNG on the number of viable sperm found in the female genital tract 24-28 hours after taking LNG.<sup>22</sup> Interference in sperm migration is also a possible explanation in women who took LNG ECP before ovulation, but had documented follicle rupture in the following 5 days, yet did not get pregnant.<sup>9</sup>

- New evidence about the interaction between sperm and progesterone suggests a possible deleterious effect of high concentrations of the progestin LNG on sperm function, that may cause sperm to be hyperactive in the absence of an egg or interfere with directionality of the sperm movement.<sup>23,24,25,26,27</sup>
- Given these results, this mechanism of action is still uncertain and warrants further studies.

### Do not have an effect on pregnancy:

- Two studies of women who became pregnant in cycles when they took LNG ECPs found no difference between pregnancy outcomes of women who had taken LNG ECPs and those who had not. Variables included miscarriage, birth weight, malformations, and sex ratio, indicating that LNG ECPs have no effect on an established pregnancy even at very early stages.<sup>28,29</sup>

### Other facts:

- Emergency contraception is not the same as early medical abortion. LNG ECPs are effective only in the first few days following intercourse before the ovum is released from the ovary and before the sperm fertilizes the ovum. Medical abortion is an option for women in the early stage of an established pregnancy, but requires a different drug from levonorgestrel.
- LNG ECPs cannot interrupt an established pregnancy or harm a developing embryo.

### Implications of the research:

- Inhibition or delay of ovulation is LNG ECPs principal and possibly only mechanism of action.
- Review of the evidence suggests that LNG ECPs cannot prevent implantation of a fertilized egg. Language on implantation should not be included in LNG ECP product labeling.
- The fact that LNG ECPs have no demonstrated effect on implantation explains why they are not 100% effective in preventing pregnancy, and are less effective the later they are taken. Women should be given a clear message that LNG ECPs are more effective the sooner they are taken.
- LNG ECPs do not interrupt a pregnancy (by any definition of the beginning of pregnancy). However, LNG ECPs can prevent abortions by reducing unwanted pregnancies.



International Consortium for  
Emergency Contraception

ICEC is hosted by Family Care International  
588 Broadway • Suite 503 • New York, NY • 10012 • USA

# References

- <sup>1</sup> Marions L, Hulthenby K, Lindell I, Sun X, Stabi B, Gemzell-Danielsson K. Emergency contraception with mifepristone and levonorgestrel: mechanism of action. *Obstetrics and Gynecology* 2002; 100(1): 65-71.
- <sup>2</sup> Durand M, del Carmen Cravioto M, Raymond EG, Duran-Sanchez O, De la Luz Cruz-Hinojosa M, Castell-Rodríguez A, Schiavon R, Larrea F. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception. *Contraception* 2001; 64(4): 227-234.
- <sup>3</sup> Hapangama D, Glasier AF, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. *Contraception* 2001; 63(3): 123-129.
- <sup>4</sup> Marions L, Cekan SZ, Bygdeman M, Gemzell-Danielsson K. Effect of emergency contraception with levonorgestrel or mifepristone on ovarian function. *Contraception* 2004; 69(5): 373-377.
- <sup>5</sup> 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(6): 442-450.
- <sup>6</sup> 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(5): 372-377.
- <sup>7</sup> 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(3): 111-121.
- <sup>8</sup> Massai MR, Forcelledo ML, Brache V, Tejada AS, Salvatierra AM, Reyes MV, Alvarez F, Faundes A, Croxatto HB. Does meloxicam increase the incidence of anovulation induced by single administration of levonorgestrel in emergency contraception? A pilot study. *Human Reproduction* 2007; 22: 434-9.
- <sup>9</sup> Noe G, Croxatto H, Salvatierra AM, Reyes V, Villaruel C, Munoz C, Morales G, Retamales A. Contraceptive efficacy of emergency contraception with levonorgestrel given before or after ovulation. *Contraception* 2011; 84: 486-492.
- <sup>10</sup> 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(2): 112-118.
- <sup>11</sup> Meng CX, Andersson K, 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. *Fertility and Sterility* 2009; 91(1): 256-64.
- <sup>12</sup> Meng CX, Marions L, Bystrom B, Gemzell-Danielsson K. Effects of oral and vaginal administration of levonorgestrel emergency contraception on markers of endometrial receptivity. *Human Reproduction* 2010; 25(4): 874-883.
- <sup>13</sup> Palomino W, Kohen P, Devoto L. A single midcycle dose of levonorgestrel similar to emergency contraceptive does not alter the expression of the L-selectin ligand or molecular markers of endometrial receptivity. *Fertility and Sterility* 2010; 94(5): 1589-1594.
- <sup>14</sup> Durand M, Seppala M, Cravioto M del C, Koistinen H, Koistinen R, Gonzalez-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(6): 451-457.
- <sup>15</sup> 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 Reproduction* 2007; 22(11): 3031-3037.
- <sup>16</sup> Müller AL, Lladós CM, Croxatto HB. Postcoital treatment with levonorgestrel does not disrupt postfertilization events in the rat. *Contraception* 2003; 67(5): 415-419.
- <sup>17</sup> Ortiz ME, Ortiz RE, Fuentes A, Parraguez VH, Croxatto HB. Post-coital administration of levonorgestrel does not interfere with post-fertilization events in the new world monkey *Cebus apella*. *Human Reproduction* 2004; 19(6): 1352-1356.
- <sup>18</sup> Kessner E, Camacho-Ortega P, Laudahn G, Schopflin G. In vitro action of progestogens on sperm migration in human cervical mucus. *Fertility and Sterility* 1975; 26(1): 57-61.
- <sup>19</sup> Kessner E, Garmendia F, Westphal N, Parada J. The hormonal and peripheral effects of d-norgestrel in post-coital contraception. *Contraception* 1974; 10(4): 411-24.
- <sup>20</sup> Brito KS, Bahamondes L, Nascimento JA, de Santis L, Munuce MJ. The in vitro effect of emergency contraception doses of levonorgestrel on the acrosome reaction of human spermatozoa. *Contraception* 2005; 72(3): 225-8.
- <sup>21</sup> Yeung WS, Chiu PC, Wang CH, Yao YQ, Ho PC. The effects of levonorgestrel on various sperm functions. *Contraception* 2002; 66(6): 453-7.
- <sup>22</sup> 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. *Human Reproduction* 2007; 22(8): 2190-5.
- <sup>23</sup> Holt WV and Fazeli A. The oviduct as a complex mediator of mammalian sperm function and selection. *Molecular Reproduction & Development* 2010; 77: 934-43.
- <sup>24</sup> Kolle S, Reese S, Kummer W. New aspects of gamete transport, fertilization, and embryonic development in the oviduct gained by means of live cell imaging. *Thermiogenology* 2010; 73: 786-95.
- <sup>25</sup> Strunker T, Goodwin N, Brenker C, Kashikar ND, Weyand I, Seifert R, Kaupp UB. The CatSper channel mediates progesterone-induced Ca<sup>2+</sup> influx in human sperm. *Nature* 2011; 471: 382-6.
- <sup>26</sup> Lishko PV, Botchkina IL, Kirichok Y. Progesterone activates the principal Ca<sup>2+</sup> channel of human sperm. *Nature* 2011; 471: 387-91.
- <sup>27</sup> Teves ME, Guidobaldi HA, Unates DR, Sanchez R, Miska W, Publicover SJ, Morales Garcia AA, Giojalas LC. Molecular mechanism for human sperm chemotaxis mediated by progesterone. *PlosOne* 2009; 4 (12): e8211; 1-11.
- <sup>28</sup> Zhang L, Chen J, Wang Y, Fangming R, Yu W, Cheng L. Pregnancy outcome after levonorgestrel-only emergency contraception failure: a prospective cohort study. *Human Reproduction* 2009; 24(7): 1605-1611.
- <sup>29</sup> De Santis M, Cavaliere AF, Straface G, Carducci F, Caruso A. Failure of the emergency contraceptive levonorgestrel and the risk of adverse effects in pregnancy and on fetal development: an observational cohort study. *Fertility and Sterility* 2005; 84(2): 296-299.



International Consortium *for*  
Emergency Contraception

*Hosted by* Family Care International  
588 Broadway, Suite 503  
New York, NY 10012  
Phone: +1 212 941 5300



**International Federation of  
Gynecology & Obstetrics (FIGO)**

Suite 3 - Waterloo Court  
10 Theed Street  
London SE1 8ST  
Phone: +44 20 7928 1166