



## MECHANISM OF ACTION OF LEVONORGESTREL EMERGENCY CONTRACEPTIVE PILLS

### BACKGROUND

The mechanism of action of emergency contraceptive pills (ECPs) has been a source of confusion since the introduction of ECPs. The FDA-approved label for levonorgestrel ECPs includes a hypothetical mechanism of action suggesting that it may prevent implantation of a fertilized egg in the uterus.<sup>1</sup> A substantial body of evidence indicates that levonorgestrel (LNG) ECPs work primarily – and perhaps exclusively – by delaying or inhibiting ovulation and have no effect once ovulation is imminent.<sup>2</sup> Based on the evidence the European Medicines Agency removed language suggesting an effect on implantation from the LNG label in 2013,<sup>3</sup> yet this language remains on the US labels.

Policy makers and courts in the United States and elsewhere have used this hypothetical mechanism to restrict access to ECPs.<sup>4</sup> Following the Supreme Court decision in *Dobbs v. Jackson Women's Health Organization* (which based on the leaked opinion suggests that it will likely allow states to severely restrict or ban abortion), some state legislatures may look to the language on ECP labels to justify significant restrictions on access to emergency contraception.<sup>5</sup> This fact sheet describes the scientific research documenting the mechanism of action of LNG ECPs.

### QUICK SUMMARY

Levonorgestrel is a progestin (a synthetic form of the naturally occurring hormone progesterone). **LNG ECPs work by interfering with the process of ovulation.** LNG ECPs impede follicular development and maturation and/or the release of the egg from the ovary.<sup>6-12</sup> If there is no egg, fertilization cannot occur. The best available evidence does not support the theory that LNG ECPs can prevent implantation of a fertilized egg.<sup>2,13</sup>

### HOW IT WORKS

**Pregnancy:** For pregnancy to occur, ovulation (release of an egg from the ovary) must occur. Ovulation happens in response to the luteinizing hormone (LH) surge. After ovulation occurs and the egg is released, it must be fertilized by sperm and implanted in the uterine lining. Without implantation of the fertilized egg, pregnancy is not established.

**Ovulation:** LNG can inhibit the LH surge, impeding follicular development and maturation, and/or ovulation, if taken before the LH surge has begun.<sup>6-12,14</sup>

**Implantation:** LNG ECPs have not been demonstrated to prevent implantation of a fertilized egg in the uterus.<sup>6,13,15,16</sup> Two studies found that 100% of expected pregnancies were prevented by LNG ECPs when taken before ovulation. Those who took LNG ECPs after ovulation got pregnant at the same rate as would be expected if they had not used ECPs at all. Therefore, they are likely ineffective when taken after ovulation and do not prevent implantation of a fertilized egg.<sup>10,11</sup>

**Sperm:** Evidence is mixed about whether LNG ECPs affect sperm function by thickening cervical mucus (thereby inhibiting sperm motility)<sup>17-20</sup> or interfering with sperm migration.<sup>10</sup> Other evidence shows that LNG could cause sperm to be hyperactive in the absence of an egg or cause sperm to disorient and move in the wrong direction.<sup>21-25</sup>

**Existing pregnancy:** If taken after implantation has occurred, LNG ECPs have no effect on an existing pregnancy and do not increase rates of miscarriage. In the two studies addressing this question, pregnant individuals who had taken LNG EC had the same rates of miscarriage and fetal malformations as those who had not.<sup>2,26,27, 28</sup>

## CONCLUSION

The best available evidence indicates that levonorgestrel ECPs prevent or delay ovulation and may inhibit fertilization by interfering with sperm function, but do not prevent implantation. Science supports removing the theoretical mechanism of action about prevention of implantation from FDA-approved LNG ECP labels.

# References

- [1] Foundation Consumer Healthcare. Plan B One-Step Drug Facts. 2018. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/021998Orig1s006lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021998Orig1s006lbl.pdf)
- [2] Gemzell-Danielsson K, Berger C, Lalitkumar PGL. Emergency contraception - mechanisms of action. *Contraception*. 2013;87(3):300-308.
- [3] Levonorgestrel 1.5mg Tablets - Summary of Product Characteristics. 2022. <https://www.medicines.org.uk/emc/product/7308/smpc#gref>
- [4] ChoGlueck C. Broadening the scope of our understanding of mechanisms: Lessons from the history of the morning-after pill. *Synthese*. 2019;198:2223–2252.
- [5] Varney S. Misinformation Clouds America's Most Popular Emergency Contraception. Kaiser Health News. Published June 7, 2022. <https://khn.org/news/article/emergency-contraception-plan-b-private-equity-abortion-debate/>
- [6] Marions L, Hultenby K, Lindell I, Sun X, Stabi B, Gemzell Danielsson K. Emergency contraception with mifepristone and levonorgestrel: mechanism of action. *ObstetGynecol*. 2002;100(1):65-71.
- [7] Durand M, Cravioto MD, Raymond E, et al. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception. *Contraception*. 2001;64(4):227-234.
- [8] Hapangama D, Glasier A, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. *Contraception*. 2001;63(3):123-129.
- [9] 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.
- [10] Noe G, Croxatto HB, Maria Salvatierra A, et al. Contraceptive efficacy of emergency contraception with levonorgestrel given before or after ovulation. *Contraception*. 2011;84(5):486-492.
- [11] 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.
- [12] 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(6):442-450.
- [13] Endler M, Li R, Gemzell Danielsson K. Effect of levonorgestrel emergency contraception on implantation and fertility: A review. *Contraception*. 2022;109:8-18.
- [14] Okewole IA, Arowojolu AO, Odusoga OL, et al. Effect of single administration of levonorgestrel on the menstrual cycle. *Contraception*. 2007;75(5):372-377.
- [15] Meng CX, Andersson KL, Bentin-Ley U, Gemzell-Danielsson K, Lalitkumar PGL. Effect of levonorgestrel and mifepristone on endometrial receptivity markers in a three-dimensional human endometrial cell culture model. *Fertility & Sterility*. 2009;91(1):256-264.
- [16] Lalitkumar PGL, Lalitkumar S, Meng CX, et al. 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.
- [17] Kessler E, Garmendi F, Westphal N, Parada J. Hormonal and Peripheral Effects of D-Norgestrel in Postcoital Contraception. *Contraception*. 1974;10(4):411-424.
- [18] Kessler E, Camacho-Ortega P, Laudahn G, Schopflin G. In vitro action of progestogens on sperm migration in human cervical mucus. *Fertility & Sterility*. 1975;26(1):57-61.
- [19] Brito KS, Bahamondes L, Nascimento JAA, 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):225-228.
- [20] Yeung WSB, Chiu PCN, Wang CH, Yao YQ, Ho P chung. The effects of levonorgestrel on various sperm functions. *Contraception*. 2002;66(6):453-457.
- [21] Yanagimachi R. Mysteries and unsolved problems of mammalian fertilization and related topics. *Biol Reprod*. 2022;106(4):644-675.
- [22] Holt WV, Fazeli A. The oviduct as a complex mediator of mammalian sperm function and selection. *Mol Reprod Dev*. 2010;77(11):934-943.
- [23] Kölle S, Reese S, Kummer W. New aspects of gamete transport, fertilization, and embryonic development in the oviduct gained by means of live cell imaging. *Theriogenology*. 2010;73(6):786-795.
- [24] Strünker T, Goodwin N, Brenker C, et al. The CatSper channel mediates progesterone-induced Ca<sup>2+</sup> influx in human sperm. *Nature*. 2011;471(7338):382-386.
- [25] Lishko PV, Botchkina IL, Kirichok Y. Progesterone activates the principal Ca<sup>2+</sup> channel of human sperm. *Nature*. 2011;471(7338):387-391.
- [26] De Santis M, Cavaliere AF, Straface G, Carducci B, 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 & Sterility*. 2005;84(2):296-299.
- [27] Zhang L, Chen J, Wang Y, Ren F, Yu W, Cheng L. Pregnancy outcome after levonorgestrel-only emergency contraception failure: a prospective cohort study. *Human Reproduction*. 2009;24(7):1605-1611.
- [28] Jatlaoui TC, Riley H, Curtis KM. Safety data for levonorgestrel, ulipristal acetate and Yuzpe regimens for emergency contraception. *Contraception*. 2016;93(2):93-112.