



March 2011

## MECHANISM OF ACTION

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

#### Levonorgestrel-only emergency contraceptive pills:

- Interfere with an oocyte (egg) being released from the ovary when taken before ovulation;
- May possibly prevent the sperm and the egg from meeting by affecting the cervical mucus, sperm motility or the ability of sperm to bind to the egg.

### The Evidence:

#### 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.

#### 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>11,12,13,14,15</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>16</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>17</sup>
- One study showed that levonorgestrel did not prevent the attachment of human embryos to a simulated (in vitro) endometrial environment.<sup>18</sup>
- Animal studies demonstrated that LNG ECPs did not prevent implantation of the fertilized egg in the endometrium.<sup>19,20</sup>

#### 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>21,22</sup> However, two in vitro studies found that LNG in doses used for EC has no direct effect on sperm function.<sup>23,24</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>25</sup> In contrast, a small pilot study evaluating post-coital tests showed that sperm progressive motility was reduced to near 0% at 8 to 24 hours after LNG ECP intake.<sup>26</sup> If more than 24 hours elapse between LNG ECP intake and ovulation, sperm in the

reservoir of the cervical crypts may not migrate to the oviducts. 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>27</sup>

- Given these results, this mechanism of action is still uncertain and warrants further studies.

### 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 ECP's 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.



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Emergency Contraception

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