

EC: An Update

Several recent studies on the mechanism of action of levonorgestrel (Plan B/LNG) continue to suggest that the drug does not have an abortifacient effect. It works by preventing ovulation and when it does not prevent ovulation, it does not work.

In a review article (“Mechanism of Action of Emergency Contraception” *Contraception* 82 [2010]: 404-409), Kristina Gemzell-Danielsson concludes by saying that “EC with a single dose of 1.5 mg of LNG acts through inhibition or postponing ovulation but does not prevent fertilization or implantation and has no adverse effect on a pregnancy” (407). In fact, she says, “the ‘window of effect’ for LNG-EC is rather narrow. It begins after selection of the dominant follicle but ends before 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” (407). For this reason, she believes there is a need to develop more effective methods of EC. “To ensure the highest efficacy and to cover the entire window of fertility, the ideal agents for EC also need to target the endometrium” (407).

In an original research article (Gabriela Noe, et al., “Contraceptive Efficacy of Emergency Contraception with Levonorgestrel Given Before or After Ovulation,” *Contraception* 81 [2010]: 414-420), the authors offer preliminary

results of their ongoing study to evaluate whether or not LNG-EC prevents pregnancy when it is given after fertilization has occurred. Their study indicated that “LNG-EC is very effective in preventing pregnancy when it is administered before ovulation but it is ineffective in preventing pregnancy once fertilization has occurred” (420). In fact, they believe that LNG-EC is less effective than regular contraceptives “and its use should be restricted to emergency situations” (420).

In another original research article (C. X. Meng, et al., “Effects of Oral and Vaginal Administration of Levonorgestrel Emergency Contraception on Markers of Endometrial Receptivity,” *Human Reproduction* 25, no. 4 [2010]: 874-883), the authors sought to determine whether repeated oral and single vaginal administration of LNG affect the endometrium and thus potentially increase the drug’s efficacy. The reason for this study, as they point out, is that the standard regimen of LNG (1.5 mg in a single dose or a dose of 0.75 mg administered twice 12 hours apart) “has been shown to have no effect on endometrial development and markers of endometrial receptivity” (874). The researchers found that “although the expression of PR [progesterone receptors] and LIF [leukaemia inhibitory factor] was affected by high-dose oral levonorgestrel, it seems unlikely that these changes would

be enough to prevent implantation and a number of other biomolecules remained unchanged following levonorgestrel exposure” (881). The authors go on to observe that “the lack of effect on implantation is positive from a religious and social acceptance perspective, but it is unfortunate from a medical point of view since an endometrial effect would improve the EC efficacy...” (881).

Another study (Wilder Alberto Palomino, Paulina Kohen, and Luigi Devoto, “A Single Midcycle Dose of Levonorgestrel Emergency Contraceptive Does Not Alter the Expression of the L-Selectin Ligand or Molecular Markers of Endometrial Receptivity,” *Fertility and Sterility* 94, no. 5 [October 2010]: 1589-1594) tested the hypothesis that a single 1.5 mg dose of LNG-EC delivered by the oral or vaginal route at the time of LH surge affects the endometrial receptivity molecular phenotype. The results of their study led them to conclude that “the fact that endometrial maturation and receptivity are unaffected suggests that there are no direct or indirect effects of LNG on endometrial function. Thus, the mechanism of action of LNG-EC, if any, at the time of the LH surge does not include the impairment of PR or the endometrial receptivity biomarkers” (1593).

Finally, in another review of English-language studies of the mechanism of action of the Yuzpe regimen and levonorgestrel (Vivian Leung, Marc Levine, and Judith A. Soon, “Mechanisms of Action of Hormonal Emergency

Contraceptives,” *Pharmacotherapy* 30, no. 2 [2010]: 158-168), the authors state that “it appears that the closer to the time of ovulation emergency contraceptives are administered, the less likely they are to interfere with ovulation. After ovulation, the available data suggest that emergency contraceptive administration is ineffective, and postovulatory effects are unlikely. ... [F]or those who consider implantation or later events to be the beginning of pregnancy, there is substantial evidence for a nonabortive mechanism, and clinicians and the general public should be aware of this” (166, 167).

In March 2011, the International Federation of Gynecology and Obstetrics and the International Consortium for Emergency Contraception issued a statement called “Mechanism of Action: How Do Levonorgestrel-Only Emergency Contraceptive Pills (LNG ECPs) Prevent Pregnancy?” The statement considers three possible mechanisms of action—delaying or preventing ovulation, preventing implantation, and affecting sperm function. Regarding ovulation, the document states that “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.” Regarding effects on the endometrium and prevention of implantation, the statement considers different types of studies. The largest group of studies, they point out, show “that LNG ECPs have no such effect on the endometrium, indicating that they have no mechanism to prevent

implantation.” The same was true of the other studies that were mentioned. The statement concludes with several implications of the research on the mechanism of action of LNG. Among them are the following:

- 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.

RH

Widespread Focus on End-of-Life Issues

The popular press and professional medical journals have paid a considerable amount of attention to issues relating to end-of-life care over the past 10-12 months. Here is a sampling. There seem to be some common themes and some important lessons to be learned.

- A review article published in a recent issue of the *Annals of Internal Medicine* (D. Wendler and A. Rid, “Systematic Review: The Effect on Surrogates of

Making Treatment Decisions for Others,” *Annals of Internal Medicine* 154, no. 5 [March 1, 2011]: 336-46) found that a third of surrogate decision makers experience stress and guilt which can last for months or even years due to their having to make treatment decisions on behalf of their loved one. However, the presence of an advance directive that specifies the patient’s wishes substantially reduces the stress as does achieving consensus with other family members and the care team. These results provide another reason for promoting advance directives. Despite all the efforts made to educate around advance directives, estimates are that only 5-25% of the population have them (cf. *The Journal of the American Medical Association*, November 3, 2010).

- According to Dr. Dan Sulmasy in a November 3, 2010 commentary in *The Journal of the American Medical Association*, physicians should take a more active role in helping surrogates, in part by developing better ways of talking to them and better ways of involving them in the decision-making process. Physicians and hospitals often fail surrogate decision makers by leaving life and death choices solely to them instead of offering them needed guidance by helping them explore patient’s values and making recommendations in light of

- them. (See Daniel P. Sulmasy and Lois Snyder, "Substituted Interests and Best Judgments," *JAMA* 304, no. 17 [November 3, 2010]: 1946-1947).
- The results of a study out of the University of Pittsburgh indicated that family caregivers who had not discussed life support measures with critically ill patients took nearly two weeks longer to decide to forego further medical intervention than those who had prior conversations about the issues. In addition, surrogates were more confident about their role when they perceived their communication with intensive care physicians to be of high quality. Dr. Doug White, the senior investigator, noted that how physicians guide family members through critical illness may greatly influence their ability to act as surrogates. It also underscored the value of patients, families and friends having conversations about the patient's end-of-life preferences so that surrogates can feel more comfortable about their decisions. The study also indicated that 55 percent of surrogate decision makers wished to retain total control over end-of-life decisions, though most also wanted the physician's opinion. Forty percent of surrogates preferred sharing decisions with doctors, while 5 percent preferred that the physician make the decision. Researchers surveyed 230 surrogate decision makers for patients in ICUs who were likely to die. (S. Johnson, et al., "An Empirical Study of Surrogates' Preferred Level of Control over Value-laden Life Support Decisions in Intensive Care Units," *American Journal of Respiratory and Critical Care Medicine* 183, no. 7 [April 1, 2011; Epub October 29, 2010]: 915-21).
 - In an article in the August 23, 2010 *New York Times* ("Frank Talk About Care at Life's End"), Jane Brody refers to a bill ("New York Palliative Care Information Act") signed into law in New York State that requires physicians who are caring for patients with a life-threatening condition to offer them or their representatives information about prognosis and options for end-of-life care. Brody notes an October 2008 study published in *The Journal of the American Medical Association* in which Boston researchers found that patients who had end-of-life discussions with their physicians "were more likely to accept that their illness was terminal, prefer medical treatment focused on relieving pain and discomfort over life-extending therapies, and have completed a do-not-resuscitate order." These patients were also more likely to be enrolled in outpatient hospice. The researchers also found that the poorest quality of life and the worst bereavement adjustment for family resulted when patients

- received aggressive care during the last week of life.
- A fairly recent *National Journal*-sponsored survey indicated that an “overwhelming percentage of Americans support public discussion of end-of-life issues with 78 percent saying that palliative care and end-of-life treatment should be part of the public discussion. More than 70 percent believed that enhancing the quality of life for seriously ill patients is more important than a longer life. Only 23 percent thought it was more important to extend life by every means possible.
(www.nationaljournal.com/healthcare/no-death-panels-please).
- The results of a three-year study published in *The New England*

Journal of Medicine last August (J. Temel, et al., “Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer,” *The New England Journal of Medicine* 363, no. 8 [August 19, 2010]: 733-42) showed that those patients with fast-growing lung cancer who received palliative care from the time of their diagnosis reported less depression and happier lives and typically lived almost three months longer than those patients receiving standard care. Commenting on the study, one palliative care physician observed that when patients’ pain and other symptoms are controlled, they not only feel better, they live longer.

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