Ella Revisited

Last November, several mainstream media outlets reported the results of a 2011 study that appeared in the journal *Contraception* that claimed that Plan B (levonorgestrel--LGN) is not effective as emergency contraception for women with a body mass index >25 kg/m.[1] In its place, the authors recommended Ella (ulipristal acetate--UPA) or an intrauterine device. In the wake of this news, CHA received several queries about the use of UPA in Catholic hospitals. These queries prompted an examination of the more recent scientific literature on the mechanism of action of ulipristal acetate. A previous examination looked at the literature from 2010 and 2011.[2] The present review looked at the literature from 2011 until 2014.

There appear to be only two pieces of original research.[3] Using mice, the first study investigated the potential of UPA in blocking ovulation after the onset of the LH (luteinizing hormone) surge which, if it did occur, would explain why UPA is more effective than LGN. LGN, "if administered at least 2 days prior to the luteinizing hormone (LH) surge. … is able to cause either a delay or an inhibition of the LH surge, thereby preventing ovulation in women. However, LNG is unable to prevent ovulation if administered when the LH level has already started to rise."[4] In the present study, the researchers used human chorionic gonadotropin (hCG) which mimics luteinizing hormone.

What the researchers found is that "a single dose (30 mg) of UPA administered immediately before ovulation delays or inhibits ovulation in comparison to placebo-treated cycles. When administered before the onset of the LH surge, UPA, like LNG, delayed the LH peak and ovulation in all cycles. However, when administered after the LH level begins to rise but before it reaches the peak, LNG is ineffective as an ovulation blocker. However, UPA is an effective inhibitor of ovulation within this time period. In humans, the time interval from the rise of LH to its peak level is 30 to 36 hours. It appears that UPA needs to be administered during this time window in order to be maximally effective as an ovulation blocker. Once the LH reaches its peak, the UPA's effect in blocking ovulation declines sharply."[5]

This study did not set out to examine whether UPA might also affect the endometrium. However, the authors do say that while it is clear why UPA has the antiovulatory effect that it does, "we also need to consider the possibility that UPA has the potential to act at other sites including the endometrium."[6]

The second study, quite different in approach, essentially confirms the findings of the first and also does not address possible effects on the endometrium.

Several review articles appeared during the time span in question that address the mechanism of action of UPA.[7] All

essentially confirm the above. Three of the reviews speak to possible effects of UPA on the endometrium.[8] All three say the same thing: "The effect of UPA on the endometrium has also been demonstrated to be dose-dependent. Treatment with 10-100 mg UPA resulted in inhibition of down-regulation of progesterone receptors (PRs), reduced endometrial thickness and delayed histological maturation with the highest doses, while the effect of lower doses equivalent to the 30 mg used for EC were similar to that of placebo."[9] All three refer to one particular study in support of this conclusion.[10] The consensus at this time seems to be that UPA at a dose of 30 mg which is what is administered for EC does not adversely affect the endometrium.

However, there is also an alternative reading of the literature upon which this conclusion rests.[11] Five physicians from the Department of Woman's and Children's Health at the University of Padua, Padova, Italy, take exception with the analysis of the mechanism of action of UPA found in four studies in the primary literature.[12] Upon these studies, "the most authoritative drug agencies and scientific societies report that UPA works by either inhibiting or delaying ovulation."[13] The authors disagree. Here is their reasoning:

> The effects of UPA were reported to be highly dependent on the levels of LH at the time of administration: before the onset of the LH surge, the ability of UPA to delay ovulation was 100%. After the onset but prior to the LH peak, it fell to 78.6%, whereas at the peak and after, it dropped to 8.3%.
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> Moreover, in the results section, when reporting the interval from UPA intake to follicular rupture, the authors stated and detailed verbatim that "*when UPA was given at the time of the LH peak, the time elapsed to rupture was similar to placebo* …."
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> This indicates that when either placebo or UPA was administered 1 to 2 days before ovulation, their effects on ovulation were null, which appears to be the opposite of the conclusions of the article. Any attempt to suggest that, even when taken on the day of the LH peak, UPA can still delay ovulation for 24 to 48 hours appears unacceptable. At that time, in fact, both the placebo and the UPA are ineffective and ovulation occurs when it was scheduled to occur, approximately two days after the intake of the tablets. …
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> This evidence suggests that the effectiveness of UPA relies on other mechanisms, particularly on its endometrial effects.[14]

The authors then go on to describe endometrial effects (essentially the same as those mentioned above) as reported in the three articles they examined.[15] They conclude:

> In our opinion, all the endometrial effects described in these 3 articles are able to interfere with the process of implantation. …
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> The UPA might also function by delaying ovulation, but this effect has only been consistently proven in the mid-follicular phase before the beginning of the fertile period when EC plays no role. Once the fertile period has started, UPA is able to delay ovulation only before LH increase. Thereafter, this effect is no longer consistent, whereas it is lost in the preovulatory days.
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> The efficacy of UPA, reported to prevent more than 80% of expected pregnancies, is thus likely to be due to the described endometrial effects that make the tissue unsuitable for embryo implantation.[16]

If these authors are correct in their analysis of the primary literature on the mechanism of action of UPA, then the use of UPA in Catholic hospitals is highly questionable from a moral perspective. If, however, the consensus is correct, then there would seem to be sufficient moral certitude at this time to make use of UPA in Catholic hospitals. In either case, additional study of the mechanism of action of UPA is desirable, especially at the dose that is used for emergency contraception.

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Editor's Note: As we were finalizing production of this issue of HCEUSA, we learned that the AP reported on July 24 that the European Medicines Agency announced, after a review of the evidence sparked by the French manufacturer of UPA's declaration that levonorgestrel as an emergency contraceptive didn't work in women weighing more than 80 kilograms (176 pounds), that the drug levonorgestrel is suitable as an emergency contraceptive for heavier women. "The EMA said it had assessed all the available evidence and announced the data 'are too limited and not robust enough to conclude with certainty' that the pill's efficacy is reduced in heavier women. It said the results of these studies should be included in the product information but that current warnings on Norlevo's packaging should be deleted."

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[1] Anna Glasier, Sharon Cameron, Diana Blithe et al. "Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel." *Contraception* 84 (2011): 363-367. Interestingly, five of the co-authors of this article are employees of HRA Pharma that produces ulipristal acetate or Ella.

[2] See Ron Hamel, "Ella (Ulipristal Acetate): Taking another Look." *Health Care Ethics USA* 20, no. 3 (Summer 2012) :17-20.

[3] Shanmugasundaram Nallasamy, Jaeyeon Kim, Regine Sitruk-Ware, Milan Bagchi, Indrani Bagchi. "Ulipristal Blocks Ovulation by Inhibiting Progesterone Receptor-Dependent Pathways Intrinsic to the Ovary." *Reproductive Sciences* 20, no. 4 (2012): 371-81; Vivian Brache, Leila Cochon, Maeva Deniaud, Horacio B. Croxatto. "Ulipristal acetate prevents ovulation more effectively

than levonorgestrel: analysis of pooled data from three randomized trials of emergency contraception regimens." *Contraception* 88 (2013): 611-18.

[4] Nallasamy, 371.

[5] Ibid., 378-79.

[6] Ibid., 379.

[7] Narendra Nath Sarkar. "The state-of the-art of emergency contraception with the cutting edge drug." *German Medical Science* 9 (2011) accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC3141844/; Shilpa Jadav and Dinesh Parmar. "Ulipristal acetate, a progesterone receptor modulator for emergency contraception." *Journal of Pharmacology & Pharmacotherapeutics* 3, no 2 (April-June 2012):109-111; Kristina Gemzell-Danielson, Cecelia Berger, P.G.I. Lalitkumar. "Emergency Contraception—mechanisms of action." *Contraception* 87 (2013): 300-08; Kristina Gemzell-Danielson, Thomas Rabe and Linan Cheng. "Emergency Contraception." *Gynecological Endocrinology* 29 (2013): 1-14; P.G.L. Lalitkumar, Cecilia Berger, Kristina Gemzell-Danielson. "Emergency Contraception." *Best Practice & Research Clinical Endocrinology & Metabolism* 27 (2013): 91-101.

[8] Gemzell-Danielson, "Emergency Contraception," p. 6; Gemzell-Danielson, "Emergency contraception—mechanisms of action," p. 304; Lalitkumar, op. cit., p.93.

[9] Lalitkumar, p. 93.

[10] P. Stratton, D. Levens, B. Hartog, et al. "Endometrial effects of a single early dose of the selective progesterone receptor modulator CDB-2914." *Fertility and Sterility* 93 (2010): 2035-41.

[11] Bruno Mozzanega, E. Cosmi, G. B. Nardelli. "Ulipristal Acetate: Critical Review about Endometrial and Ovulatory Effects in Emergency Contraception." *Reproductive Sciences* 21, no. 6 (2014): 678-85. See also, Bruno Mozzanega, S. Gizzo, S. Di Gangi, E. Cosmi, G. B. Nardelli. "Ulipristal acetate in emergency contraception: mechanism of action." *Trends in Pharmacological Sciences* 24, no. 4 (April 2013): 195-96.

[12] The four articles are: V. Brache, V., L. Cochon, C. Jesam, et al. "Immediate preovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture." *Human Reproduction* 25, no.9 (2010):2256-63; P. Stratton, B. Hartog, N. Hajizadeh, et al. "A single midfollicular dose of CDB-2914, a new antiprogestin, inhibits folliculogenesis and endometrial differentiation in normally cycling women." *Human Reproduction* 15, no. 5 (2000): 1092-99; Stratton et al., op. cit. (2010); M.D.Passaro, J. Piquion, N. Mullen, et al. "Luteal phase dose response relationships of the antiprogestin CDB-2914 in normally cycling women." *Human Reproduction* 18, no. 9 (2003): 1820-27.

[13] Mozzanega, p. 680.

[14] Ibid., 681.

[15] Ibid.

[16] Ibid., 682.