Ella (Ulipristal Acetate): Taking Another Look

Ella, the newest and considered to be the more effective emergency contraceptive on the market, has been in the news again of late. One the one hand, the Republican presidential candidate and two former Republican presidential candidates have referred to emergency contraceptives (which are either Plan B or Ella) as “abortive pills.” Much if not most of the opposition, written and verbal, to the Obama administration’s “contraceptive mandate” refers to “abortion-inducing drugs” and some of it explicitly refers to Ella as such.

On the other hand, a recent New York Times article (Pam Belluck, “Abortion Qualms on Morning-After Pill May Be Unfounded,” June 5, 2012) takes a different stance. It suggests that the scientific evidence is not present to claim that either Plan B or Ella have an abortifacient effect. Regarding Ella, the author writes “Research on Ella, approved in 2010, is less extensive [than Plan B], but the F.D.A., Dr. Blithe [of the N.I.H.], and others say evidence increasingly suggests it does not derail implantation, citing, among other things, several studies in which women became pregnant when taking Ella after ovulating. The studies, focused on Ella’s effectiveness, were not designed to determine if it blocked implantation, but experts still consider them significant.”

Most recently, the mechanism of action of emergency contraceptive medications was addressed on NPR’s “Science Friday” both in a blog written by James Trussell and Kelly Cleland (“Emergency Contraception: How It Works—How It Doesn’t,” at http://sciencefriday.com/blogs/06/15/2012/emergency-contraception-how-it-works-how-it-doesnt.html and in an interview (“How the Morning-After Pill Works” at http://sciencefriday.com/topics/body-brain/segment/06/15/2012/how-the-morning-after-pill-works.html) with Kristina Gemzell-Danielson, professor of obstetrics and gynecology at the Karolinska Institute in Stockholm, Sweden. Trussell and Gemzell-Danielson have done extensive work over many years on the mechanism of action of emergency contraception drugs. The latter states categorically that Ella’s mechanisms of action occur prior to ovulation and that Ella has no post-ovulation effects. Were that the case, Ella would be more effective. Trussell and Cleland write: “[T]here is no evidence that, at the doses used for EC, these methods [including ulipristal] would effectively prevent implantation. There is some evidence that ulipristal acetate can produce changes in the uterine lining, but whether these changes would impair the implantation of a fertilized egg is unknown.”

While neither the New York Times article nor the “Science Friday” contributions definitively resolve the matter of Ella’s mechanism of action, they do invite another look at the scientific literature.
Several observations can be made based on a review of a great deal of the literature—both original research and review articles.

- While it is true that ulipristal acetate is a cousin of RU486 (an undisputed abortifacient), it is also true that ulipristal acetate, one of several drugs in the class of selective progesterone receptor modulators (SPRMs) is a different drug with different effects. As one article puts it: “Among all SPRMs studied, mifepristone, the pioneer drug, somehow remains a separate entity because its properties as an antagonist are unique and because mifepristone is the only SPRM that is able to interrupt pregnancy in several species, including humans.”¹ Hence, it would not be accurate to claim that ulipristal must be capable of an abortifacient effect just because mifepristone is capable of such as I did in two past “Ethical Currents.”² Not only are the different compositions and effects of the two drugs significant, so are the dosages administered. The mechanism of action of ulipristal needs to be determined on its own and cannot simply be inferred by its chemical relationship to mifepristone.

- Some have interpreted ulipristal’s longer effectiveness (it can be effective up to 120 hours unlike levonorgestrel’s 72 hours) to be an indication that it can have an abortifacient effect if it does not prevent ovulation. This is not, however, what the scientific literature suggests. There is another explanation for ulipristal’s increased effectiveness. In the words of one original study: “’[T]he ability of LNG [levonorgestrel] to interfere with the ovulatory process is limited to its administration during the period preceding the onset of the LH surge. Once the ovulatory process has been triggered by the LH surge, this progestogen agent cannot prevent the follicle from rupturing and releasing the oocyte, an event that normally takes place 36 h[ours] later. … Our results show that the ability of UPA [ulipristal acetate] to interfere with follicular rupture appears to depend on when the drug is administered in relation to LH levels. When administered before the onset of the LH surge, UPA delayed the LH peak and follicular rupture in all cycles; when administered after onset of the LH surge but before the LH peak, the magnitude of the effect was still significant. In contrast, in cycles in which the UPA treatment took place on the day of the LH peak, when a significant rise in P had already occurred, follicular rupture followed within 24-48 h with the exception of one woman. . . .”³

In other words, ulipristal can inhibit or significantly delay rupture of the follicle that releases an egg for over five days if
administered immediately before ovulation by postponing the LH peak. The 5-day window is important because it corresponds to the estimated lifespan of sperm in the female genital tract.

Other researchers offer a similar explanation. “By the time the follicle reaches 18-20 mm (and ovulation should occur within 48 h[ours]) and the probability of conception is over 80%, ovulation is prevented by levonorgestrel in only 12% of cycles (compared with 13% in the placebo group). By contrast, when ulipristal acetate is given in the presence of a follicle measuring 18-20 mm, it prevents ovulation in 60% of cycles, therefore potentially preventing pregnancy in substantially more women than does levonorgestrel. The ability of ulipristal acetate to inhibit ovulation even when it is given just before ovulation is particularly important because at this time in the cycle the probability of conception is at its peak and the frequency of sexual intercourse is at its highest.”

At this point in time, an endometrial effect cannot be excluded, however, there is virtually no scientific evidence to support such an effect. In the words of Anna Glasier et al.: “Progesterone-receptor modulators, including ulipristal acetate, given at high or repeated doses [emphasis added] have an effect on endometrial histology and histochemistry that could theoretically impair implantation of a fertilized oocyte. Although an endometrial effect, and therefore an additional postovulatory mechanism of action, cannot be excluded, the dose of ulipristal acetate used in this trial was specifically titrated for emergency contraception on the basis of inhibition of ovulation and might be too low to inhibit implantation.”

More research needs to be done on post-ovulatory effects, if any, of ulipristal. The research to date has focused almost exclusively on effectiveness and safety of the drug and in determining its impact on the ovulatory process. At the present time, there does not seem to be the scientific evidence to come to a conclusion one way or the other regarding a potential abortifacient effect of ulipristal.

In light of the above, there seems to be good reason to be cautious about descriptions of the mechanism of action of ulipristal acetate. There does not seem to be the scientific evidence to categorically label the drug as having an abortifacient effect. And good ethics, as is often said, begins with good facts or, in this case, good science.

Also, given the state of the science regarding the mechanism of action of ulipristal when administered post ovulation, the use of Plan B...
(levonorgestrel) seems to offer a safer course for Catholic hospitals. Much more is known about its mechanism of action. RH

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2 “Ethical Currents,” Health Care Ethics USA, Summer 2010 and Summer 2011.
5 Ibid. Glasier et al. cite a study by Pamela Stratton, Eric Levens, Beth Hartog et al., “Endometrial Effects of a Single early Luteal Dose of the Selective Progesterone Receptor Modulator CDB-2914,” Fertility and Sterility 93, no. 6 (April 2010): 2035-2041. Their female subjects received a single dose of CDB-2914 (10, 50, or 100 mg) or placebo administered after ovulation and within two days of the LH surge. Researchers found a delay in endometrial maturation in some subjects (especially those receiving 50 mg and 100 mg doses) and a significant dose-dependent alteration in endometrial thickness. Another study examined the effects on the endometrium of a mid-luteal phase (post-ovulatory) administration of CDB-2914 (another term for ulipristal). Subjects were given either a 1, 10, 50, 100 or 200 mg dose of the drug. At a dose of 200 mg, the drug consistently induced early endometrial bleeding, but this occurred much less frequently at lower doses. The dose used for emergency contraception is 30 mg. See Maureen Passaro, Johann Piquion, Nancy Mullen, et al., “Luteal Phase Dose-Response Relationships of the Antiprogestin CDB-2914 in Normally Cycling Women,” Human Reproduction 18, no. 9 (2003): 1820-1827.