Ulipristal and Embryotoxicity—An Alternative Viewpoint

Karim Anton Calis, Pharm.D., M.P.H., FASHP, FCCP

Key Words: obesity, endocrinology, drug safety, nutrition, public health, women's health, drug information.
(Pharmacotherapy 2012;32(9):e176–e177)

In a recent article in the Journal, Shrader, et. al. reviewed the use of levonorgestrel and ulipristal for hormonal emergency contraception.[1] Their stated goal was to educate clinicians and address misconceptions about these drugs. The authors, however, omitted essential safety information about ulipristal that is critical for patient counseling. Although they correctly emphasized that the progestin levonorgestrel will not terminate a pregnancy after implantation of an embryo, they neglected to address the same issue as it relates to ulipristal. This is of concern because unlike levonorgestrel, ulipristal, a mixed progesterone agonist/antagonist, can indeed terminate an established pregnancy. The authors state that "ulipristal should not be used if patients know or suspect that they are pregnant," yet they fail to clarify that ulipristal—the active ingredient in Ella—is pharmacologically related to the abortifacient mifepristone (RU-486, Mifeprex) and can induce serious embryotoxicity and terminate an early pregnancy after implantation. These are relevant facts that should be disclosed and highlighted, not minimized or obscured. The FDA-approved label for Ella identifies "existing or suspected pregnancy" as a contraindication to the use of ulipristal and designates the drug as Pregnancy Category X.[2] Unlike mifepristone, controlled studies with ulipristal in pregnant women were not conducted since the manufacturer elected to develop the drug for pregnancy prevention rather than the more controversial indication of pregnancy termination. Nonetheless, ulipristal exposure in pregnant rabbits and rats results in predictable embryotoxicity and fetal loss comparable to that reported in the nonclinical studies with mifepristone.[2] This is vital scientific information that should be communicated to women in a manner that acknowledges and respects their diverse values and beliefs. In the interest of full disclosure, health care professionals have an obligation to educate prospective ulipristal recipients about the drug's abortifacient potential. Without this information some women will be denied the opportunity to make an informed choice.

For reprints, visit https://caesar.sheridan.com/reprints/redir.php?pub=10089&acro=PHAR. For questions or comments, contact Karim Anton Calis Pharm.D., M.P.H., FASHP, FCCP; e-mail: k.a.calis@gmail.com.

References

1. **Shrader SP, Hall LN, Ragucci KR, Rafie S.** Updates in hormonal emergency contraception. Pharmacotherapy. 2011Sep;31(9):887–95.
2. **Watson Pharma, Inc.** Ella (ulipristal) package insert. Morristown, NJ; 2010.

Authors' Reply

The comments provided by Dr. Calis address an important matter. Limited scientific data, especially in humans, are available for this debated area of clinical practice. Ulipristal is a selective progesterone receptor modulator with a similar structure to mifepristone. Mifepristone is also a selective progesterone receptor modulator and is administered at a dose of 600 mg in conjunction with misoprostol, a prostaglandin, for medical termination of a pregnancy.[1] However, the doses of mifepristone necessary for pregnancy termination are higher and not equipotent to the dose used of ulipristal for emergency contraception. While there are limited and small studies available regarding the poten-

tial of ulipristal inhibiting implantation in rats and rabbits, there are no studies reporting pregnancy termination.[2, 3] It is also important to note, that potential histologic changes in the endometrium that occur with various forms of emergency contraception would be unlikely to result in inhibiting implantation in humans.[4] Additionally, pregnancy is defined as the period from implantation to delivery, so prevention of implantation would be an additional contraceptive mechanism.[5, 6] Certainly controversy exists with this newer emergency contraceptive option. At this time, there is no clear evidence in humans that ulipristal inhibits implantation or terminates a pregnancy. However, we do agree with Dr. Calis that more clinical data in this area are needed for women to make the most informed decision about their contraceptive options.

References

1. Mifeprex prescribing information. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020687s015lbl.pdf. Accessed December 21, 2011.
2. **Hild SA**, **Reel JR**, **Hoffman LH**, **Blye RP.** CDB-2914: anti-progestational/anti-glucocorticoid profile and post-coital anti-fertility activity in rats and rabbits. Hum Reprod 2000;15:822–9.
3. **Reel JR**, **Hild-Petito S**, **Blye S.** Antiovulatory and postcoital antifertility activity of the antiprogestin CDB-2914 when administered as single, multiple, or continuous doses to rats. Contraception 1998;58:129–36.
4. **American College of Obstetricians and Gynecologists.** ACOG practice bulletin no. 112: emergency contraception. Obstet Gynecol 2010; 115: 1100–9.
5. United States code of federal regulations: protection of human subjects. 45 CFR 46.202, Effective July 14, 2009. Available from http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html. Accessed December 21, 2011.
6. **Hughes EC (ed.)**. Committee on terminology, The American College of obstetricians and gynecologists, *Obstetric-Gynecologic Terminology*. Philadelphia PA: F.A. Davis Company, 1972.

Sarah P. Shrader, Pharm.D.
Larissa N. Hall, Pharm.D.
Kelly R. Ragucci, Pharm.D.
Sally Rafie, Pharm.D.