Ulipristal Acetate

The Newest Emergency Contraceptive

JEANNE M. WILTON, RN, MS, WHNP-BC

Even with the many contraceptive options available to American women, more than 50 percent of pregnancies in the United States are unplanned (Hatcher et al., 2007). It's estimated that the probability of pregnancy after unprotected intercourse or failed contraception is as high as 30 percent, depending on the time in the menstrual cycle when intercourse occurs (Faculty of Family Planning & Reproductive Health Care Clinical Effectiveness Unit, 2006; Hatcher et al.).

Emergency contraception has been shown to possibly reduce the risk of pregnancy as much as 75 percent (Hatcher et al., 2007). The goal of emergency contraception is to inhibit or delay ovulation, though it's not always administered at the time of ovulation (Hatcher et al.). Studies on the effectiveness of different methods of emergency contraception are, therefore, based on when the drugs are administered during the menstrual cycle.

To review, there are four phases to the menstrual cycle. Day 1 is the first day of menses and begins the follicular phase. A rise in gonadotropin-releasing hormone (GNRH) from

Abstract More than 50 percent of pregnancies in the United States are unplanned. Emergency contraception has been shown to possibly reduce the risk of pregnancy by as much as 75 percent. Ulipristal acetate is a selective progesterone receptor modulator that was approved by the U.S. Food and Drug Administration (FDA) for emergency contraceptive use in August 2010. This article reviews information on its mechanism of action, efficacy, safety and implications for women's health nurses. DOI: 10.1111/j.1751-486X.2012.01752.x

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Rx

the hypothalamus stimulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) to be released from the anterior pituitary (Hatcher et al., 2007). The increase in FSH stimulates ovarian follicular development. One follicle eventually dominates and is supported by the release of estrogen. This causes a negative feedback loop, decreasing GNRH and FSH, causing menstrual flow to stop. As the midcycle LH surge begins, around day 14, the ovulatory phase

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begins. This promotes follicular rupture and release of the oocyte (egg). Ovulation generally occurs 24 to 36 hours after this estradiol peak and 10 to 12 hours after the LH surge (Hatcher et al.). This makes the window of fertilization beginning 5 days before ovulation through 1 day after ovulation. Highest rates of conception occur within 2 days of ovulation (Hatcher et al.). The luteal phase is this time from the end of ovulation to the beginning of the next menstrual cycle. During this phase, estrogen and progesterone prepare the endometrium for implantation. If fertilization does not occur, levels of these hormones decline and the endometrium is shed, beginning the menstrual phase.

Current Methods of Emergency Contraception

The currently available methods of emergency contraception work by altering the various stages of the menstrual cycle, therefore reducing unplanned pregnancies.

Copper-releasing IUDs are approved by the American College of Obstetricians and Gynecologists (ACOG) as an effective method of emergency contraceptive in women who want long-term contraception (ACOG, 2010). When inserted as emergency contraception, they are considered effective at reducing unwanted pregnancy to rates of 0.0 to 0.2 percent. The mechanism of action for IUDs used in this way is to prevent fertilization (Zhou & Xiao, 2001).

In the mid-1960s, high doses of estrogen were found to prevent unplanned pregnancies (Hatcher et al., 2007). Since this method caused a significant amount of nausea and vomiting, a Canadian professor, A. Albert Yuzpe, introduced a combination of low estrogen and progestin method in 1974. Referred to as the "Yuzpe method," it consists of 200 mcg of ethinyl estradiol and 1 mg of norgestrel administered 12 hours apart within 72 hours of intercourse (Hatcher et al.). Until the late 1990s, this was the main oral method of emergency contraception. Currently, progestin-only (levonorgestrel) emergency contraception has become the standard method because it is simpler to administer and lacks the side effect of nausea. It is given either in two doses of 0.75 mg separated by 12 hours or a single 1.5-mg dose (Box 1) (Hatcher et al., 2007; Richardson & Maltz, 2011). However, once the LH surge has begun and the time from ovulation increases, levonorgestrel cannot exhibit its effect on ovulation. Therefore, its efficacy declines as the duration of time between administration and intercourse increases, thereby limiting its time of administration to a maximum of 72 hours post intercourse (ACOG, 2010). In practice and according to some authorities, levonorgestrel can be given up to 120 hours after intercourse, but is more effective within those first 72 hours (Hatcher et al.). Both the single- and two-dose combinations are now available without a prescription to women 17 years and older and by prescription only for those under age 17 (ACOG).

Mifepristone is a selective progesterone receptor modulator (SPRM) that works by delaying ovulation and preventing implantation. It is not available for use as an emergency contraceptive in the United States (Hatcher et al., 2007). It is, however, used in combination with a prostaglandin analogue as an abortifacient (Hatcher et al.).

Ulipristal Acetate (Ella)

Ulipristal acetate (Ella) is an SPRM that is similar to mifepristone but with less antiglucocorticoid activity (Richardson & Maltz, 2011). The FDA approved Ella for emergency contraception in August 2010 (Richardson & Maltz).

Pharmacology and Mechanism of Action

Ulipristal acetate has both agonistic and

Jeanne M. Wilton, RN, MS, WHNP-BC, is a women's health nurse practitioner at Wheaton Franciscan Healthcare Medical Group-All Saints in Racine, WI.
The author reports no conflicts of interest or relevant financial relationships.
Address correspondence to: jeanne.wilton@wfhc.org.

Box 1.

Progestin-Only Oral Methods of Emergency Contraception

Brand Name	Generic Name	Dosage
Plan B	Levonorgestrel	0.75 mg × 2 doses 12 hours apart within 72 hours of intercourse
Next Choice	Levonorgestrel	0.75 mg × 2 doses 12 hours apart within 72 hours of intercourse
Plan B One-Step	Levonorgestrel	1.5 mg × 1 dose within 72 hours of intercourse

antagonistic effects on the progesterone receptor (Watson Pharmaceuticals, 2010). Once bound to this receptor, it interferes with the receptor's DNA transcription (Richardson & Maltz, 2011). The principal effect is to inhibit ovulation, but the mechanism may vary depending on when the drug is administered during the menstrual cycle (McKeage & Croxtall, 2011; Richardson & Maltz). During the follicular phase, it is believed to block the LH surge and follicular development; during the luteal phase, it is thought to alter the endometrium (Richardson & Maltz). At least two studies have shown suppression of follicular development in more than half of treatment cycles within 5 days of ulipristal acetate administration and, when given before the LH surge, 100 percent follicular rupture (Brache et al., 2010; Stratton et al., 2000). However, when administered after the LH peak, rupture was stopped in only 8.3 percent of cycles (Brache et al.).

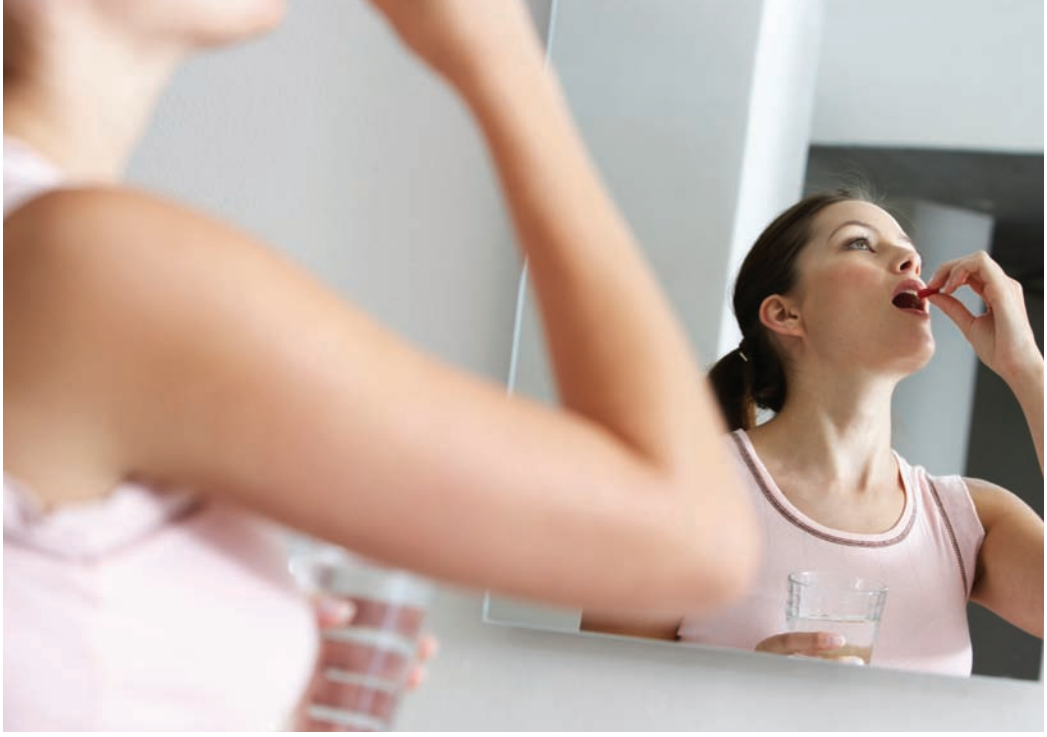
Effectiveness

One Phase II and two Phase III trials have evaluated ulipristal acetate.

In the Phase II trial, Creinin and colleagues studied 1,549 women, 775 who received 30 mg of ulipristal acetate and 774 who received 0.75 mg of levonorgestrel 72 hours after unprotected intercourse (Creinin et al., 2006). A total of 20 pregnancies occurred in this study, 7 in the ulipristal acetate group and 13 in the levonorgestrel group, which is a 50 percent reduction in pregnancies in the ulipristal acetate group (Creinin et al.).

In one Phase III trial, Fine and colleagues conducted a multicenter, open-label study of women who presented at Planned Parenthood clinics across the United States 48 to 120 hours after unprotected intercourse (Fine et al., 2010). The primary efficacy endpoint was pregnancy rate. Women were followed up for 5 to 7 days after expected onset of menses (Fine et al.). Women were excluded if, at presentation, they were pregnant, breastfeeding, using an IUD, post-tubal ligation, unsure about their menstrual cycle or their partner had a vasectomy. After this screening, 1,533 received treatment with ulipristal acetate, but only 1,241 women were included in the efficacy population (Fine et al.). Reasons for exclusion from efficacy analysis were age > 35 years, no unprotected intercourse at screening, pregnancy status at follow-up unknown, repeated enrollment and pregnancy not considered due to emergency contraception failure (Fine et al.). One half (52.5 percent) of participants were found to be between days 10 and 20 of their cycle (i.e., in the fertile window). The overall pregnancy rate was 2.1 percent (26 women). The expected pregnancy rate would have been 5.5 percent or 69 pregnancies, which is significantly higher (Fine et al.).

Glasier et al. (2010) conducted a randomized, multicenter, noninferiority trial of 2,221 women at 35 family planning clinics in the United Kingdom, Ireland and the United States. Women were offered emergency contraception within 120 hours of unprotected intercourse and were randomized to receive either 30-mg ulipristal acetate or 1.5-mg levonorgestrel. Eligibility criteria and pregnancy outcome were similar to the Fine et al. study described above. Of the 2,221 women, 1,696 received emergency contraception within 72 hours. There were 15 pregnancies in the ulipristal acetate group and 22 in the levonorgestrel group. In the 203 women who received emergency contraception



Ulipristal acetate is administered as a 30-mg, one-time oral tablet within 120 hours (5 days) of unprotected intercourse

between 72 and 120 hours, only three pregnancies occurred, all in the levonorgestrel group. Ulipristal acetate was statistically more effective in preventing pregnancies than levonorgestrel up to 5 days after unprotected intercourse ($P < 0.037$) (Glasier et al.).

Dosage

Ulipristal acetate is administered as a 30-mg, one-time oral tablet within 120 hours (5 days) of unprotected intercourse (Richardson & Maltz, 2011; Watson Pharmaceuticals, 2010). It can be taken with or without food and at any point during the menstrual cycle (Watson Pharmaceuticals). If vomiting occurs within 3 hours, the dose should be repeated (Watson Pharmaceuticals).

Adverse Effects

In the studies conducted by Fine et al. and Glasier et al., the most commonly reported adverse events were headache (18 percent to 19 percent), nausea (12 percent to 13 percent) and abdominal pain (8 percent to 15 percent) (Fine et al., 2010; Glasier et al., 2010). Dysmenorrhea, fatigue and dizziness were also reported but at much lower rates. Both studies also reported changes in menstrual cycles. Women receiving ulipristal acetate in the Fine study had delayed menses by 2.8 days and in the Glasier study by 2.1 days (Fine et al.; Glasier et al.).

Considerations/Precautions

Ulipristal acetate should not be used more than once during a menstrual cycle, because the safety of this practice has not been determined (Watson Pharmaceuticals, 2010). It is contraindicated during pregnancy and is not used to terminate a pregnancy, so pregnancy should be ruled out before administration (Watson Pharmaceuticals). Fertility will return quickly, so it is important to return to routine contraception immediately after administration (Watson Pharmaceuticals). However, barrier methods of contraception are recommended until the start of the next menstrual period due to the high binding affinity of ulipristal acetate to progesterone receptors (McKeage & Croxtall, 2011; Watson Pharmaceuticals).

No studies have evaluated ulipristal acetate in women with hepatic or renal failure. The company warns that the drug not be used in those with severe hepatic impairment (McKeage & Croxtall, 2011).

Since ulipristal acetate is primarily metabolized by the CYP3A4 pathway, there may be interactions with other drugs that inhibit or induce CYP3A4. Although this has

not yet been studied in humans, it is recommended that ulipristal acetate not be administered with proton-pump inhibitors, antacids or potent CYP3A4 inhibitors such as ketoconazole or clarithromycin (McKeage & Croxtall, 2011). Currently, there are no data on use of this drug in women who are breastfeeding (Watson Pharmaceuticals, 2010).

Cost

The cost of ulipristal acetate (Ella), $43, is comparable to the $41 cost of levonorgestrel 1.5 mg (Plan B One Step) and $35 for two 0.75-mg levonorgestrel (Next Choice). Thomas, Schmid and Cameron (2010) did a cost analysis study comparing levonorgestrel 1.5 mg and ulipristal acetate 30 mg. They took the costs of both drugs and the costs of the consequences of unintended pregnancies (miscarriages, induced abortion and birth) and compared them in a decision model from the perspective of the National Health Service in the United Kingdom (Thomas et al.). Their findings showed that the cost of preventing one additional unintended pregnancy was £311 (US$493), ranging from 183 to 500 pounds (US$290 to $793) (incremental cost-effectiveness ratio). All of these costs were less than the estimated cost of the unintended pregnancy at 948 pounds (US$1,504) or induced abortion at 672 pounds (US$1,066) (Thomas et al.).

Implications for Nurses

As demonstrated in these studies, ulipristal acetate may reduce the risk of unintended pregnancy by as much as 75 percent (Richardson & Maltz, 2011). It's important for ambulatory care OB/GYN nurses and nurse practitioners to counsel women on the availability of emergency contraceptive options when they're discussing other methods of contraception, because condoms break and women sometimes forget to take birth control pills.

If administering ulipristal acetate, it is important to do a pregnancy test first and a good medical history to rule out any of the contraindications described above. Also, remember that this is often a difficult and stressful situation for the woman involved. Be respectful and responsive to her needs. In cases of rape or incest, it is important that appropriate referrals and reporting measures be followed and that it is emphasized to the patient that this will be kept confidential (Hatcher et al., 2007). Women, particularly in this situation, may also need prophylaxis for sexually transmitted infection (Hatcher et al.).

Follow-up is important to make sure the patient uses an alternate method of contraception and gets her next menses. Even though there were no incidences of ectopic pregnancies in the studies of ulipristal acetate, it is important to review this possibility with the patient, as well as signs of severe abdominal pain 3 to 5 days after administration (Watson Pharmaceuticals, 2010).

Conclusion

Ulipristal acetate (Ella) is a new and effective emergency contraceptive that can be used within 5 days of unprotected intercourse. Nurses should add this to their current repertoire of contraceptive counseling. **NWH**

References

American College of Obstetricians and Gynecologists (ACOG). (2010). Emergency contraception. Practice bulletin no. 112. *Obstetrics and Gynecology, 115*, 1100–1109.

Brache V., Cochon L., Jesam, C., Maldonado, R., Salvatierra, A. M., Levy, D. P., … Croxatto, H. B. (2010). Immediate pre-ovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture. *Human Reproduction, 25*(9), 2256–2263.

Creinin, M., Schlaff, W., Archer, D. F., Wan, L., Frezieres, R., Thomas, M., … Higgins, J. (2006). Progestin receptor modulator for emergency contraception: A randomized control trial. *Obstetrics & Gynecology, 108*(5), 1089–1097.

Faculty of Family Planning & Reproductive Health Care Clinical Effectiveness Unit. (2006). FFPRHC guidance: Emergency contraception. *Journal of Family Planning and Reproductive Health Care, 32*, 121–128.

Fine, P., Mathe, H., Ginde, S., Cullins, V., Morfesis, J., & Gainer, E. (2010). Ulipristal acetate taken 48–120 hours after intercourse for emergency contraception. *Obstetrics & Gynecology, 115*(2 PT 1), 257–263.

Glasier, A. F., Cameron, S. T., Fine, P. M., Logan, S. J., Casale, W., Van Horn, J., & Gainer, E. (2010). Ulipristal acetate versus levonorgestrel for emergency contraception: A randomized non-inferiority trial and meta-analysis. *Lancet, 375*(9714), 555–562.

Hatcher, R. A., Trussel, J., Nelson, A. L., Cates, W., Stewart, F., & Kowal, D. (Eds.) (2007). *Contraceptive technology* (19th ed.). New York: Ardent Media, Inc.

McKeage, K. & Croxtall, J. D. (2011). Ulipristal acetate: A review of its use in emergency contraception. *Drugs, 71*(7), 935–945.

Richardson, A. R., & Maltz, F. N. (2011). Ulipristal acetate: Review of the efficacy and safety of a newly approved agent for emergency contraception. *Clinical Therapeutics, 34*(1), 24–36.

Stratton, P., Hartog, B., Hajizadeh, N., Piquion, J., Sutherland, D. Merino, M., … Nieman, L. K. (2000). A single mid-follicular dose of CDB-2914, a new antiprogestin, inhibits folliculogenesis and endometrial differentiation in cycling women. *Human Reproduction, 15*(5), 1092–1099.

Thomas, C. M., Schmid, R., & Cameron, S. (2010). Is it worth paying more for emergency hormonal contraception? The cost-effectiveness of ulipristal acetate versus levonorgestrel 1.5 mg. *Journal of Family Planning & Reproductive Health Care, 36*(4), 197–201.

Watson Pharmaceuticals. (2010). Ella (ulipristal acetate) prescribing information. Morristown, NJ.

Zhou, L., & Xiao, B. (2001). Emergency contraception with multi-load cu-375 SL IUD: A multicenter clinical trial. *Contraception, 64*, 107–112.