Ulipristal Acetate Taken 48–120 Hours After Intercourse for Emergency Contraception

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OBJECTIVE: To evaluate the efficacy and safety of ulipristal acetate as emergency contraception in women presenting 48–120 hours after receiving ulipristal acetate for unprotected intercourse.

METHODS: Women aged 18 years or older with regular cycles who presented for emergency contraception 48 to 120 hours after unprotected intercourse were enrolled in 45 Planned Parenthood clinics and treated with a single dose of 30 mg ulipristal acetate. Pregnancy status was determined by high-sensitivity urinary human chorionic gonadotropin testing and return of menses.

RESULTS: A total of 1,241 women were evaluated for efficacy. Twenty-six were pregnant at follow-up, for a pregnancy rate of 2.1% (95% confidence interval 1.4–3.1%). These results satisfy the protocol-defined statistical criteria for success because the pregnancy rate was lower than both the estimated expected pregnancy rate and a predefined clinical irrelevance threshold. In addition, efficacy did not decrease over time: pregnancy rates were 2.3% (1.4–3.8%), 2.1% (1.0–4.1%), and 1.3% (0.1–4.8%) for intervals of 48 to 72 hours, more than 72 to 96 hours, and more than 96 to 120 hours, respectively. Adverse events were mainly mild or moderate, the most frequent being headache, nausea, and abdominal pain. Cycle length increased a mean of 2.8 days, whereas the duration of menstrual bleeding did not change.

CONCLUSION: Ulipristal acetate is effective and well-tolerated for emergency contraception 48–120 hours after unprotected intercourse.

LEVEL OF EVIDENCE: II

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Emergency contraception is a woman's second chance for primary prevention of pregnancy. A reproductive-age woman is a candidate for emergency contraception if she seeks care within 120 hours of unprotected intercourse, which is the window of pregnancy risk associated with a given act of intercourse based on the estimated lifespan of sperm in the genital tract.[1] Current hormonal methods of emergency contraception prevent at least half of expected pregnancies if taken within 72 hours of unprotected intercourse.[2]

Levonorgestrel, at a total dose of 1.5 mg (taken in a single dose or two 0.75-mg doses 12 hours apart), is the current standard for hormonal emergency contraception and is approved for use up to 72 hours after unprotected intercourse. Clinical trials involving levonorgestrel used for emergency contraception more than 72 hours after intercourse do not conclusively establish efficacy rates because of insufficient sample size. Nevertheless, these studies reveal a trend toward markedly higher failure rates when levonorgestrel is taken 48 hours or more after unprotected intercourse.[2,3] This trend may be explained by the mode of action of levonorgestrel for emergency contraception. Levonorgestrel acts by interfering with the luteinizing hormone peak but does not seem to interfere with the ovulatory process when taken close to ovulation, a time when intercourse is most likely to lead to fertilization.[4–6] Ulipristal acetate, on the other hand, has been shown to prevent ovulation and thus fertilization even after the luteinizing hormone surge has begun (Croxatto H, Brache V, Cochon L, Jesam C, Salvatierra AM, Levy D, et al. The effects of immediate pre-ovulatory administration of 30mg ulipristal acetate on follicular rupture

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For a woman who presents for emergency contraception more than 72 hours after intercourse, the only currently available method proven to be highly effective is insertion of a copper intrauterine device (IUD). However, IUDs are not widely available in many countries, and insertion can only be performed by a trained clinician. Furthermore, many women decline IUD insertion as a method of emergency contraception because the procedure is invasive, is relatively expensive, and has a risk of complications, including uterine perforation on insertion.[7] Additionally, many women seeking emergency contraception are not seeking a long-acting contraceptive method.

There is, therefore, a need for a new hormonal emergency contraceptive that can be used and is highly effective up to 120 hours after unprotected intercourse. Ulipristal acetate (also known as CDB-2914) is a selective progesterone receptor modulator that inhibits or delays ovulation in a dose-dependent fashion.[8] In a double-blind noninferiority trial, ulipristal acetate was shown to be as efficacious as levonorgestrel for preventing pregnancy when used within 72 hours of unprotected intercourse.[9] Moreover, study data suggest improved efficacy in preventing pregnancy from 48 to 72 hours when levonorgestrel efficacy markedly wanes. The hypothesis for this study is, therefore, that ulipristal acetate will act as an effective emergency contraceptive up to 120 hours after unprotected intercourse. The objective of this prospective, multicenter, open-label study is to evaluate the efficacy and safety of ulipristal acetate as emergency contraception in women presenting 48–120 hours after unprotected intercourse.

METHODS

This study was conducted in accordance with International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, and the U.S. Code of Federal Regulations and was approved by Chesapeake Institutional Review Board. All 45 participating sites were Planned Parenthood family planning clinics located in the United States.

Women aged 18 years and older who presented for emergency contraception 48–120 hours after unprotected intercourse and who met the inclusion/exclusion criteria were enrolled into the study after signing the institutional review board–approved informed consent. Women were enrolled between November 2006 and March 2008, with follow-up and data collection completed by May 2008. The inclusion criteria were regular menstrual cycles 24–35 (±5) days in length, no current use of hormonal contraception, willingness not to use hormonal contraception until study completion, and agreement to use barrier methods of contraception from enrollment to study completion. Exclusion criteria included pregnancy, breastfeeding, IUD, tubal ligation or partner vasectomy, and uncertainty about recent menstrual history.

A total of up to three visits were scheduled over the course of the study. The first visit, considered day 1, included the screening and treatment phases. A high-sensitivity urine pregnancy test (level of detection 20 milliinternational units/mL) was performed, and a blood sample was taken and stored for later serum quantitative β-hCG testing to exclude preexisting pregnancy if a pregnancy was detected during the study.

Women were provided daily diaries in which to record further acts of intercourse, contraception used, vaginal spotting or bleeding, concomitant medication, and adverse events during study duration.

At the first follow-up visit (5–7 days after expected onset of menses), a high-sensitivity urine pregnancy test was performed.

- If the urine pregnancy test result was positive, this was confirmed by a serum β-hCG test. The pretreatment serum specimen was also assayed for β-hCG to verify whether the pregnancy predated intake of the study drug.
- If the urine pregnancy test result was negative and menses had occurred, no further follow-up was performed, and study participation was completed.
- If the urine pregnancy test result was negative but menses had not occurred, a second follow-up visit was scheduled 1 week later, and the same procedures were repeated.
- Women with negative pregnancy test results but whose menses had not occurred by the second follow-up visit were contacted every 2 weeks, and periodic pregnancy testing was performed until return of menses. If menses had not returned by 60 days, clinically appropriate testing for secondary amenorrhea was performed (thyrotropin, follicle-stimulating hormone, luteinizing hormone, estradiol [E2], prolactin, progestin challenge, and ultrasonography).

Confirmed pregnancies were further evaluated by serum quantitative human chorionic gonadotropin testing and transvaginal ultrasonography to determine the estimated fertilization date. The estimated day of fertilization and the fertile window of −5 to +1 days were based on transvaginal ultrasonography. All pregnancy outcomes were collected, including elec-

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tive or spontaneous abortion or ongoing prenatal care and delivery.

Safety was assessed by the reporting of adverse events and changes in menstrual patterns. In addition, biochemical parameters (complete blood count, liver and renal function, lipids, and random glucose) were evaluated in a subset of 100 women using blood specimens drawn at enrollment and study completion at two predefined participating sites.

A data safety monitoring board consisting of independent experts reviewed all pregnancy and safety data. Meetings were held after completion of 200, 600, and 900 women and at study completion. Rules for stopping the study because of excessive pregnancies or safety concerns were applied. In addition, the data safety monitoring board assessed each pregnancy and determined whether it was compatible with study drug failure in providing emergency contraception.

Women could enroll in the study more than once, but they must have completed prior study participation before reenrolling. Safety laboratory testing, as described previously, was performed on all women repeating enrollment.

The primary efficacy measurement was the pregnancy rate, defined as the number of pregnancies after administration of ulipristal acetate for emergency contraception divided by the number of women treated. The primary efficacy analysis compared this pregnancy rate to the pregnancy rate that would have been expected in the absence of emergency contraception treatment, which was calculated according to the method of Trussell et al[10] using the pooled recognizable set of conception probabilities and the estimated cycle day of unprotected intercourse based on self-reported date of last menstrual period, cycle length, and date of unprotected intercourse. The observed pregnancy rate was considered to be statistically significantly lower than the expected pregnancy rate if the upper bound of the two-sided 95% confidence interval (CI) of the observed pregnancy rate calculated using the Agresti-Coull method[11] was below the estimated expected pregnancy rate.

The main secondary efficacy analysis compared the upper bound of the 95% CI of the observed pregnancy rate with a clinical irrelevance threshold of 4%. This threshold corresponds to a reduction by half of the expected 8% pregnancy rate in the absence of contraception as observed in previous international studies.[2,3,12] The study was to be considered a success only if both the primary efficacy and the main secondary analyses were conclusive. Other secondary analyses included calculation of the prevented fraction, defined as the number of pregnancies prevented (expected minus observed) divided by the number of pregnancies expected, and analysis of trend in pregnancy rates over time (by 24-hour interval) using a logistic regression model.

The population analyzed for primary efficacy excluded women who were lost to follow-up and women aged 36 years and older, because of reduced fertility in this age category based on U.S. Food and Drug Administration guidance.[13] Further participations in the study allowed by protocol were also excluded from primary efficacy evaluation, as well as pregnancies that were determined as not compatible with study drug failure by the data safety monitoring board.

Safety was evaluated by frequency and intensity of adverse events as well as clinically significant changes in laboratory results. Variations in menstrual cycle characteristics, including cycle length and duration of menses, were assessed by comparing baseline with posttreatment bleeding patterns using a paired *t* test.

The sample size was estimated to reach at least 80% power for statistical analyses comparing the observed pregnancy rate with the expected pregnancy rate as well as with a clinical irrelevance threshold (set at 4%, corresponding to a 50% reduction in the expected pregnancy rate as estimated in previous clinical trials of emergency contraceptive methods).[2,3] Using the hypothesis of a 2.5% pregnancy rate with ulipristal acetate for treatment 48–120 hours after unprotected intercourse, 1,200 participants were needed to demonstrate that the pregnancy rate was lower than the clinical irrelevance threshold. Study enrollment was stopped when 1,200 participants meeting the criteria for the primary efficacy analysis had completed the study.

RESULTS

Overall, 1,623 requests for emergency contraception led to screening for enrollment into the study, of which 90 were screen failures, leaving 1,533 women treated, which comprised 1,449 unique participants plus 84 emergency contraception treatments on subsequent (repeat) enrollment. Demographics and baseline characteristics as well as safety information are described for all women treated (safety population). Pregnancy status was unknown in 106 women (6.9%), mainly because they were lost to follow-up. Of the safety population, 1,241 were eligible for inclusion in the population used for primary efficacy analysis (primary efficacy population); those excluded were for reasons of age greater than 35 years (90 women), unknown pregnancy status at follow-up (106 women), repeat enrollment (84 women), and pregnancies deemed

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not compatible with emergency contraception failure by the data safety monitoring board (three women). Enrollment details are presented in Figure 1.

Study participants were primarily young (mean age 24.4 years), white (60.3%), and healthy weight to overweight (mean body mass index [in kg/m^2] 25.3) (Table 1). Demographic and baseline characteristics were similar between the safety population and the primary efficacy population (data not shown).

Data from the obstetric and gynecologic history showed that more than one half of women reported a history of pregnancy (52.4%), and a similar proportion reported past use of emergency contraception (52.5%) (Table 2). Women enrolled reported a mean menstrual cycle length at screening of 29 days and requested emergency contraception primarily for reasons of intercourse without contraception (72.3%) or condom breakage or slippage (25.3%). Just more than half of the participants (55.6%) took the study drug 48–72 hours after unprotected intercourse, with the others presenting later.

Women reported unprotected intercourse throughout the entire cycle (range, cycle day 1–41). Unprotected intercourse tended to have taken place during the periovulatory fertile window, as shown in Figure 2. Indeed, the majority of women (52.5%) presented with unprotected intercourse that took place between cycle days 10 and 20.

A total of 29 pregnancies were detected at follow-up in women enrolled in this study. Three pregnancies were excluded from the primary efficacy analysis population because the data safety monitoring board determined that they were not compatible with emergency contraception failure (ie, one pretreatment and two posttreatment pregnancies). The primary efficacy population comprised 1,241 women with 26 pregnancies, for an overall pregnancy rate of 2.1% (95% CI 1.4–3.1%). The expected pregnancy rate using the methodology of Trussell et al was 5.5%, meaning that 69 pregnancies would have been expected in the primary efficacy population had no emergency contraception been given.[10] The upper limit of the two-sided 95% CI of the observed pregnancy rate (3.1%) was therefore significantly lower than the expected pregnancy rate as well as the clinical irrelevance threshold (4%), so the results met the protocol

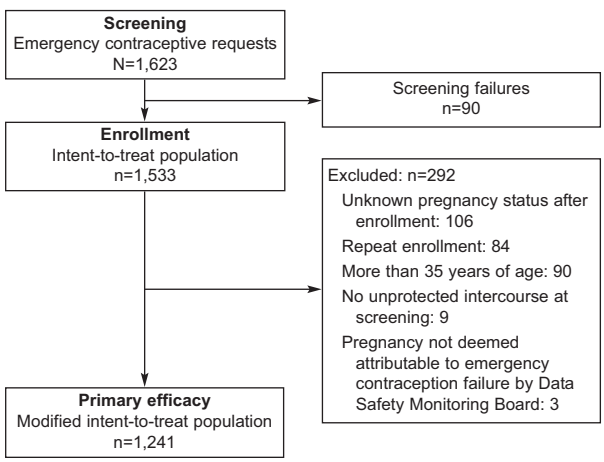

Fig. 1. Enrollment details.

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Table 1. Demographics and Baseline Characteristics

Characteristic	ITT Population (n=1,533)
Age (y)	24.4±6.1 (23.0 (18.0–50.0))
Age category (y)	
18–20	29.1
21–25	39.9
25–30	16.8
31–35	7.8
36 and older	6.5
Race	
White	60.3
African American	21.5
Asian	2.3
Other	13.9
Ethnicity	
Not Hispanic	77.8
Hispanic	22.2
Education	
Less than 12 y	8.6
High school graduate	21.7
Some college	50.1
College graduate	17.6
Master or doctorate level	2.0
Body mass index	25.3±6.2 (23.5 [16.1–61.3])
Smoking status	
Current smoker	32.0
Former smoker	18.9
Never smoked	49.1

ITT, intention-to-treat.
Data are mean±standard deviation (median [minimum–maximum]) or percentage.

Table 2. Gynecologic History

Gynecologic History	ITT Population (n=1,533)
Ever been pregnant (yes)	52.4
Previous use of emergency contraception (yes)	52.5
Cycle length at screening (d)	29.0±1.8 (29.0 [24.0–35.0])

ITT, intention-to-treat.
Data are percentage or mean±standard deviation (median [minimum–maximum]).

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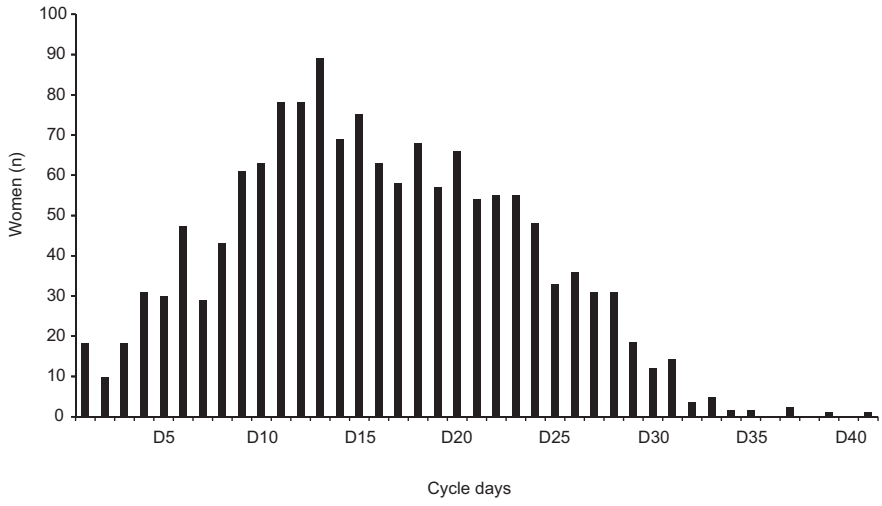

Fig. 2. Distribution of unprotected intercourse across reported cycle days.

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definition of study success. Efficacy was also confirmed in the safety population of 1,533 women where the observed pregnancy rate was 1.9% (95% CI 1.3–2.8%) compared with an expected pregnancy rate of 5.7%.

The proportion of pregnancies prevented by ulipristal acetate overall was 62.3% (95% CI 41.9–75.6%). The pregnancy rates and prevented pregnancy fraction were analyzed by 24-hour time intervals after unprotected intercourse, as presented in Table 3 below. There is no evidence of change in efficacy over time as confirmed when testing the linear trend of pregnancy rates over time in a logistic regression model (P=.44). It should be noted that 14 of the 26 observed pregnancies occurred in women whose unprotected intercourse took place outside of the presumed fertile window that extends from day −5 to day +1 relative to ovulation.

Overall, 876 (61.4%) of the women treated experienced a total of 2,232 adverse events, of which 49.6% were considered to be at least possibly treatment related. The majority (89.1%) of the adverse events were mild or moderate in intensity and resolved spontaneously. The most frequent adverse events are listed in Table 4 below.

Table 4. Most Common Related Adverse Events*

Event	ITT Population (n=1,533)
Headache	9.3
Nausea	9.2
Abdominal pain	6.8
Dysmenorrhea	4.1
Dizziness	3.5
Fatigue	3.4

ITT, intention-to-treat.
Data are %.
Adverse events were assessed as certainly, probably, or possibly treatment-related by the investigator.
* Intention-to-treat population (n=1,533).

No women were discontinued from the study because of adverse events. The percentage of women who experienced at least one adverse event was comparable in the safety population (n=1,533) and in the primary efficacy population (n=1,241). Women who enrolled more than one time did not experience adverse events more frequently than women who enrolled only once.

Menstrual cycle length increased from a mean of 29.0 days as reported at inclusion to 31.8 days accord-

Table 3. Efficacy According to Time After Unprotected Intercourse*

	All	48 to 72 h	More Than 72 to 96 h	More Than 96 to 120 h
Exposed (n)	1,241	693	390	158
Expected pregnancies (n)†	69	42	19	8
Observed pregnancies (n)	26	16	8	2
Expected pregnancy rate (%)	5.5	6.0	5.0	4.9
Observed pregnancy rate (%) (95% CI)	2.1 (1.4–3.1)	2.3 (1.4–3.8)	2.1 (1.0–4.1)	1.3 (0.1–4.8)
Effectiveness (prevented %) (95% CI)	62.3 (41.9–75.6)	61.9 (36.3–77.2)	57.9 (14.6–79.2)	75.0 (6.2–93.3)

Data are n, %, or % (95% confidence interval).
* Modified intention-to-treat population.
† Based on pooled recognizable set of conception probabilities.[10]

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ing to data collected in diaries. A total of 256 women (19.2%) reported a delay of greater than 7 days in the onset of menses after treatment, and 94 (7%) experienced a delay of 15 days or more. Delay in menses was not associated to a particular demographic or medical history profile. After treatment, 134 women (8.7%) experienced intermenstrual bleeding other than menses, whereas intermenstrual bleeding rate before enrollment based on the last 3 months was reported by 51 women (3.3%) (Table 5). In 91.8% of these women, the intermenstrual bleeding was described as spotting. There were no changes in the biochemical parameters (complete blood count, liver and renal function, lipids, and random glucose) in the 100 women monitored before and after treatment that were considered as clinically significant.

Of the 26 women who became pregnant, 15 elected to have induced abortion, five had spontaneous abortion, five decided to carry the pregnancy to term, and one was lost to follow-up with pregnancy outcome unknown. Of the five women continuing their pregnancies, one delivered a healthy neonate and efforts are ongoing to obtain information on birth outcome for the other four.

DISCUSSION

This study demonstrates that a single 30-mg dose of ulipristal acetate is effective when used as emergency contraception 48–120 hours after unprotected intercourse. Of particular clinical relevance is the sustained efficacy of ulipristal acetate up to 120 hours of unprotected intercourse. A comparison of expected versus observed numbers of pregnancies shows a statistically significant benefit of the treatment in reducing pregnancy risk throughout the time interval of 48–120 hours, with sample sizes in the intervals of 72–96 hours and 96–120 hours warranting further investigation with larger numbers.

Although the majority of women enrolled in this study presented for emergency contraception after midcycle unprotected intercourse (days 11–16), a large proportion of women were enrolled after unprotected intercourse that took place outside their presumed fertile window as defined by the conception probabilities model of Trussell et al.[10] This explains why the expected pregnancy rate estimated in this study (5.5%) is notably lower than that in previous large emergency contraception trials (8%).[2,3] However, it should be noted that 14 of the 26 pregnancies observed occurred in women whose unprotected intercourse took place outside their presumed fertile window and who were, therefore, according to the method of Trussell et al, assigned a conception probability of zero. The results of this study therefore reinforce previous data that suggest that unprotected intercourse outside of the supposed midcycle fertile period may indeed result in pregnancy[14] and support current practice guidelines recommending that emergency contraception be administered regardless of cycle day of unprotected intercourse. These data also suggest that the expected pregnancy rate might be an underestimation and, consequently, that the actual prevented fraction might be higher than the 62% calculated.

The currently available emergency contraception drug levonorgestrel is approved for use up to 72 hours after unprotected intercourse and is also used off-label beyond 72 hours, but its efficacy has been shown to decrease in a statistically significant fashion over time.[2,3] The time-dependent nature of the efficacy of levonorgestrel was one of the main driving factors in widespread efforts to render emergency contraception easily and rapidly accessible for women in need, including making levonorgestrel emergency contraception available on an over-the-counter basis in some 30 countries worldwide. Despite broad-scale educational campaigns regarding the importance of early emergency contraception intake for optimal efficacy, significant numbers of women continue to present several days after unprotected intercourse. According to data from a large World Health Organization study of emergency contraception,[3] 1 in 10 women present more than 72 hours after unprotected intercourse. Because ulipristal acetate has already been shown to be as effective as levonorgestrel for intake 0–72 hours after unprotected intercourse,[9] this study was designed to obtain evidence regarding

Table 5. Changes in Menstrual Cycle*

	Cycle Characteristics Reported at Screening and Based on the 3 mo Before the Study	Cycle Characteristics Observed During Treatment Cycle
Cycle length (d)	29.0±1.8	31.8±10.2
Duration of menses (d)	4.7±1.1	5.1±1.8
Intermenstrual bleeding	51 (3.3)	134 (8.7)

Data are mean±standard deviation or n (%).
* Intention-to-treat population (n=1,533).

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efficacy in the late intake time window, hence the enrollment starting at 48 hours and later. Indeed, almost 50% of women in this study presented for emergency contraception more than 72 hours after unprotected intercourse. Insertion of a copper IUD is a highly effective but poorly accessible method of emergency contraception. There is, therefore, a clear need for a highly effective hormonal method of emergency contraception for late intake.

Overall, ulipristal acetate is well tolerated. The adverse events reported here were usually mild or moderate in intensity and resolved spontaneously. No patient was discontinued from the study because of adverse events. The nature and frequency of the most common adverse events reported in this study (headache, nausea, and abdominal pain) mirror those reported in similarly sized studies of approved levonorgestrel emergency contraception products.[3]

Ulipristal acetate use was associated with a slight increase in menstrual cycle length, but the majority of women experienced normal menses within 7 days of the expected date, thereby reinforcing current recommendations for pregnancy testing if menses is more than 1 week late. The majority of treated participants had no change in duration of menstrual bleeding, and only a small proportion experienced posttreatment intermenstrual bleeding, primarily light bleeding or spotting. Intermenstrual bleeding (not related to menses) has been observed at a higher incidence (some 15–30%) in studies of levonorgestrel emergency contraception, but a head-to-head comparative trial would be required to establish whether this is an advantage of ulipristal acetate.

This study was designed in compliance with international regulatory agencies, including the U.S. Food and Drug Administration, and its results are strengthened by the study's prospective design and large, geographically and racially/ethnically diverse cohort. Additionally, the proportion of women who were lost to follow-up after study drug intake was small, although the limited follow-up regarding continuing pregnancy outcomes is a study limitation.

In conclusion, the results of this study demonstrate that ulipristal acetate prevents pregnancies when used as emergency contraception up to 120 hours after intercourse, making it the first hormonal method of emergency contraception with solid evidence of efficacy for late intake. In addition, the drug was well tolerated. This study served as a pivotal trial in the European registration dossier for the recently approved product ellaOne (ulipristal acetate 30 mg tablet; HRA Pharma, Paris, France) (European Union Commission Decision, May 15, 2009), making ulipristal acetate the first progesterone receptor modulator approved as emergency contraception and the first hormonal method of emergency contraception labeled for use up to 120 hours after unprotected intercourse. After European market introduction, it is anticipated that ellaOne will become available in the United States and worldwide, pending regulatory approvals.

REFERENCES

1. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation: effects on the probability of conception, survival of the pregnancy, and sex of the baby. N Engl J Med 1995;333:1517–21.
2. von Hertzen H, Piaggio G, Van Look PF. Emergency contraception with levonorgestrel or the Yuzpe regimen. Task Force on Postovulatory Methods of Fertility Regulation. Lancet 1998;352:1939.
3. von Hertzen H, Piaggio G, Ding J, Chen J, Song S, Bartfai G, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. Lancet 2002;360:1803–10.
4. Croxatto HB, Brache V, Pavez M, Cochon L, Forcelledo ML, Alvarez F, et al. Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. Contraception 2004;70:442–50.
5. Marions L, Cekan SZ, Bygdeman M, Gemzell-Danielsson K. Effect of emergency contraception with levonorgestrel or mifepristone on ovarian function. Contraception 2004;69:373–7.
6. Wilcox AJ, Baird DD, Dunson DB, McConnaughey DR, Kesner JS, Weinberg CR. On the frequency of intercourse around ovulation: evidence for biological influences. Hum Reprod 2004;19:1539–43.
7. Grimes D. Intrauterine devices. In: Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart FH, Kowal D, editors. Contraceptive technology. 18th ed. New York (NY): Ardent Media; 2004. p. 499–502.
8. Stratton P, Hartog B, Hajizadeh N, Piquion J, Sutherland D, Merino M, et al. A single mid-follicular dose of CDB-2914, a new antiprogestin, inhibits folliculogenesis and endometrial differentiation in normally cycling women. Hum Reprod 2000;15:1092–9.
9. Creinin MD, Schlaff W, Archer DF, Wan L, Frezieres R, Thomas M, et al. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. Obstet Gynecol 2006;108:1089–97.
10. Trussell J, Rodriguez G, Ellertson C. New estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception 1998;57:363–9.
11. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportion. Am Statist 1998; 52:119–26.
12. Piaggio G, von Hertzen H, Grimes DA, Van Look PF. Timing of emergency contraception with levonorgestrel or the Yuzpe regimen. Task Force on Postovulatory Methods of Fertility Regulation. Lancet 1999;353:721.
13. Center for Drug Evaluation and Research. Guidance for development of vaginal contraceptive drugs. January 27, 1995. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071704.pdf. Retrieved November 10, 2009.
14. Wilcox AJ, Dunson D, Baird DD. The timing of the "fertile window" in the menstrual cycle: day specific estimates from a prospective study. BMJ 2000;321:1259–62.

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