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Ulipristal Acetate: Critical Review About Endometrial and Ovulatory Effects in Emergency Contraception

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Abstract

The effectiveness of emergency contraception (EC) is usually estimated by comparing the number of observed pregnancies to that of expected pregnancies after unprotected intercourse. Second-generation selective progesterone receptors modulators have been developed and evaluated for EC use. Among these compounds, ulipristal acetate (UPA) has been proven to share the same antiprogestin activity as mifepristone, and as with mifepristone, UPA has been demonstrated to be effective up to 120 hours after unprotected intercourse. The UPA is more effective than levonorgestrel (LNG) in preventing the appearance of clinically evident pregnancies. The LNG delays ovulation only when taken at the beginning of the fertile period; taken later, it is ineffective on ovulation, while it has been proven to impair the subsequent luteal function. The effectiveness of LNG decreases as time elapses and is limited to 72 hours after unprotected intercourse. The UPA maintains consistent effectiveness for 5 days after unprotected intercourse, and this effectiveness is independent on which of these 5 days it is taken. The ability of UPA to delay ovulation decreases progressively as ovulation approaches and is null at the time of the luteinizing hormone (LH) peak: 1 to 2 days before ovulation, UPA behaves as a placebo. The persistent effectiveness of the drug cannot be due to antiovulatory action, as it decreases sharply as LH approaches its peak level. The effectiveness is most likely due to the dramatic endometrial effects of the drug that are produced regardless of when it is taken. These effects are consistently present, as the threshold for altering endometrial morphology is lower than the threshold for altering folliculogenesis.

Keywords

ulipristal acetate, emergency contraception, ovulation delay, endometrial effects, unexpected pregnancy

Introduction

Emergency contraception (EC) is defined as the use of any drug or device after unprotected intercourse with the aim of preventing an unwanted pregnancy.[1]

Unprotected intercourse can lead to pregnancy only if it occurs in the fertile period of the cycle, that is, in the 4 to 5 days preceding ovulation and on the ovulation day itself. Among the fertile days, the preovulatory day is the day on which intercourse is more frequent and the probability of conception is highest, followed by the ovulation day and by the second day preceding ovulation.[2-5] On these same days, the frequency of pregnancy from unprotected intercourse peaks.[6]

The effectiveness of EC is usually estimated by comparing the number of observed pregnancies to that of expected pregnancies after unprotected intercourse.[5] These calculations are difficult[7] and the effectiveness of EC in some cases may have been overestimated.[8]

The most widely used drug is levonorgestrel (LNG), which is typically taken at an oral dose of 1.5 mg within 72 hours of intercourse.[9,10] We detailed our observations on its mechanism of action in a previous article.[11]

The LNG is reported to interfere with ovulation.[12] However, ovulation is mostly inhibited only when EC is taken early in the cycle, when the risk of conception is low. Ovulation is not inhibited when LNG is taken in the advanced follicular phase, that is, in the most fertile days of the cycle.[11-14]

In a recent study, among patients treated in the preovulatory phase, ovulation was observed in 66% (57 of 87 patients). Nevertheless, no clinically evident pregnancies were observed of the 13 expected.[15]

The official statements "*How do Levonorgestrel-only emergency contraceptive pills (LNG-ECPs) work to prevent pregnancy?*"[(p1)] that were issued by the International Consortium for Emergency Contraception (ICEC) and the International Federation of Gynecology & Obstetrics (FIGO) in

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2008, 2011, and 2012[16(p2)] state that "*inhibition or delay of ovulation is LNG-ECPs' principal and possibly only mechanism of action*." Surprisingly, the statement authors themselves,[17] in their own articles, report that "*when LNG-ECPs were administered in the advanced pre-ovulatory phase, follicle rupture was inhibited in only 14.6% women,*"[12(p445),14(p2262),18(p436)] a conclusion that sharply clashes with that offered to the whole world as a conclusive FIGO statement.

In some of the studies quoted in the statements, the preovulatory administration of LNG frequently ended in a normal ovulation followed by a short or inadequate luteal phase,[11,19-23] which can lead to inadequate endometrial development. These effects might explain the effectiveness of LNG despite its poor antiovulatory effect.

More recently, the availability of selective progesterone receptor modulators (SPRMs)—which are highly effective for pregnancy termination—has also led to attempts to use them in EC. Among these drugs, mifepristone has been proven effective even when taken up to 120 hours after intercourse.[24-28] The optimal dose of mifepristone for EC is 25 to 50 mg.[10]

Many controversies, however, limit its widespread use.[27,29] The SPRMs, in fact, proved able to prevent the secretive differentiation of the endometrium and the shift of the maternal innate immune system to the condition of tolerance toward the embryo. Both the actions, which are produced by progesterone, are critical for a successful implantation.[30,31]

Second-generation SPRMs have been developed and evaluated for EC use. Among these drugs, ulipristal acetate (UPA) has been proven to share the same antiprogestin activity as mifepristone and, as with mifepristone, it has been proven to be effective up to 120 hours after unprotected intercourse.[6,13] The UPA is marketed as Ella(One) (Laboratoire HRA Pharma, 5 rue Beranger, Paris) in Europe and Ella in the United States; it is presented as an antiovulatory drug.

In this review, we evaluate the articles that analyze the effects of UPA in the various phases of the menstrual cycle. Our aim is to understand which effects are the most crucial to explaining the efficacy of UPA in EC.

Data Sources

We considered articles published in English on UPA and EC. Our search was conducted through PubMed, Cochrane Library, ClinicalTrials.gov, and official documents by HRA Pharma (Paris, France), the manufacturer of the UPA, in particular its briefing materials for the Food and Drug Administration (FDA).[32]

Primary literature was obtained to clarify UPA's mechanisms of action. Review articles were also used but only to report their conclusions on this specific topic. We limited the search to articles published after September 2010 and through March 2013.

We also took into consideration phase II and III studies that evaluated the efficacy of UPA and compared it with that of LNG. The product labeling approved by the US FDA and by the European Medicines Agency (EMA) was also carefully evaluated.

Our keywords for the search were "Ulipristal Acetate" and "Selective Progesterone Receptor Modulators." We combined these keywords with "emergency contraception," "unintended pregnancy," "ovulation," and "endometrium." The references of the retrieved articles were also examined to identify significant articles that might have been missed during the main search.

Results

We identified 4 studies in the primary literature[14,33-35] dealing with the UPA mechanism of action in women and, in particular, with its effects on the ovarian follicles and the endometrium. These studies are the same experimental articles on which HRA Pharma,[32] the FDA,[36] and the EMA[37] base their official conclusions. Two studies describe the effects of UPA on follicles,[14,33] and 3 describe the effects on the endometrium.[33-35] One study examines both.[33] The careful evaluation of these 4 articles will take up the bulk of our review and is the main purpose of our review.

Before focusing on the articles, however, we will describe the UPA molecule and its reported efficacy in preventing the appearance of clinically evident pregnancy after unprotected intercourse in the fertile period of the menstrual cycle.

Ulipristal Acetate Pharmacology and Pharmacodynamics

Ulipristal acetate is an orally active SPRM that acts as an antagonist in progesterone-responsive tissues. It binds to progesterone receptors with high affinity[38,39] and interferes with progesterone receptor-mediated DNA transcription.

In addition, binding to progesterone receptors, it also binds to receptors for glucocorticoids and androgens, although with lower affinity.[29,38-41] The doses required for such in vivo low-affinity binding activities are approximately 50-fold higher than the doses required for progesterone receptor binding.[42] The UPA antiprogestin activity is similar to that of mifepristone, the most well-known SPRM, but the former's antiglucocorticoid activity is lower.[40,41,43,44]

Once taken, UPA is highly bound (94%) to plasma proteins such as high-density lipoprotein and albumin and is cleared slowly.[29,39,45] The compound is metabolized to monodemethyl-UPA, the active molecule. In healthy women, the half-life of monodemethyl-UPA in plasma is approximately 33 hours.

In the initial studies, UPA was administered in gelatin capsules containing its nonmicronized molecular form. Currently, UPA is marketed for clinical use in tablets containing its micronized form.[13]

In humans, the nonmicronized UPA serum levels peak 60 to 90 minutes after intake. Increasing the doses up to 50 mg leads to proportional increases in the peak levels, but further increases to 100 and 200 mg do not produce any further dose-dependent increase, suggesting saturation of carrier sites.[39]

Micronized UPA, on the other hand, when administered under fasting conditions, reaches peak serum levels at 60 minutes,[29] with both the C_{max} and area under the curve double those of monodemethyl-UPA. After a high-fat breakfast, its absorption rate is reduced but the absorption time is increased.[29] Thus, the drug can be administered without regard to meals.

As for their metabolic effects, 30 mg of micronized UPA are equivalent to 50 mg of nonmicronized UPA.[13]

Ulipristal Acetate Efficacy in EC

Ulipristal acetate efficacy appears very high.[6,13,46,47]

Nonmicronized 50 mg UPA was evaluated in 1 phase II study comparing 775 UPA-treated women to 774 LNG users.[46] The treatment was administered within 72 hours of intercourse. Pregnancies occurred in 7 (0.9%) and 13 (1.7%) cases, respectively. Based on the estimated cycle day of unprotected intercourse, 85% and 69% of expected pregnancies, respectively, were averted.

Micronized 30 mg UPA tablets, Ella(One), was tested in 2 phase III studies.[6,13]

In the first study,[6] a total of 26 women became pregnant during the follow-up of the 1241 patients, with an overall pregnancy rate of 2.1%. This rate was significantly lower than the expected pregnancy rate of 5.5% (69 pregnancies).[5] Ella(One) was administered within 120 hours of exposure. No decrease in its efficacy was detected over time.

The second study[13] was a multicenter, single-blind, noninferiority trial comparing the efficacy of Ella(One) (844 women) with that of LNG 1.5 mg (852 women). Regardless of drug type, EC was always taken within 120 hours of the unprotected intercourse. A total of 37 pregnancies were observed in women that received EC within 72 hours: 15 (1.8%) in the UPA group and 22 (2.6%) in the LNG group. In both the groups, the observed pregnancy rates were significantly lower than the expected rates (5.5% for UPA and 5.4% for LNG). Three pregnancies were reported in the subgroup of 203 women (97 UPA and 106 LNG) treated 72 to 120 hours after unprotected intercourse. All of those pregnancies were in the LNG group.

Thereafter, these same patients were pooled and evaluated together with those from the phase II study,[46] given the equivalence of the UPA treatments. This meta-analysis confirmed a lower pregnancy rate in the UPA group than in the LNG group: 0.9% versus 2.5% at 24 hours, respectively; 1.4% versus 2.2% at 72 hours, respectively; and 1.3% versus 2.2% at 120 hours after an unprotected intercourse, respectively, against an expected rate of approximately 5.5%.[13]

Finally, a recent meta-analysis pooled together the women treated with Ella(One) in the 2 aforementioned phase III studies. A total of 41 pregnancies were reported of the 2183 women.[47] The pregnancy rates were higher in women with additional unprotected intercourse in the same cycle and among obese women. The range varied from 1.3% among nonobese women with no additional unprotected intercourse to 8.3% among obese women with subsequent unprotected intercourse.

All these data suggest that Ella(One) can prevent the appearance of 80% of the pregnancies expected after unprotected intercourse and obese women may require higher doses.

Given this high efficacy, we can suppose that UPA is mostly effective after unprotected intercourse occurring in the most fertile days of the menstrual cycle, that is, in the day preceding ovulation, which is the most fertile day, and in the 2 days around it.[2,3] In fact, most fertilizations are expected in these days in which the probability of conception is highest,[3-5] intercourse is more frequent, and unprotected intercourse peak.[3-6]

Ulipristal Acetate Effects in EC: Official Positions, Guidelines, and Reviews

The most authoritative international drug agencies and scientific societies report that UPA works by either inhibiting or delaying ovulation.[36,37,48]

Indeed, the FDA also indicates that alterations to the endometrium, possibly affecting implantation, may contribute to the efficacy of UPA,[36] whereas the EMA, in its official summary on UPA, only stresses that "*UPA, even when taken immediately before ovulation is scheduled to occur, is able to postpone follicular rupture in some women.*"[37(p7)] In the EMA package leaflet, the only information given to the users is that "*ellaOne® is thought to work by stopping your ovaries from releasing an egg.*"[37(p19)]

The ICEC and FIGO jointly state in their official guidelines that Ella(One) has been demonstrated to prevent ovulation both before and after the luteinizing hormone (LH) surge has started, delaying follicular rupture for at least 5 days. They add that UPA is unable to prevent implantation.[48]

In addition, most reviews published after July 2010[42,49-53] report that UPA works by either inhibiting or delaying ovulation even when it is taken immediately before it. This logic is based on Brache article,[14] code number 511 in the 2010 HRA Pharma briefing materials for the FDA.[32] Other articles, however, though reporting these same conclusions, also focus on the UPA endometrial effects that can prevent embryo implantation.[54-58]

Finally, HRA Pharma excludes any possible interference of UPA with implantation and based its conclusions on the 3 articles investigating the effects of UPA in women's endometria[33-35]: code numbers 505, 506, and 503 in its briefing materials.[32]

Ulipristal Acetate Effects on Ovulation—Primary Literature

Only 1 study evaluates the effects of Ella(One) on ovulation in the different days of the fertile period.[14] In the abstract and in their conclusions, the authors suggest that UPA is able to inhibit or significantly delay follicular rupture for over 5 days, even if administered immediately before ovulation, a point that is emphasized in the title.

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%.

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 (1.54 ± 0.52 versus 1.31 ± 0.48)*."[14(p2259)]

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[59-61] appears unacceptable. At that time, in fact, both the placebo and the UPA are ineffective[14] and ovulation occurs when it was scheduled to occur, approximately 2 days after the intake of the tablets.

We stress again that these are the most fertile days in the menstrual cycle[2-4] and that in approximately 20% of women ovulation may occur even 3 days or more after the LH surge.[34,62,63]

Given that the fertile days are the 4 to 5 days preceding ovulation and the ovulation day itself, we conclude that UPA can consistently delay ovulation only when taken on the first and, maybe, second fertile day, whereas in the most fertile days it mostly behaves as a placebo in regard to ovulation.[14]

Despite these evident limitations, the UPA effectiveness in preventing pregnancies is very high (≥80%) and does not decrease depending on which of the 5 days it is taken after unprotected intercourse.[6,13] This appears surprising if we assume that UPA effectiveness is due to an antiovulatory action that decreases sharply as LH levels approach to peak. Indeed, we should expect a progressive reduction in its effectiveness as days elapse.[64]

In addition, we wonder how UPA, if taken after ovulation, could ever delay a follicular rupture that may have already occurred up to 4 days earlier, such as the case of intercourse on the preovulatory day (with eventual fertilization within 48 hours) and UPA administered up to 5 days later.

This evidence suggests that the effectiveness of UPA relies on other mechanisms, particularly on its endometrial effects.[64]

However, we also want to point out that in no case ovulation appears delayed for 5 days when UPA is administered on any of the fertile days. Despite her article's conclusions, Brache results indicate that the delay, when observed, is around 3 days (6.85 vs 3.53).[14] The only circumstances in which this delay can be 5 days or longer is when UPA is administered during the mid-follicular phase when the dominant follicle size is 14 to 16 mm.[33] In this case, 50 mg of nonmicronized UPA, which is the dose equivalent to Ella(One), usually arrests the growth of the lead follicle, which mostly resumes within 4 days. Only when the lead follicle is suppressed and a new one begins to grow, the rupture of the latter can be delayed even beyond 5 days.

In the controls of this study, who were administered placebos at the mid-follicular phase and were at the same cycle phase as the treated patients, the time from treatment to follicle collapse was 5.8 ± 0.6 days, as expected. This indicates that all the women in the study[33] were still in the infertile phase of their cycle as is normal in the mid-follicular phase. At that time, UPA is really and consistently effective in delaying follicular rupture, but EC is useless, as sperm cannot enter the cervix and fertilization cannot consequently occur.

In conclusion, in the 2 to 3 most fertile days of the cycle, UPA proved unable to delay ovulation. Sperm, observed in the fallopian tube within minutes after insemination, can consequently fertilize the released ovum.[65] To understand the basis of the high efficacy of UPA, we will evaluate the endometrial effects of UPA.[33-35]

Ulipristal Acetate Effects on the Endometrium: Primary Literature

The first observation we wish to highlight is that every study investigating the effects of UPA on endometrium concludes that the threshold for altering endometrial morphology is lower than that required for altering folliculogenesis.[33-35] The UPA inhibitory effect acts directly on the tissue because of its inactivating link to progesterone receptors, and this effect is observed even after a single administration of its lowest dose.[34]

When nonmicronized UPA (10, 50, or 100 mg) was administered in the mid-follicular phase,[33] all the doses inhibited luteal-phase endometrial maturation in a similar manner. This effect was long lasting. It was observed even in the very delayed luteal phases following the coalescence of a new leading follicle and persisted until the next menstrual flow. This indicates that all unprotected intercourse occurring in the cycle after UPA intake might end in fertilization but with no chance for successful embryo implantation.

When nonmicronized UPA (10, 50, or 100 mg) was administered in the early luteal phase,[34] there was always, at any dose, a significant reduction in endometrial thickness, without any effect on luteal phase hormones. Moreover, the highest doses of 50 mg, equivalent to Ella(One), and 100 mg significantly inhibited the endometrial expression of progesterone-dependent markers of luteal phase differentiation: peripheral node addressins, as assayed by immunohistochemistry through the antigen MECA-79, were significantly reduced. Node addressins are important L-selectin ligands on the surface of the endometrial epithelial cells. They are upregulated during the implantation window, allowing the uterus to be more receptive to the trophoblast.[66,67] Human blastocysts, in fact, utilize L-selectin to initiate implantation by binding to endometrial ligands.[67,68] Their absence is associated with implantation failure.[68]

Finally, when nonmicronized UPA was administered in the mid-luteal phase[35] at single doses of 1, 10, 50, 100, or 200 mg, the highest dose consistently induced early endometrial bleeding. This effect was also observed in 50% of the women treated with 50 mg, which is the dose equivalent to Ella(One).

Discussion

As we already reported, the most authoritative international drug agencies and scientific societies report that UPA works by either inhibiting or delaying ovulation.[36,37,48] Other than the FDA,[36] they exclude the possibility that endometrial alterations affecting implantation may contribute to UPA efficacy. HRA Pharma maintains this same position[32] and officially supports it based on the 3 articles investigating the effects of UPA on the endometrium.[33-35]

In our opinion, all the endometrial effects described in these 3 articles[33-35] are able to interfere with the process of implantation. Consequently, we believe that the high efficacy of Ella(One) in preventing the appearance of clinically evident pregnancies can be attributed to these effects rather than to ovulation delay, which is not observed on the most fertile days of the cycle.[14]

Passaro reported that 50 mg of nonmicronized UPA provoked endometrial bleeding in half of the women treated in the mid-luteal phase, which is the time of implantation.[35] She concluded that the UPA effects are direct and are similar to those of mifepristone, suggesting that both the drugs are roughly equivalent in this regard.[35]

Many effects are shared by UPA and mifepristone. Initially, a meta-analysis conducted on studies from China confirmed that mifepristone, at doses of 25 to 50 mg, is highly effective for EC.[24] In addition, when given during the follicular phase, mifepristone 50 mg can lead to a delay in follicular maturation, ending in a subsequent ovulation delay. Alternatively, ovulation returns when a new leading follicle has been recruited,[69] an event often observed at higher doses, such as 200 to 600 mg.[70,71] These are roughly the same results observed after the administration of much lower doses of UPA (10-100 mg) in the midfollicular phase of the cycle.[33]

When administered in the early luteal phase, 200 mg of mifepristone is highly effective in preventing the clinical appearance of pregnancy, with minimal disturbance of both hormonal parameters and menses.[72-74] Fertilization, of course, would already have occurred at this point. The same effects have also been observed with lower doses of UPA.[34]

A single low dose of mifepristone (10 mg) resulted in no evident alteration in endometrial morphology, but Dolichos Biflorus Agglutinin (DBA)-lectin binding, reflecting endometrial secretory activity, was reduced in 4 of the 6 patients, and downregulation of progesterone receptors was mostly inhibited.[19] This indicates that a normal endometrial morphology cannot guarantee endometrial receptivity,[75] as is also observed after UPA administration.[34]

Finally, when administered in the mid- and late-luteal phase, mifepristone doses above 25 mg frequently induce endometrial bleeding, which has also been observed after administration of 50 mg of nonmicronized UPA, the dose equivalent to Ella(One).[35] Bleeding, of course, does not necessarily indicate either pregnancy termination[74] or complete endometrial shedding.

The above-mentioned data appear to indicate that UPA and mifepristone share the same effects on both folliculogenesis and endometrial differentiation with the advantages, for UPA, of a lower required dose[33-35] and lower antiglucocorticoid activity.[40,41,43,44]

In addition, both UPA[76,77] and mifepristone[77-79] have been demonstrated to be capable of decreasing fibroid size with exactly the same schedule and doses. Currently, micronized UPA has been licensed, in Western Europe, for fibroid reduction prior to surgery and has proven effective in reducing both their volume and uterine bleeding, without the side effects associated with other medications. It is marketed as 5-mg tablets in a blister pack of 28 tablets.

Conclusions

Our evaluation suggests that UPA succeeds in preventing the clinical appearance of pregnancies mainly by its negative effects on endometrial receptivity, which is a postfertilization mechanism.

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.

The efficacy of UPA, reported to be able 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.

As a final suggestion, we believe we should be extremely prudent when dealing with molecules that can affect embryo implantation. As previously discussed, UPA and mifepristone share this ability.

A single mid-luteal dose of 200 mg of nonmicronized UPA consistently produced early menses as did 200 mg of mifepristone, which is the dose required for pregnancy termination.

The UPA has never been tested for termination, but it shares roughly the same effects as mifepristone on the endometrium, folliculogenesis, and reproductive tissues.

We wish to offer a reminder that 200 mg of nonmicronized UPA is equivalent to 120 mg of micronized UPA, the amount contained in 4 tablets of Ella(One) or in just 24 of the 28 tablets contained in the blister packs marketed for the treatment of uterine fibroids.

This should be carefully considered when deciding the prescription rules and limitation of any UPA-containing drug.

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