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Combined oral contraceptive interference with the ability of ulipristal acetate to delay ovulation: A prospective cohort study

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Abstract

Objective—To determine if a combined oral contraceptive (COC) initiated shortly after ulipristal acetate (UPA) administration interferes with its mechanism of action.

Study design—Healthy, reproductive-age women of normal BMI with proven ovulation (serum progesterone 3ng/mL) were enrolled for 3 cycles (Cycle 1, UPA only; Cycle 2 washout; Cycle 3 UPA plus COC). During Cycles 1 and 3, subjects were monitored with transvaginal ultrasound and blood sampling for progesterone and LH every other day until a dominant follicle measuring 15 mm was visualized. In both treatment cycles, subjects received UPA (30mg) and were followed daily with similar monitoring for up to 7 days. In Cycle 3 only, subjects initiated a daily COC (0.15 mg levonorgestrel/30 µg ethinyl estradiol) 2 days after UPA. The study had 80% power to detect a 15% difference in the proportion of cycles with at least a 5-day delay in follicle rupture. We assessed follicle rupture as >50% decrease in mean size and adjudicated unclear outcomes with serum hormones.

Results—A total of 36 women enrolled and 33 completed all study procedures [age 28.4 yr (SD 3.9); BMI 23.4 (SD 2.4)]. Compared to Cycle 1, more subjects demonstrated evidence of follicle rupture in <5 days in Cycle 3 [1/33 (3%) vs. 9/33 (27%), $p = .008$]. We also included data from 2 subjects who experienced rupture prior to COC dosing in the analysis.

Conclusion—UPA's effectiveness is significantly reduced by administering COCs 2 days later.

Implications—This study demonstrates that UPA's efficacy as an emergency contraceptive is reduced with early exposure to COCs.

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Keywords

emergency contraception; ulipristal acetate; oral contraceptives; contraceptive initiation; ovulation inhibition; pharmacodynamics

1. Introduction

The availability of highly effective options for emergency contraception is critical for women wanting to avoid pregnancy following an act of unprotected intercourse. An antiprogesterin, ulipristal acetate (UPA; ella[®], Afaxys Pharma LLC, Charleston, SC), has emerged as the most effective oral option [1]. UPA works by delaying ovulation and/or inhibiting ovulation up to 5 days or more. *In vitro* studies have shown that UPA binds to and prevents progesterone receptor signaling, leading to the theoretical concern that progestin-containing hormonal contraceptives might negate or diminish UPA action [2–5]. We currently lack critical information regarding the practical use of UPA and when to start a progestin-containing contraceptive method [6].

Ideally, women who do not desire pregnancy should immediately initiate a regular method of contraception following the use of an oral emergency contraceptive (EC). Clinical guidelines currently recommend that women delay initiation of hormonal contraception no sooner than 5 days following UPA given the concern regarding the interaction between UPA and hormonal contraception [7, 8]. Women are left unprotected during this time unless they plan to abstain or use a barrier method. In reality, clinicians and women are left with the difficult choice of either a gap in contraceptive coverage or the use of a less effective oral EC method, levonorgestrel, which does not interfere with immediate initiation of a hormonal contraceptive method.

In the absence of clinical trial evidence, the basis of the 5-day delay between UPA and hormonal contraception initiation was based on UPA's observed delay in follicle rupture [9] and the duration of time sperm are viable in the reproductive tract [10]. Recently, Brache et al. demonstrated that a progestin-only pill (POPs) containing desogestrel, started immediately after UPA administration, significantly increased the rate of ovulation before 6 days [6]. Cameron et al. studied the impact of UPA on the ability of combined oral contraceptives (COCs) to cause ovarian 'quiescence' but the study was not designed to determine the reverse, if COCs impact UPA's efficacy [11]. We designed this study to determine the impact of COC's on UPA in order to see if hormonal contraception can be started sooner than 5 days. We hypothesized that early use of COCs following UPA administration will adversely impact UPA's ability to delay ovulation similar to POP use.

2. Materials and Methods

We conducted a prospective open-label study at Oregon Health & Science University (OHSU) in Portland, Oregon from October 2015 to June 2017. The OHSU Institutional Review Board approved the study protocol and all subjects underwent informed written consent. The OHSU-hosted REDCap electronic data capture tool was used for data collection and management.

We recruited otherwise healthy, BMI ≥ 28 kg/m², reproductive-aged (18–35 years old) women with regular menstrual cycles (21–35 days). During screening, we obtained a serum progesterone level from women during their luteal phase to confirm ovulatory status (progesterone level ≥ 3 ng/mL). Subjects were required to be either not at risk for pregnancy or, if at risk, to use a non-hormonal method of contraception (e.g. condoms, permanent contraception, copper intrauterine device). Major exclusion criteria included: intolerance or allergy to study medications, metabolic disorders including uncontrolled thyroid dysfunction and polycystic ovary syndrome (PCOS), any Centers' for Disease Control Medical Eligibility Criteria for Contraceptive Use category 3 or 4 for combined oral contraceptives [7], pregnancy, breastfeeding, those seeking pregnancy, current use of drugs that interfere with metabolism of sex steroids, and smoking.

Subjects underwent a referent cycle (Cycle 1) in which they took UPA only, followed by a washout cycle (Cycle 2). In Cycle 3, subjects took UPA that was followed 2 days later by COCs (treatment cycle). The study utilized the following drugs: UPA 30 mg po (ella[®], Afaxys Pharma LLC, Charleston, SC) and a COC containing 0.150 mg levonorgestrel/30 μ g of ethinyl estradiol (Portia[®], Barr Laboratories Inc., Montvale, NJ). Subjects ingested EC under direct observation by study staff and COC use was retrospectively confirmed with the presence of levonorgestrel (LNG) in a serum sample from Cycle 3, Day 3 of COC intake [11].

We initially dosed UPA at a dominant follicle size of 18 mm [6, 12]. However, we modified the protocol after enrollment of 2 subjects to dose UPA at a dominant follicle size of 15 mm as we determined that a follicle size of 18 mm placed us at high risk for dosing at or after the LH surge [6]. During Cycles 1 and 3, subjects were monitored every other day with transvaginal ultrasound for follicular activity and blood sampling for progesterone (P4) and luteinizing hormone (LH) until a dominant follicle measuring ≥ 15 mm in at least one diameter was visualized. Following confirmation of a negative urine pregnancy test, subjects were dosed with UPA and then underwent daily visits with blood sampling and ultrasound monitoring until evidence of follicle rupture (complete disappearance or $>50\%$ reduction of the mean size of the leading follicle) or for up to 7 days. In Cycle 3, subjects initiated a daily COC (0.15 mg levonorgestrel/30 μ g ethinyl estradiol) 2 days after UPA and continued this for up to 5 days and then exited the study. Women could choose to continue with the rest of the COC cycle post-study exit.

Our primary outcome was the difference in the proportion of subjects with a delay in follicle rupture of 5 days (yes/no) between the referent (Cycle 1) and treatment cycles (Cycle 3). If the date of follicle rupture was unclear by ultrasound imaging (e.g. collapse was seen but reduction of size was $<50\%$), we utilized serum hormone levels to adjudicate day of rupture. Three investigators independently reviewed the following parameters to determine day of rupture: day of noted follicle collapse, day of LH rise, day and value of highest LH, day of P4 rise, and day and value of highest P4. Additionally for these cycles, we confirmed that the enlarged follicle being monitored was dominant based on an estradiol >100 pg/mL on the day of UPA dosing. The study had an 82% power to detect a 15% difference with a 5% significance level in the proportion of cycles with at least a 5-day delay in follicle rupture

(yes/no). Demographics were analyzed using descriptive statistics and the primary outcome was analyzed with McNemar's test for paired data.

Hormone assays were performed by the Endocrine Technologies Support Core (ETSC) at the Oregon National Primate Research Center (ONPRC, Beaverton, Oregon <http://www.ohsu.edu/xd/research/centers-institutes/onprc/research-services/research-support/endocrine-technology.cfm>). Total serum LNG levels were determined by ultra-high performance liquid chromatography-tandem triple quadrupole mass spectrometry (LC-MS/MS) with a sensitivity of 20 pg/mL. Serum E2, P4, and LH were analyzed by a Roche Modular E170 chemiluminescence-based automatic clinical platform (Roche Diagnostics, Indianapolis, IN). The sensitivities of the E2, P, and LH assays for the Roche E170 is 5 pg/ml, 30 pg/ml, and 0.1 mIU/ml, respectively. The intra- and inter-assay variation with the Roche E170 is consistently less than 7% for all assays. Quality control samples and validations were repeated prior to each assay run.

3. Results

A total of 36 women enrolled and 33 completed all study procedures [age 28.4 yr (SD 3.9); BMI 23.4 (SD 2.4)]. At the time of UPA dosing, the average largest follicle measurement was similar in both cycles (Cycle 1: 15.7mm SD 2.3, Cycle 3: 16.2 SD 1.5). See Table 1 for demographic details. Compared to Cycle 1, more subjects demonstrated evidence of follicle rupture in less than 5 days in Cycle 3 [1/33 (3%) vs. 9/33 (27%), $p = .008$]. As part of the intent-to-treat analysis, we included 2 subjects who experienced rupture following UPA intake but prior to COC dosing in Cycle 3. A retrospective analysis of their LH levels revealed that UPA intake likely occurred too late at or after the LH surge. If we remove these subjects from the analysis of the primary outcome, the difference still persists between the two groups ($p = 0.016$).

All subjects in Cycle 1 (referent cycle) had complete disappearance of their dominant follicle or a greater than 50% reduction in mean size and thus, no adjudication was necessary to determine date of rupture. For Cycle 3, eight subjects experienced follicle collapse but the reduction in size was less than 50%. However, for all eight cycles, the adjudicated day of rupture was determined to be 5 days or longer from UPA intake.

Figure 1 visually depicts the number of subjects who experienced rupture each day post-UPA dosing in Cycle 1 and 3. Subjects in Cycle 1 consistently had a 5 day or more delay in ovulation. The only subject in Cycle 1 that did not have a delay in ovulation was dosed after the LH surge.

LNG was present in the serum for all subjects in Cycle 3 except for the 2 subjects that did not receive COCs due to early follicle rupture and an additional subject with an undetectable level who ruptured on Day 5. No serious adverse events occurred during the study but one subject reported a significant malar rash several hours after UPA dosing in Cycle 1 that resolved on its own and did not reoccur with UPA dosing in Cycle 3.

4. Discussion

This study was designed to determine if a COC initiated shortly after UPA administration interferes with UPA's mechanism of action as an EC. We found that early initiation of a COC, 2 days later, does significantly interfere with UPA's ability to delay rupture for 5 days. These findings have important clinical relevance in that they provide further support for the current clinical guidance to delay initiation of a hormonal contraceptive for five days after UPA-EC intake [7, 8]. As a pharmacodynamic study, we did not directly measure the outcome of interest following EC use, pregnancy. However, pregnancy does not occur without ovulation.

Our study design was based on the methodology utilized in other EC comparator studies [6, 13]. We monitored daily for signs that follicle rupture occurred within the last 24 hours. The actual time/day of follicle rupture is likely to be slightly earlier or even up to a day earlier than illustrated in Figure 1. As such, the proportion of cycles with follicle rupture earlier than 5 days may be greater than our findings of 15%. We did utilize hormonal data to adjudicate the date of follicle rupture in some UPA-COC cycles. The adjudicated dates did not impact our main finding as they were all categorized as 5 days or greater. If some or even all of the adjudicated dates were categorized as earlier than 5 days, the proportion of cycles with earlier rupture would also be greater than 15%. One subject appears to be noncompliant with COC dosing; perhaps if compliant, follicle rupture would have occurred earlier which also would have increased the proportion of cycles with rupture earlier than 5 days. Finally, our main findings were not affected by the inclusion or exclusion of the data from the 2 subjects who experienced rupture prior to COC dosing. We missed the ovulation window in one subject due to inclement weather and in the other subject, we missed the pre-LH surge window in both cycles as we were dosing at a dominant follicle size of 18mm – this prompted our protocol change to dose at 15 mm instead [6]. A follicle size of 15 mm ensured that we could capture the window where UPA is maximally effective or prior to the LH surge [12]. Our own experience, and that of other investigators, support that if we had dosed at a follicle size of 18 mm we would have missed this optimal time period for UPA dosing in up to 50% of cycles [12]. Given that we used the same criteria in baseline and treatment cycles, any effect of misclassification bias would have been non-differential.

Weaknesses of our approach include misclassification bias, as the use of a single maximum diameter may have led to the identification of a non-dominant follicle as dominant. We chose to utilize the one largest measurement for ease of efficiency with determining when to dose. We looked back on our data, and in all cases the identification of a 15 mm follicle occurred in the setting of rising estradiol levels consistent with the development of a dominant follicle. Furthermore, we did obtain measurements of the follicle in 3 dimensions and the overall mean follicle size for all subjects in Cycle 1 and Cycle 2 was 15 mm.

Our study design did not permit the evaluation of the complete luteal phase hormonal profile to consider the “normalcy” of the ovulation, or the fate of the unruptured follicle past 7 days. We stopped monitoring women on the day of clear follicle rupture by ultrasound or on day 7 after dosing in the absence of rupture. Therefore, we cannot conclude that the follicle rupture events would necessarily place a woman at risk for pregnancy. However, we

carefully designed our experiment to evaluate whether dosing of a combined pill interfered with the primary mechanism of UPA as an emergency contraceptive; the ability to block follicle rupture for 5 days. Given the intense monitoring required by this study, we did not want to extend the burden on participants beyond this observation window. Our study design does not permit us to speculate on the natural course of an unruptured follicle more than 7 days after UPA dosing. Cameron et al [11] reported that women experienced either ovarian quiescence within 14 days or ovulated within 7 days after quick starting UPA and COCs.

The strengths of our study include a simple but robust methodology that allowed subjects to serve as their own controls with confirmation of an individual's baseline ovulatory status and response to UPA without COC exposure followed by a washout cycle. Although small, we were powered for our main outcome, delay in ovulation for 5 days (yes/no). Our results confirm the findings of Brache, et al [6] who found that quick-starting (e.g. same day) a progestin-only pill and UPA-EC also impacted the ability of UPA to delay follicle rupture. The studies differed in their magnitude of effect with Brache, et al demonstrating that approximately 45% of subjects [6] ovulated earlier than 5 days in comparison to our findings which only had a quarter of subjects ovulate earlier than 5 days. The studies did differ in timing of hormonal contraceptive initiation, 24 versus 48 hours and the exposure intervention, POP versus COC. We find it difficult to speculate if this is a finding of significant importance as both studies are relatively small and thus the difference in magnitude could be due just to chance. The fact that we observed a similar direction in effect with initiation of a COC following a 2-day delay confirms the findings of this earlier study [6] and suggests that the interference in the mechanism of action of UPA by hormonal contraception is significant throughout this time interval. It remains unknown if initiating hormonal contraception between 3 to 5 days post-UPA would also impact the efficacy of UPA.

In conclusion, our findings along with Brache et al. [6] support the existence of a critical window in which hormonal contraception can interfere with UPA's ability to delay ovulation. Our results provide evidence-based guidance to delay initiation of hormonal contraception after UPA-EC use and support the current clinical guidance of delaying initiation of contraception 5-days post UPA use [7].

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Figure 1.

Table 1

Demographic Characteristics of the Study Cohort

	Study Subjects (n = 36 [*])
Age (years)	28.4 (SD 3.9)
Ethnicity	
White, non-hispanic	30 (83%)
Hispanic/Latina	6 (17%)
Nulliparity	23 (64%)
Weight (lbs)	138 (18)
BMI (kg/m ²)	23.4 (SD 2.4)

* 33 women completed all study procedures