Official Title:
Determining the Impact of Combined Hormonal Contraceptives on Ulipristal Acetate

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Determining the impact of combined hormonal contraceptives on ulipristal acetate
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Specific Aim:

1. To define whether starting COCs in close succession (2days) following the administration of the anti-progestin, ulipristal acetate, interferes with its efficacy as an EC.
2. To determine if differences exist between obese and normal BMI women in the pharmacokinetics of ulipristal acetate-based EC (pilot data)

Background

The availability of highly effective options for emergency contraception (EC) is critical for women wanting to avoid pregnancy following an act of unprotected intercourse. An anti-progestin, ulipristal acetate (UPA; ella™), has emerged as one of the most effective oral options[1]. *In vitro* studies have shown that UPA binds to the genomic progesterone receptor (PGR) with high affinity[2-5], leading to the theoretical clinical concern that using UPA in close succession with hormonal contraception may adversely impact the effectiveness of either or both methods. A pharma-sponsored trial under review for publication studied the impact of UPA on the ability of combined oral contraception (COC) to suppress ovulation. Moreover, that study was not designed to determine COC's impact on UPA (*personal communication, S Cameron, 3/2015*). This knowledge gap places women at further risk for unplanned pregnancy. A woman choosing to take UPA and wanting to initiate a hormonal method can either (1) delay initiation of a hormonal contraception for 14 days or until her next menstrual cycle[8,9] and continue to be at risk for pregnancy using a less effective barrier method or (2) immediately initiate the method and possibly decrease the effectiveness of UPA. Discussions during the CDC Working Group for US Selected Practice Guidelines for Contraceptive Use (Atlanta, GA 10/2011) as well as the recent WHO Medical Eligibility Steering committee meeting (2014) noted that this issue should be a priority in light of increasing UPA use.

Our proposal has been designed to address this gap in knowledge and will focus on the impact of COCs on UPA's main mechanism of action. **Our hypothesis is that starting COCs shortly after UPA use adversely impacts UPA's ability to delay ovulation.** Our primary aim is to define whether starting COCs 2 days following the administration of the anti-progestin, UPA, interferes with its efficacy as an EC. The goal of this aim is to obtain evidence to support or refute the current recommendation to have women using UPA for EC to wait to delay initiation of their hormonal method. Our proposed studies focus on the interaction of COCs and UPA as COCs are one of the most commonly used hormonal methods.

Glasier et al[11] demonstrates that there may be differences in the effectiveness of UPA EC in women of varying BMIs. Drug therapeutics or how well a drug works is based on several key pharmacokinetic parameters – specifically for EC, maximum concentration and time to maximum concentration are considered critical. We would like to perform a substudy within this proposal to obtain pilot data to determine if there is a difference in pharmacokinetic parameters between obese and normal BMI women taking UPA-EC.

Methods:

Study design: Prospective cohort study. Women will act as their own controls.
Study Population: Women (total=34) of reproductive-age with a BMI of 18.5-28 will be recruited from the Portland area. To account for screen fails and dropouts, we plan to enroll up to 60. Individuals will be recruited through several different venues using IRB approved materials including flyers, internet recruiting, and the CWH website. Individuals meeting inclusion and exclusion criteria for the

study will be enrolled following completion of informed written consent. The only contraindication for use of UPA-based EC is known current pregnancy but participants will also be exposed to COCs. Study inclusion and exclusion criteria include:

Major inclusion criteria include:

- Generally healthy women aged 18 to 35 with regular menses (every 21-35 days).
- BMI of 18.5-28
    - Additional substudy group of 5 women will have BMI >28
- Proven ovulation with a screening serum progesterone of ≥3ng/mL
- Willing to use condoms (if sexually active with a male partner), willing to not have sex with men during the study, or have had a tubal ligation (or have a partner who has had a vasectomy) or have a copper IUD.

Major exclusion criteria include:

- Known intolerance or allergy to any of the study medication
- Known metabolic disorders including polycystic ovarian syndrome or uncontrolled thyroid disorder
- Overweight or obese BMI (except for additional substudy group of 5 women)
- Any CDC Medical eligibility criteria category 3 or 4 for COC use[12].
- Pregnancy, breastfeeding, or seeking pregnancy; recent (8 week) use of hormonal contraception
- Current use of drugs that interfere with metabolism of sex steroids
- Smokers.

General methods: Subjects will undergo a referent cycle (Cycle 1, UPA only), followed by a washout cycle (Cycle 2) and finally UPA with COCs dosed 2 days later (Cycle 3, treatment cycle) (see **Table 1**). Due to the extensive number of visits, blood draws, and exams, the patients will be compensated for their time. Subjects will either receive compensation through the Greenphire debit card system or as a check. During the referent and treatment cycles (Cycle 1 and 3, respectively), subjects will undergo every other day visits starting on cycle day 6 followed by daily visits for up to 7 days once a dominant follicle measuring 15mm or greater in one diameter is visualized. At each visit, subjects will undergo blood sampling via a single venipuncture for P and LH levels and transvaginal ultrasonography (TUS). Study medication will be dosed on the day a 15 mm follicle is visualized. Women will be given a single dose of 30 mg UPA orally in Cycle 1 or a single dose of 30 mg UPA orally followed 2 days later by a COC (0.150 mg levonorgestrel/30 µg of ethinyl estradiol) in Cycle 3. Prior to ingesting study medication, women will undergo urine pregnancy testing. Women can choose to continue the COC for the entire 21 days or they can discontinue after 7 days. Women will have a washout cycle between the referent and treatment cycles where they will remain in contact with study staff for scheduling and retention purposes but will not have any scheduled study visits. Study end will be at the onset of menses (defined as two consecutive days of spotting/bleeding).

Table 1. Study flow (n = 34)

	+ing	**Cycle 1 Referent cycle** UPA only	**Cycle 2** Washout	**Cycle 3** UPA+COC 2 days later
Study Procedures	Luteal phase ovulation testing	-Starting day 6 until 15 mm follicle: every other day P, LH, & TUS -15 mm follicle: study medication dosed and daily P, LH, & TUS for up to 7 days		-Starting day 6 until 15 mm follicle: every other day P, LH, & TUS -15 mm follicle: study medication dosed and daily P, LH, & TUS for up to 7 days -COCs dosed 2 days after study medication

Data Analysis &Sample Size:

The primary outcome will be the difference in the proportion of women with a delay in follicular rupture up to 5 days (yes/no) between their referent and treatment cycles[13]. Follicle rupture will be defined as the disappearance or >50% reduction of size of the leading follicle. Confirmation of ovulation will be supported by LH and P levels. Demographics will be reported and descriptive statistics will be utilized to report LH and P levels [mean (standard deviation], follicular diameter [median (range)], and cycle day [median (range)] on the day of UPA ingestion during the referent and treatment cycles. Additionally, inhibition of follicular rupture will be plotted by LH status (no surge, start of LH surge, or after LH peak; defined in Brache et al.[13]) for each cycle as well as mean LH and P levels over time and the time of treatment to follicular rupture.

A sample size of 34 will achieve 82% power to detect a 15% difference in the proportion of cycles that demonstrate at least a 5-day delay in follicular rupture (yes/no) using a two-sided exact binomial test with a 5% significant level. We plan to recruit up to 60 women to account for drop out. We based this assumption on the overall effect of UPA which causes persistence of the dominant follicle for at least 5-days in 58% of cycles[13]. If COCs adversely impact UPA by 15% then UPA's efficacy would be similar to that of a levonorgestrel-EC which would be clinically significant.

Substudy: UPA Pharmacokinetics

Our control group (normal BMI) will be recruited from women enrolling in the main study. Up to 5 women enrolled in the main study may choose to participate in this substudy. They may choose to participate in this substudy either during Cycle 1 or Cycle 3, whichever cycle is most convenient for them. The substudy will be performed over 1 visit but this visit will take approximately 3 hours to complete. During this visit, women will undergo serial blood sampling from a "single stick" venipuncture or from an indwelling intravenous catheter – per the subject's choice. One tube (10mL) of venous blood will be collected at the following time intervals in conjunction with UPA ingestion (0, 0.5, 1, 1.5, 2, 2.5 hours). UPA will be ingested under fasting conditions and directly observed intake will occur. Women volunteering for this substudy will be compensated for this additional time. An additional 5 obese women will be recruited only to participate in this substudy as obesity is an exclusion criteria for the main study. This group must meet the main study's eligibility criteria except for BMI and confirmed ovulatory status by P value. Serial blood sampling will be timed to occur during the follicular phase of the obese participant's menstrual cycle.

Human subjects protection:

Human Subjects Involvement and Characteristics. Reproductive-aged (18-35 year old), ovulatory, healthy women with no contraindications to the study medications and not at risk for or seeking pregnancy will constitute the target population for this study.

Setting. All enrollment and clinical evaluations will be performed at OHSU in Portland, Oregon. Serum samples will be prepared at OHSU and analyzed at the ONPRC Endocrine Core Laboratory under the direction of Dr. David Erickson.

Sources of Materials. The sources of research material for the clinical portion of this proposal will be new specimens (blood) and ovarian ultrasound data obtained purely for this research protocol. The study investigators and/or research assistants/nurses will perform all study procedures.

Potential Risks. In regard to the UPA-based emergency contraceptive used in this study, the only contraindication to this medication is current pregnancy (CDC 2013) and this is an exclusion criterion for study participation. The use of EC can affect the timing and duration of a woman's next menstrual period and very rarely can cause nausea and/or headache. This information will be reviewed with participants and if necessary, an anti-emetic can be provided. For the COC utilized in the study, we will use a COC that is commercially available and screen women according to the CDC Medical eligibility for contraceptive use guidelines. We plan to use these medications in accordance with FDA-labeling.

Women may feel some pain when their blood is drawn through venipuncture or the use of an indwelling venous catheter but there is minimal risk involved. There is a small chance the needle will cause bleeding, a bruise, or an infection.

There are no known harmful effects of a transvaginal ultrasound. Women may experience slight vaginal discomfort.

Risk of pregnancy is always present in women who are sexually active. Women who are not at risk for pregnancy due to the use of permanent contraception (male or female), use of a copper IUD, or have a female partner will be eligible for the study. Those women at potential risk of pregnancy will be asked to abstain or to use condoms for the duration of the study.

Recruitment and Informed Consent. Attempts to enroll a diverse study population will be made through placement of IRB approved recruitment material in the community, community outreach such as receiving an emailed newsletter they have opted to receive, and through the availability of foreign language interpreters and research staff. Women may also learn of the study through their routine visits in clinics or by working at OHSU.

Women will be screened for eligibility and if they meet the basic criteria and agree to participate, they will undergo informed written consent. The protocols and consent will be reviewed and approved by the OHSU IRB prior to initiation of the study. Information we collect and create in order to conduct and oversee this research study will be stored in the Women's Health Research Unit repository (IRB# 6748) for possible future research.
Protection Against Risk. Confidentiality of personal health information will be maintained according to HIPAA requirements for research. All subjects will receive a study number to which all subsequent data will refer. Personal identifiers will not be on questionnaires, data, abstract sheets, or in the main

database. All data will be kept in locked files or a password protected computer in the Principal Investigator's (PI) office. We will do our best to keep information confidential by keeping it coded and on password-protected computer.

Potential Benefits of the Proposed Research to the Subjects and Others. There are no direct benefits to study participants.

Importance of Knowledge to be Gained. It is anticipated that the results from this study will determine whether close administration of a COC with UPA will inhibit the ability of UPA to function effectively as an EC. Since UPA works via its ability to serve as a PGR antagonist, the immediate administration of PGR agonists present in COCs will possibly increase the failure rate of UPA due to competing actions on PGR signaling. UPA effects include preventing or delaying the midcycle surge of LH that is critical for ovulation[11] and the expression of progesterone (P) regulated genes in the ovulatory follicle necessary for its rupture[2]. Thus, it is necessary to establish whether the PGR agonists present in COCs will negate the ability of UPA to prevent the cellular processes crucial for ovulation and consequently fertilization. This information will be critical for determining when to initiate COCs in women seeking this form of birth control. In addition, our research team is one of only a very few studying molecular and associated clinical aspects of novel and established contraceptives

We anticipate that the study results will provide evidence for direct clinical guidance regarding co-administration of COCs and UPA. We plan to disseminate the data through publication and presentations as well as highlighting the results to relevant governmental entities (e.g., CDC) and interested parties (e.g., HRA Pharma).

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