Improving the effectiveness of orally dosed emergency contraceptives in women of varying weights/BMIs

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Funding: Investigator initiated, National Institutes of Health

Specific Aim:

1. **To determine if dose escalation for emergency contraception containing levonorgestrel results in improved pharmacodynamics outcomes for obese women.**
2. **To compare the pharmacokinetic parameters and pharmacodyanmic profile of emergency contraception containing ulipristal acetate between obese and normal BMI women, and to determine if dose escalation improves how well it works in obese women.**

Background

Emergency contraception (EC) provides a woman with an additional line of defense against unintended pregnancy following an act of unprotected intercourse. Orally-dosed EC [levonorgestrel (LNG) or ulipristal acetate (UPA)] works by blocking ovulation and reduces the risk of pregnancy for a single act of unprotected intercourse by up to 90% [1–3]. Unfortunately as the majority of U.S. women are either overweight or obese, LNG-based EC has diminished or no efficacy, the equivalent of taking a placebo pill [4–6]. Prevention and planning of pregnancies is critical as obese pregnant women are at higher risk of pregnancy complications endangering their own health and the development and post-natal health outcomes of the fetus [7]. Prior research from our group and others has proven that obesity adversely impacts the pharmacokinetics (PK) of contraceptive steroid hormones in combined (estrogen and progestin) oral contraceptive pill users [8,9]. In particular, drug half-life and clearance are affected. These changes in turn, cause a lower maximum concentration (Cmax) and a time delay in achieving Cmax and steady state [8–11]. This prior work provides insight into a possible mechanism for EC failure in obese users. As a single-dose therapy, EC is reliant on achieving a rapid peak level at a critical time point prior to the LH surge [12,13]. The PK profile following oral administration of LNG-EC is similar to that of LNG-based oral contraceptives, just a magnitude higher due to differences in the dosage [14]. We suspected that a critical level of the drug sufficient to block the LH surge is not being achieved in obese EC users. To test this, we performed preliminary studies and demonstrated that Cmax levels following oral administration of LNG-based EC are 50% lower in women of obese relative to normal body mass index (BMI) (15).

We also tested an alternative dosing strategy in an effort to counteract these PK changes and demonstrated that obese women taking double the approved LNG EC dose normalized the PK profile to that of normal BMI women. Although a “take two” strategy could be rapidly implemented into clinical practice, we have no data on the resulting end-organ effects. Further studies are needed to document if PK normalization results in improved pharmacodynamic (PD) outcomes. Another alternative treatment strategy is to use a UPA-based EC instead. UPA is slightly more effective than LNG-based EC as it has a longer window of action (e.g. effective until LH peak vs. LH rise) [2]. However, published data demonstrate a possible decline in efficacy for obese women [4]. Detailed PK and PD studies for UPA have yet to have been performed in obese women but unpublished data from a colleague at Columbia University also demonstrated PK differences (*personal communication 4-2016*).

The overall goal of this research is to improve EC effectiveness and quality of clinical care for obese women. We hypothesize that increasing the dose of LNG- and UPA-based EC will normalize PK (specifically the time needed to reach a therapeutic drug level) and PD outcomes (follicle rupture) in obese women who weigh 80kg or greater. In this application we propose to expand our model for LNG- to UPA-based EC, assess the pharmacodynamic outcomes of these alternative dosing regimens (“take two”) in obese women and to assess the safety and acceptability of these regimens in this population.

Methods:

Study design: This is a 2-part study: Part 1 will be focused on LNG-EC and Part 2 will be focused on UPA-EC. Eligible women can take part in both aspects of the study and in no particular order. If they do chose to enroll

in both aspects of the study, then the screening visit does not need to be repeated unless it has been greater than 12 months since the original screening visit.

Part 1 LNG-EC is a randomized control trial. Part 2 UPA-EC is a randomized cross-over study with an additional non-randomized control arm.

This study will be conducted at Oregon Health & Science University (OHSU) in Portland, OR and a subcontract site, Eastern Virginia Medical School (EVMS) in Norfolk, Virginia. EVMS will be overseen by their own IRB.

Study Population: Generally healthy, ovulatory women of reproductive-age (18-35yo) will be recruited from the Portland area. To account for screen fails and dropouts, we plan to enroll up to 80 women in Part 1 and 92 women in Part 2 (80 obese, 12 normal BMI).

Individuals will be recruited through several different venues using IRB approved materials including but not limited to 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 LNG-EC or UPA-EC is a known current pregnancy.**

Study inclusion and exclusion criteria include:

Major inclusion criteria include:

- Generally healthy women aged 18 to 35 with regular menses (every 21-35 days).
- Have a BMI of < 25mg/k^2 and a weight of less than 176 lbs
  OR have a BMI of >30 mg/k^2 and a weight of 176 lbs or more.
- 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, 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 diabetes, polycystic ovarian syndrome, or uncontrolled thyroid disorder
- History of bariatric surgery
- Initiating or participating in a weight loss program
- Pregnancy, breastfeeding, or seeking pregnancy
- Recent (8 week) use of hormonal contraception
- Current use of drugs that interfere with metabolism of sex steroids
- Smoking or vaping
- Chronic marijuana use (3-4 days per week or more)

Recruitment and Informed Consent: Attempts to enroll a diverse study population will be made through placement of IRB approved recruitment material in the community. Women who express interest in participating will be telephone screened to assess initial eligibility. Participants may also complete the Women's Health Research Unit contact form found online. This will allow study staff to contact potential participants about the study. In order to collect protected health information (PHI) prior to participants signing consent, a Waiver of Authorization (WoA) will be requested. Participants will also be asked whether or not they prefer to receive a secure or non-secure emails from the study team. Secure emails would be sent when message includes PHI while non-secure would be for study visit reminders.

Information collected through the telephone screen and the online WHRU contact form will be stored in a locked office, with access limited to study staff. For subjects electing to enroll in the study, this information will become a part of their protected research record. For subjects choosing not to enroll, all PHI will be stored confidentially with the research study information in a locked cabinet and archived with other study-specific documents at the close of the trial. All potential participants that contact the department for research studies

will be added to a password-protected log listing their contact information, only accessible through OHSU password-protected computers by study staff. Telephone screens and the log containing potential participants' information are saved to ensure that our department has a record of contact with the participant and to monitor our recruitment outreach efforts. Confidentiality of personal health information will be maintained according to HIPAA requirements for research and all data will be kept in locked files or in a password-protected document on a password protected computer.

Women will be screened for eligibility and if they meet the basic criteria and agree to participate, they will undergo informed written consent. Study participants may also be asked to review the consent with study staff over the phone or video conference in order to limit time spent in clinic during the COVID-19 pandemic. In this case, a copy of the consent form will be emailed to study participants prior to the consenting process. After fully reviewing the consent with a participant and answering all study-related questions, study staff will note on the verbal consent memo both the date and time that the virtual consent was obtained or denied. In the case that verbal consent is given, participants will wet-sign the consent form and the attestation of verbal consent memo when coming in for required in-person activities.

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 may be stored in the Women's Health Research Unit repository (IRB# 6748) for possible future research if the participant opts to participate in the repository.

Compensation: Women will be compensated for study participation via ClinCard debit card or check. If they discontinue early, they will receive a prorated amount based on the number of visits completed. The compensation amount will depend on the part of the study women participate in and is listed as follows:

- **UPA Obese full PK:** up to $1520
- **UPA Obese no PK:** up to $1220
- **LNG obese:** up to $620
- **UPA Normal BMI control:** up to $720

Participants who participate in the PK portion of the study will also receive a $10 gift card to OHSU cafes.

PART 1. LNG-EC (obese BMI and a weight of 176 lbs or more), randomized controlled trial

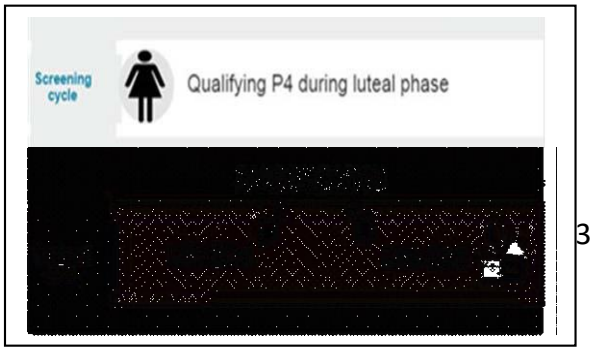
Specific Aim: To determine if dose escalation for emergency contraception containing levonorgestrel results in improved pharmacodynamics outcomes for obese women.

Hypothesis: A dose increase of LNG-EC will provide greater follicle delay/inhibition in obese women.

Rationale: Dose escalation is a commonly used strategy in pharmacotherapuetics [16]. We have already tested this strategy in our preliminary studies and demonstrated that we can normalize the LNG peak level in obese women by doubling the dose. It remains unknown if this improved drug level will translate into better end-organ suppression. However, we have had prior success with improved end organ suppression with dose escalation in our studies of oral contraceptives in obese women [11] thus we have confidence in this strategy for EC. The findings of our proposed studies, whether positive or negative, will provide critical information as we will have either proven or disproven if this potential solution works.

Part 1 LNG-EC:

The study flow for Part 1 is depicted in the graphic below. Part 1 will be performed as an open-label randomized control trial. Randomization will occur in a 1:1 fashion utilizing a computer generated random permuted block randomization scheme with block size 4, 6 and 8.



Demographic information will be obtained including but not limited to race, ethnicity, parity, and prior contraceptive use. After

confirmation of ovulation via an elevated P4 of 3ng/mL or greater in the screening cycle.
Subjects will be randomized to treatment group [LNG-EC 1.5 mg (ECx1) or LNG-EC 3mg (ECx2)] and undergo a treatment cycle.

During the treatment cycle, subjects will undergo every other day visits starting on cycle day 6-8 followed by daily visits for up to 7 days once a dominant follicle measuring 15mm or greater in one diameter is visualized (see procedure flow below). Daily visits will cease prior to 7 days if evidence of follicle rupture (disappearance of or greater than 50% reduction in size of the dominant follicle) occurs. At each visit, subjects will undergo blood sampling via a single venipuncture for P4, E2 and LH levels and high-resolution transvaginal ultrasonography (TUS) (GE Ultrasound OR, 9900 Innovation, Voluson eBT11) to monitor follicular development and evidence of ovulation.

During the treatment cycle, study medication will be dosed on the day a ≥15 mm follicle is visualized. Women will be randomized to either LNG ECx1 (1.5mg LNG) or LNG ECx2 (3mg LNG). Study medications will be given by study staff and ingestion will be directly observed. Prior to ingesting study medication, women will undergo urine pregnancy testing to confirm non-pregnant status.

Study end will be at the onset of menses at the end of the treatment cycle (defined as two consecutive days of spotting/bleeding). We estimate up to 12 visits in the treatment cycles depending if delay in ovulation occurs. Subjects will have the option to undergo a washout cycle and participate in the studies detailed in Part 2; if they chose to do so, they will not have to undergo another screening visit or control cycle.

Procedure flow:

	Visit 0 (Screening Visit)	**Treatment Cycle Starting Cycle 1 day 6-8**
Consent, Screening tests and medical history	X	
blood draws	X	X
ultrasound		X
Study Medication & urine pregnancy test		X*
Total time	2 hour	30 min/visit

*Visit number study medication will be taken depends on ultrasound findings.

Data Analysis & Sample Size: All analyses will be performed on an intention-to-treat (ITT) basis. To demonstrate equality between treatment arms at baseline, we will compare participant demographics using two sample t-test or chi-square test, and descriptive statistics such as mean, median and percentages within each group will be reported. **The primary outcome analysis will compare the proportion of women with no follicular rupture (yes/no) between the treatment groups using a Chi-square test.** As mentioned previously, follicle rupture will be defined as the disappearance of or >50% reduction of size of the leading follicle [2,17].

Confirmation of the timing of ovulation will be supported by LH, P4, and E2 levels. If necessary, we will address any unanticipated imbalances between the treatment groups after randomization by adjusting for these confounders in analysis using a logistic regression. 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 EC ingestion during the treatment cycle within each group. Additionally, the proportion of inhibition of follicular rupture by LH status (no surge, start of LH surge, or after LH peak) [2,17] for each cycle will by compared between treatment groups using fisher's exact test. Mean LH, P4, and E2 levels over time will be plotted by treatment group. Time from treatment intake to follicular rupture will be assessed by a survival

analysis using Kaplan-Meier curve and log-rank test. All statistical analyses will be performed with the SAS version 9.4 (Cary, NC, USA).

We believe that the difference between groups will be large (50% or greater) given that LNG ECx1 in obese women appears to be equivalent to placebo (normal ovulation) as well as the large PK differences we found in our preliminary studies. However, we have chosen a more conservative difference (30%) in which to base our sample size calculations to ensure we have the ability to capture a range of differences. A sample size of 62 will achieve 80% power to detect a 30% difference in the proportion of cycles that demonstrate inhibition of follicular rupture (yes/no) using a two-sided Z test with a 5% significant level assuming 90% rate of normal time to ovulation in LNG ECx1 dose group. **We plan to screen up to 80 women to account for screen failures and enroll a total of 70 women to account for drop out.**

Part 2 UPA-EC, obese BMI and a weight of 176 lbs or more and normal BMI and a weight of less than 176 lbs, randomized cross-over trial.

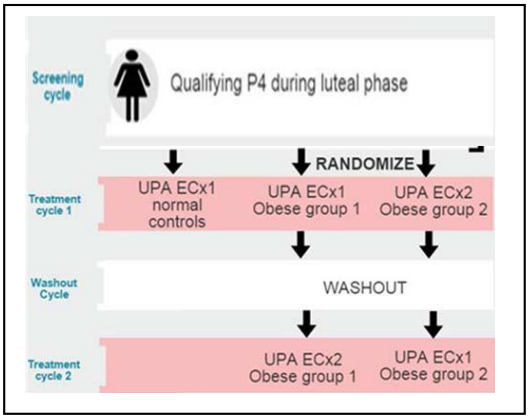
Specific Aim: To compare the pharmacokinetic parameters and pharmacodyanmic profile of emergency contraception containing ulipristal acetate between obese and normal BMI women, and to determine if dose escalation improves how well it works in obese women.

Hypothesis: The peak drug level of UPA-EC is lower in obese women than in normal BMI women which adversely impacts the therapeutic effect and dose escalation will improve drug efficacy for obese women.

Rationale: Published data indicate a possible decline in the efficacy of UPA-EC for obese BMI women [4]. This lack of clarity is leading to concern among clinicians that no orally-dosed EC agent is effective in women of higher weight or BMI. UPA is metabolized differently than LNG. LNG is highly protein bound and our studies have established that obesity adversely impacts LNG clearance, half-life and specific to LNG EC, peak levels [9,10]. UPA, unlike LNG, binds distinctly to alpha-acid glycoproteins and high density lipoproteins. Obesity is known to alter serum/plasma profiles of both drug-binding proteins: Alpha-acid glycoprotein levels are usually doubled [19], and dyslipidemia of obesity is often characterized by low HDL [20]. The net effect of obesity induced changes in UPA binding proteins is unknown yet, however could be speculated as high degree of binding resulting in reduced concentration of pharmacologically relevant drug. Detailed PK and PD studies for UPA in an obese cohort have not been performed. We propose to perform these studies as a randomized cross-over study. This design will reduce variability in the PK data as obese subjects will act as their own controls for comparisons between ECx1 and ECx2. **We have also chosen to include a small control group of normal BMI subjects in order to verify the accuracy of our PK findings.**

Part 2 UPA-EC:

The study flow for Part 2 is depicted in the graphic to the right. Part 2 will be performed as an open-label randomized cross-over study. Randomization will occur in a 1:1 fashion utilizing a computer generated random permuted block randomization scheme with block size 4, 6 and 8.



Demographic information will be obtained including but not limited to race, ethnicity, parity, and prior contraceptive use. If subjects did not participate in Part 1, they will undergo confirmation of ovulation via an elevated P4 of 3ng/mL or greater in the screening cycle. =.

During the treatment cycles, subjects will undergo every other day visits starting on cycle day 6-8 followed by daily visits for up to 7 days once a dominant follicle measuring 15mm or greater in one diameter is visualized. Daily visits will cease if evidence of follicle rupture occurs, either disappearance of or greater than 50% reduction in size of the dominant follicle. At each visit, subjects will undergo blood sampling via a single venipuncture for P4, E2 and LH levels and transvaginal ultrasonography

(TUS). The TUS will be performed using a high-resolution transvaginal ultrasonography (GE Ultrasound OR, 9900 Innovation, Voluson eBT11) to monitor follicular development and evidence of ovulation. During the treatment cycles, study medication will be dosed on the day a 15 mm follicle is visualized. Both the normal and obese BMI groups will undergo treatment cycle 1 and receive a standard dose of UPA EC (30mg) or ECx1. After at least one washout cycle, only the obese group will complete treatment cycle 2 and receive a double dose of UPA EC (60mg). Study medications will be given by study staff and ingestion will be directly observed. Prior to ingesting study medication in each treatment cycle, women will undergo urine pregnancy testing. Study end will be at the onset of menses at the end of the treatment cycle (defined as two consecutive days of spotting/bleeding). We estimate that approximately up to 12 visits in the treatment cycles depending if delay in ovulation occurs.

During each treatment cycle, PK parameters will be obtained via serum samples through an indwelling catheter. IV placement in obese women can be challenging. We will enlist the assistance of OHSU's NIH funded CTSA nursing staff or IV therapy, if necessary, to place IVs in our obese cohort in order to ensure the least traumatic process for our subjects. We plan to obtain samples at 0.5, 1, 1.5, 2, 3, 4, 24, 48, 72, 96, and 120 hours for our normal controls in treatment cycle 1 and a subset of the obese cohort (n=30) in both treatment cycle 1 and 2.The IV will be left in place for the closely spaced samples and then single samples via phlebotomy will be obtained on the samples timed at 24 hours and later. This extended sampling scheme will allow us to determine a more accurate area under the curve by having observed rather than estimated values. Furthermore a prolonged sampling scheme will enable estimation of additional PK parameters that can lead to mechanistic insights.

Of note, Eastern Virginia Medical School will not be recruiting or enrolling participants for the Part 2 – UPA Normal BMI cohort as enrollment of the 12 participants for this group is complete.

Procedure flow for obese BMI study groups

	Screening Visit (1 visit)	Treatment Cycle 1 Starting Cycle day 6-8 (up to 12 visits)	Washout Cycle 2 (no visits)	Treatment Cycle 3 Starting Cycle day 6-8 (up to 12 visits)
Consent, Screening tests and medical history	X			
Phone or email contact			X	
Blood draws	X	X		X
Ultrasound		X		X
Study Medication & urine pregnancy test		X*		X*
Longer series of blood draws (over 5 hours)		X**		X**
Total time	2 hours	30 min/visit for all but 2 visit which will be 2 or 5 hours		30 min/visit for all but 2 visit which will be 2 or 5 hours

*Visit number study medication will be taken depends on ultrasound findings.
**The study visit on the day the study medication is taken will last 2 hours (curtailed PK) or 5 hours (full PK)

Procedure flow for Normal BMI control group

	Screening Visit (1 visit)	Treatment Cycle 1 Starting Cycle day 6-8 (up to 12 visits)
Consent, Screening tests and medical history	X	
blood draws	X	X
ultrasound		X
Study Medication & urine pregnancy test		X*
Longer series of blood draws (over 5 hours)		X**
Total time	2 hour	30 min/visit for all but 1 visit which will be 5 hours

*Visit number study medication will be taken depends on ultrasound findings.
**The study visit on the day the study medication is taken will last 5 hours

Data Analysis & Sample Size: To ensure equality between treatment arms at baseline, we will compare participant demographics using t-test or chi-square test and descriptive statistics, such as mean, median and percentages within each group will be reported. The primary outcome analysis will compare the proportion of women with a delay in follicular rupture of at least 6 days (yes/no) between obese women taking UPA ECx1 versus ECx2 using McNemar's test. Only the women who have completed the two treatment cycles will be included in this portion of the analysis. Although we expect absence or ignorable "period" effect, we will further describe the difference between ECx1 and ECx2 with odds ratios using the generalized estimation equation adjusted for period and any other confounders using all available data. We will check the accuracy of our findings against a normal BMI control group using standard dosing, ECx1 using chi-square test. Follicle rupture will be defined as the disappearance of or >50% reduction of size of the leading follicle. Confirmation of ovulation will be supported by LH, P4, and E2 levels. 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 EC ingestion during the treatment cycle. Additionally, inhibition of follicular rupture will be plotted by LH status (no surge, start of LH surge, or after LH peak) [2,17] for each cycle as well as mean LH, P4, and E2 levels over time and the time of treatment to follicular rupture.

PK parameter analysis. UPA PK parameters will be generated by noncompartmental methods using WinNonLin (Pharsight, Mountain View, CA). Cmax and time to maximum Cmax will be observed values. Area under the curve (AUC) will be calculated from Time 0 to 120hr (AUC0-120) using the linear trapezoidal rule and then extrapolated to infinity which provide a more accurate calculation of drug clearance (Rowland 1980). Drug half-life (t1/2), oral clearance (CL), and volume of distribution (VD) will be generated using standard pharmacokinetic calculations ($t1/2 = 0.693/\lambda z$ where λz is the terminal elimination rate constant; CL=dose/AUC0-infinity; VD=CL// λz). Descriptive statistics will be generated for each parameter [mean(standard deviation)], concentration-time curves will be generated for all of the doses and their respective BMI groups. Depending on the normality of the data, parametric or nonparametric testing will be performed for each parameter between the normal and obese BMI ECx1 groups and paired statistics will be utilized to compare obese BMI ECx1 and ECx2.

We also plan to perform analyses to compare PD outcomes in obese users ingesting LNG and UPA, ECx1 and ECx2. UPA and LNG are the only two orally-dosed EC agents available on the market. A logical sub analysis is the comparison of the different dosing strategies to help guild future studies or even clinical management of orally-dosed EC in obese women if dose escalation appears effective. We will utilize the data collected in Aim 1 and 2. The proportion of women with a delay in follicular rupture (yes/no) in 4 different treatment regimens obtained in the trial in aim1 and 2 will be compared and test if there's significant difference

between LNG ECx2 and UPA LNG ECx2 using Chi-square test. Due to exploratory purpose of these analyses, the analysis will be descriptive but given the projected sample size (35 per group in Part 1 and 80 per group in Part 2) we will achieve more than 80% power with 5% of significance level to detect 23% difference in delay in follicular rupture. In addition, one of the secondary outcomes of time from treatment intake to follicular rupture will be compared among treatment groups using survival analysis.

A sample size of 73 will achieve 80% power to detect a 20% difference in the proportion of cycles that demonstrate at a delay in follicular rupture (yes/no) using a two-sided McNemar test with a Bonferroni-adjusted 2.5% significant level. We estimate that 40 women will choose to participate in Aim 2 after completing Aim 1 studies and plan to screen an additional 58 women to account for screen failures for a total enrollment of 80 women to account for drop out. We believe that the difference between groups will likely be smaller given the clinical information (50% or less). We have chosen a difference of 20% in which to base our sample size calculations. We have consciously chosen not to enroll an adequately sized normal BMI group to detect the same amount of difference (20%) given that there are published PK/PD standards. We are utilizing this group to verify the accuracy of our findings under our environment, the targeted 10 total number of subjects (after 12 screening) in the control arm would achieve the 80% power to detect 47% difference in follicular rupture given the 73 of women taking UPA ECx1 using two-sided Z test with 2.5% significance level. The total number of subjects in the control arm was chosen as a convenience sample but this number of subjects should supply us with an adequate amount of data to ensure that our PK/PD results are similar to published values in a normal BMI cohort.

Protection of human subjects:

1. Risks to Subjects

Human Subjects Involvement and Characteristics

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

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. De-identified pharmacokinetic data will be analyzed by our consulting pharmacokinetic specialist, Dr. Ganesh Cherala.

Sources of Materials

The sources of research material for the clinical portion of this proposal will be new specimens obtained purely for this research protocol. The study investigators and/or research assistants/nurses will perform all study procedures.

Potential Risks

One key contraindication exists for both of the emergency contraceptives used in this study and that is current pregnancy. Current pregnancy 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 rarely can cause nausea. This information will be reviewed with participants and if necessary, an anti-emetic can be provided.

Our research plan describes using EC in accordance with FDA-labeling (single dosing) as well as doubling the dose. In regard to LNG-EC, LNG is considered one of the safest progestins among contraceptive steroid hormones with no associated serious adverse events and no upper dose limit known to cause toxicity [PHS 1,2]. We experienced no serious adverse events during our preliminary studies of LNG-ECx2. In regard to UPA-EC, UPA is similarly safe and well tolerated over a wide range of dosages and duration of treatment (published studies report on maximum dosing as follows: up to 200 mg unmicronized UPA single and 50mg micronized UPA for 10 days) [PHS 3-5]. In reality, as EC only covers a single act of intercourse and there is no limit on the number of times per month EC can be used, a woman could take multiple doses of EC in close proximity with little adverse consequences except for the affect the timing and duration of a woman's next menstrual period [PHS 6].

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

Risk of pregnancy is always present in women who are sexually active. Current recommendations for contraceptive-use in obese women are no different than for normal BMI women. Women who are not at risk for pregnancy due to the use of permanent contraception (male or female) 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.

There are no known harmful effects of a vaginal probe ultrasound but participants may experience slight vaginal discomfort. Care will be taken to ensure that participants are treated with respect and the exam made as comfortable and efficient as possible to limit exposure time.

Other potential risks include stigmatization or embarrassment due to issues surrounding body weight. Counseling resources are available through the Center for Women's Health at OHSU and within the community. A resource list will be available to study participants upon request. A referral will be made upon a study participant's request or because of investigator concern but only after discussion and permission from the participant.

2. Adequacy of Protection Against Risk

Recruitment and Informed Consent

Attempts to enroll a diverse study population will be made through placement of IRB approved flyers in the community, community outreach (newsletters and print ads) and through the availability of foreign language interpreters and research staff (see Inclusion of women and minorities). Women may also learn of the study through their routine visits in clinics or by working at OHSU. We also intend to utilize an EPIC Cohort search to identify and contact potential participants via phone, email, letter, and/or MyChart messages. We will also be using TrialSpark for recruitment through social media. 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 and OCTRI Scientific Advisory Committee prior to initiation of the study.

Protection Against Risk

The EC utilized in this study will be used in accordance with the FDA and at a dosage that is still considered to be safe. Women will be informed of this off-label dosing but that we have specifically chosen a dose and length of exposure time to the drug or compound with extremely low potential for significant side effects or serious risks (see above potential risks). Women will undergo screening for any known contraindications to the study drugs chosen to trial in women.

Women will have access to appropriate counseling for emotional distress regarding body weight issues.

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.

Data and safety monitoring of plans for clinical trials

The PI and study staffs are responsible for recording the data, and they will be verifying its accuracy throughout the process. The PI will be reviewing the data in-depth upon completion of Aim 1, Aim 2 and again at the study's conclusion. The PI will also be overseeing that the study procedures are being carried out as per the approved protocol via close supervision of study visits and procedures and through frequent communication with the study staff. The PI will also be conducting an initial assessment and periodic assessments of the study and its procedures. If any safety concerns arise, a data safety monitoring board will

be convened to review the study. As this study will be performed in conjunction with the Women's Health Research Unit's (WHRU), an independent chart audit to ensure data integrity and completeness will be performed after the first 5 subjects have been enrolled and then at regular 6 months intervals.

The PI will adhere to OHSU's Institutional Review Board (IRB) policies regarding protection of human subjects and the reporting of study deviations and adverse events. In the rare case of an adverse event, she will utilize the WHRU data safety monitoring board (DSMB) to review the event and rule on a course of action. The WHRU DSMB is made up of individuals knowledgeable about women's reproductive health and therapies and will have no conflict of interest with the study or its outcomes.

3. Data Storage

   Data for this project will be stored in OCTRI's installation of REDCap, a highly secure and robust web-based research data collection and management system.

   Features of REDCap that protect participants' privacy and data security include:
   - Physical Security: OCTRI's REDCap software is housed on servers located in ITG's Advanced Computing Center providing locked physical security
   - Electronic Security: The REDCap servers are housed behind both the OHSU firewall and a second ACC firewall. All web-based data transmissions are encrypted with industry-standard SSL methods.
   - Controlled User Access. REDCap employs a robust multi-level security system that enables researchers to easily implement "minimum necessary" data access for their research staff, including specification of data fields that are identifiers. This feature includes "single click" ability to provide completely deidentified (removing all identified data fields and shifting dates) for analysis or other purposes. User activities are logged to enable auditing of all data access. Access is integrated with OHSU's network such that all users who are OHSU employees are authenticated against their OHSU network credentials.
   - Data Integrity: REDCap is jointly managed to accordance with OSU Information Security Directives by ACC staff and members of OCTRI's Biomedical Informatics Program, ensuring fidelity of database configuration and back-ups. User activities are logged to enable auditing of all data changes.

4. Potential Benefits of the Proposed Research to the Subjects and Others

There are no direct benefits to study participants.

5. Importance of Knowledge to be Gained

This study will increase the knowledge regarding obesity and failure of contraception. It may help to increase awareness regarding an additional health concern specific to obese women and the need for individualizing birth control for this group to avoid unplanned pregnancies. It may go beyond the identification of a problem, but also help in providing the potential mechanism of action and intervention for this phenomenon.

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