Protocol and SAP	
Study Title:	*A pilot prospective, randomized pharmacodynamic study with assessment of ulipristal acetate on ovarian activity following quickstart of the etonogestrel contraceptive implant*
Institution Name	**University of Utah**
Investigator	**Principal Investigator: Lori Gawron, MD, MPH**
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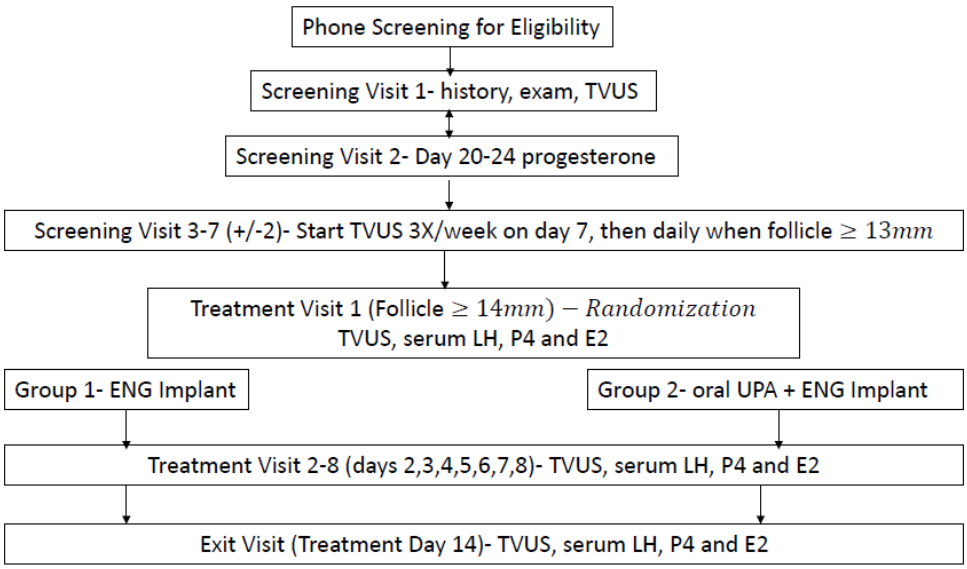
Protocol	
Study Design	Study design: Pilot randomized, single site clinical trial with blinded analysis Participant recruitment and study site: We will recruit participants interested in using the ENG contraceptive implant but not currently at risk for pregnancy from University of Utah Hospital and Community clinics, and through targeted social media ads. All study procedures will occur at the University of Utah Hospital Outpatient OBGYN Clinic Sample size: This is a pilot proposal to recruit a total of 40 participants across 2 study arms: (1) ENG implant only (n=20) and (2) UPA + same day ENG implant insertion (n=20). Our null hypotheses are: 1) ENG implant along with UPA administration in the presence of a dominant ovarian follicle will not change the expected 97% ovulation suppression within 5 days of UPA use. 2) ENG implant insertion alone in the presence of a dominant ovarian follicle will not sufficiently interrupt ovulation. Inclusion criteria: Healthy people, age 18-35 years, fluent in English and/or Spanish, BMI < 30 kg/m2, no known contraindication to either the ENG contraceptive implant or UPA using the CDC Medical Eligibility Criteria for Contraceptive Use 2016, not currently pregnant and not at risk of pregnancy (defined as not having penile-vaginal intercourse or using a non-hormonal method of contraception such as a barrier method, condoms, diaphragm, or cervical cap, a copper IUD, or permanent contraception), know the date of their last menstrual period, have a regular menstrual cycle (24-35 days), be willing to comply with the study requirements, and be willing to avoid pregnancy for study duration. Exclusion criteria: Current pregnancy or breastfeeding, use of hormonal contraception or exogenous hormones (estrogen, progestogen, or HCG) in the last month (or past 6 months for depo medroxyprogesterone acetate) planned use during the study, vaginal bleeding of unknown etiology, allergy to UPA or ENG, regular or planned use of glucocorticoids during the study, or current or planned use of any medication that potentially interacts with UPA or ENG. Participant adherence: Screening protocol will ensure willingness to comply with all study procedures. Participants will receive compensation for each component of the protocol.

Study Flowchart	
Study Procedures	Randomization scheme: block randomization with block size of 4 Blinding protocol: This study will not be blinded as a pilot. The feasibility of the study, including clinic space limitations and provider time, relies on the same healthcare provider for implant insertion and ultrasound in many patients. All statistical analyses will be blinded to the statistician. Participant procedures: Screening Visit (Screening Visit 1): Subjects will be screened for eligibility and interest in the study. Each subject will have the study explained and, if they desire to participate, she will sign the informed consent prior to any study procedures. The screening visit will include: review of medical, surgical and social history, medications, menstrual dating, sexual history and contraceptive use, physical exam, including breast and pelvic, and a transvaginal ultrasound to ensure ability to document ovarian follicular activity in the treatment cycle. Progesterone Visit (Screening Visit 2): This brief visit will occur on days 20-24 of the menstrual cycle and may be combined with the screening visit (Visit 1) if the timeframe is met. This visit will include a review of any interim changes (if completed separate from the screening visit) in history, medications, pregnancy risk/contraception, and a serum progesterone level will be drawn. The participants will notify the study coordinator of the 1st day of their next menses. Ovarian monitoring (Screening Visits 3-7 +/- 2 visits): Participants will undergo transvaginal ultrasound evaluation of their ovaries three times a week starting on cycle day #7 (+/- 2 days). If/ When we identify a lead follicle with a mean diameter of >13mm in at least 2 dimensions, we will switch to daily monitoring. Treatment Day #1 (Treatment Visit #1): Once a lead follicle (≥14mm) is identified then participants will be randomized to one of two treatment groups: 1) ENG implant insertion 2) UPA 30mg PO tablet and same-day ENG implant insertion Assigned treatment will be administered (UPA and/or ENG implant insertion). We will obtain serum progesterone, LH levels, and estradiol levels. Treatment Days #2-8 (Treatment Visits #2-8): Participants will follow up daily for Days 2-8. Each day we will obtain transvaginal ultrasound measurement of ovarian follicle size, serum progesterone, LH levels, and estradiol levels. We will obtain daily

	transvaginal ultrasounds until either follicle rupture is documented, the follicle is <12 mm on two consecutive visits, or Day 8 ultrasound occurs (7 days after implant insertion), whichever occurs first. Treatment Day #14 (Exit Visit): Repeat ultrasound will occur on Day 14 following ENG implant insertion, and this will be the exit visit. Data collection: Source documents for each participant and visit number will be completed by the study personnel at the time of the visit. Form development, data collection, and data management will occur in RedCAP, secure web platform for building and managing online databases and surveys. Source documents maintained in individual participant binders. Assessing and reporting adverse events: The reporting period for AEs is the period immediately following the subject signing the informed consent through the 30 days following the final study visit. Each visit will include assessment of how the participant felt since the last visit, review of adverse event reports, implant insertion site reactions, lab results, and vital signs and physical exam findings. AEs will not be reported for screen failures unless a SAE is experienced during screening. For all AEs, the investigator will pursue and obtain information adequate to determine the outcome of the AE and to assess whether it met criteria for a SAE. Participants who have ongoing AEs or SAEs will be followed until resolution or stabilization or referred for additional care. AEs will be documented both on source documents and in the clinical database with SAEs reported per IRB guidelines. Participants will be provided instructions for contacting the study site to report any untoward medical occurrences. With permission from the participant, whenever possible records from all non-study medical providers related to medical occurrences will be obtained for review. AEs and SAEs will be reviewed by the Data Safety Monitoring Board as below (section 2.9).
Statistical Analysis Plan	The investigator and study team will be responsible for analyzing the study data. The official clinical database in RedCAP will not be analyzed until medical/scientific review has been completed, protocol violators have been identified (if appropriate), and data has been declared complete. Variables/Time Points of Interest The primary outcome is delay in rupture of the dominant follicle by 5 days (yes/no) between group 1 (ENG implant alone) and group 2 (UPA with same day ENG implant). If the date of follicle rupture was unclear by ultrasound alone, we will utilize serum hormone levels to adjudicate day of rupture. These measures include day of follicle collapse, day and value of highest LH, day and value of highest progesterone level. We will use an estradiol level of >100pg/ml to confirm the enlarged follicle is the dominant follicle on the treatment day. Statistical Methods The primary and secondary dichotomous outcome measures of ovulation by 5 days will be assessed by Wilcoxon sign rank test and demographic will be analyzed using descriptive statistics. Power/Sample Size: This is a pilot study to obtain point estimates for future study proposals. Current data on ovulatory function with mid-cycle implant insertion or the pharmacodynamics interactions between same day UPA and ENG are lacking.