A prospective observational study of preference for and efficacy of oral levonorgestrel emergency contraception with same day etonogestrel contraceptive implant compared to established pregnancy rates with oral levonorgestrel emergency contraception alone

Protocol Summary

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Background and Introduction

Emergency contraception (EC) includes products that prevent pregnancy after an episode of unprotected intercourse (UPI). The recommended options for EC by the CDC Selected Practice Recommendations (CDC SPR) include oral EC (levonorgestrel (LNG), ulipristal acetate (UPA), or combination oral contraceptive pills), or the copper intrauterine device (IUD). A recent randomized clinical trial found the LNG IUD alone to be non-inferior to the copper IUD. (Clinicaltrials.gov: NCT02175030) Once these data are published, women presenting for EC may be offered either the copper or LNG IUD alone or may initiate any another contraceptive method, if oral LNG EC is co-administered. This recommendation leaves out the only other LARC method, the ENG implant, based upon lack of EC efficacy data. **The CDC SPR guidelines allow for same-day ENG implant initiation at the time of an EC encounter, as long as oral LNG EC is co-administered.**

General insertion guidelines for the ENG implant recommend initiation within 5 days of last menstrual period (LMP) to avoid the risk of a luteal-phase pregnancy (LPP). Two studies provide data on risk of LPP with same-day initiation beyond 5 days after LMP. First, a retrospective study based in Colorado had pregnancy outcome data on 57% of adolescents who initiated the implant outside the guidelines. They reported a LPP rate of 0.9% (10/1066; 95% CI=0.5–1.7%), and only 8.2% of participants received same-day oral EC for recent reported unprotected intercourse (UPI). [1] A secondary analysis of the HER Salt Lake study reported pregnancy risk of same-day implant initiation in women reporting UPI within the past 14 days with and without oral EC use was 1.2% (95% CI=0.03%- 6.5%). Despite a small sample size, this group included women at high risk of pregnancy in the cycle evaluated because several reported UPI beyond the 5-day eligibility for oral EC and multiple episodes of UPI. [2] These data show a low risk of LPP in women receiving outside-of-guideline initiation, even in those reporting UPI. **Clinicians, and implant users lack robust data on pregnancy risk for the guideline-adherent, EC-eligible population desiring same-day ENG implant placement and oral EC.**

Women presenting for EC often need ongoing contraception, but clinical practice is not standardized in same-day counseling and initiation due to system-, provider-, and client-level barriers. Understanding the interest in same-day LARC initiation would help interventions to overcome these barriers, but data are again limited on this topic. One retrospective chart review from 2011-2013 reported on an intervention to offer comprehensive contraceptive counseling at the time of EC encounters. The authors found increased uptake of all LARC methods from zero women initiating the same day as EC prior to intervention and 12% (38/328) with same-day initiation during the intervention (33 copper IUDs, 3 LNG IUDs, and 2 ENG implants). At 3-month follow-up, 10% of women had initiated a LARC method prior to the intervention. This increased to 22% post-intervention. [3] Since execution of that study two important trends support the need for execution of this proposal. **Interest in LARC use continues to steadily increase as does the practice of same-day contraception initiation (quick-start). Because of these changes in user demand and provider supply, we need new estimates of interest in same-day LARC initiation at the time of EC encounters.**

Women presenting for EC may not have considered LARC options prior to the encounter and same-day initiation may impact continuation rates. A prospective observational trial assessing

same-day initiation of IUDs at time of EC encounters found one-year continuation rates of 60% in copper IUD users and 70% in LNG IUD plus oral LNG users. [4] **Data on implant continuation rates at time of same-day initiation with an EC encounter are lacking.**

The ENG implant is a synthetic progestin with a quick rise in serum levels which, in theory, could stabilize a dominant follicle and serve as EC without the addition of oral LNG. Thus, eventually we may have evidence that the ENG implant alone is sufficient for EC. However, now EC users desiring same-day implant initiation and clinicians willing to provide the service need **baseline data on pregnancy rates for guideline-adherent same-day initiation of the ENG implant with oral LNG EC. We propose to generate a baseline estimate and compare it with historical controls of oral LNG EC alone.**

Study design: Prospective observational single site clinical trial

Participant recruitment and study site: All women age 18-35 years old who present to a Planned Parenthood Association of Utah (PPAU) clinic requesting EC will receive a one-page handout offering (1) same-day method initiation with oral LNG + ENG implant or other hormonal method, (2) copper or LNG IUD alone, or (3) UPA with delayed initiation of hormonal contraception if BMI >30. Women initiating an ENG implant + oral LNG EC will be offered enrollment into a prospective observational survey study. All study procedures will occur at PPAU clinics. Standard clinical counseling at participating health centers includes differences in efficacy between oral LNG and UPA by BMI and in those between 3-5 days out from UPI. Women desiring the most effective oral method of EC will be offered ulipristal acetate.

Sample size: This is an observational trial to gain a point estimate for pregnancy rate following guideline-adherent, same-day method initiation with oral LNG + ENG implant compared to published pregnancy rates following oral LNG EC alone. [5] Our maximum sample goal is 300 women with 1-month pregnancy outcome data and the 1st 100 women will be followed for the secondary outcomes of 12-month continuation or reasons/timing of discontinuation. We will use the 2 PPAU clinics that dispense the greatest EC volume for this study (960 total EC visits in 2019) and plan to achieve our recruitment goal in 24 months. We are confident in our recruitment plan based on the 1,122 EC users receiving IUDs at these clinics who have enrolled in prospective clinical trials.

Our null hypotheses are:

1) ENG implant along with oral LNG EC will not have a pregnancy rate greater than published oral LNG EC (2.5%; 95%CI 1.3-4.6). [5]

2) Uptake of same-day ENG implants will be lower than same-day IUD uptake for EC.

Purpose and Objectives

Primary:

1. To determine a point estimate for the one-month pregnancy rate following guideline supported same-day initiation of an etonogestrel (ENG) implant plus oral levonorgestrel (LNG) emergency contraception (EC).
2. To determine the proportion of EC clients willing to initiate a same-day ENG implant with oral LNG EC compared to same-day initiation of intrauterine devices for EC.

Secondary:

- Describe the 6- and 12-month continuation rates of the ENG implant with same-day initiation at an EC encounter.
- Describe the timing and reasons for ENG implant discontinuation in the 12 months following same-day initiation at an EC encounter.

Clinical hypotheses.

- Combined oral LNG EC administration with same-day ENG implant insertion will not increase pregnancy rate point estimate compared to oral EC alone.
- EC clients willing to initiate a same-day LARC method will preferentially chose the ENG implant over IUDs and
- Clients initiating a same-day ENG implant will continue the method at the same rate as users who initiate at other encounters.

Study Population

Age of Participants: Women age 18-35

Sample Size:
At Utah:
All Centers:

Inclusion Criteria:
Healthy women, age 18-35 years, fluent in English and/or Spanish

BMI < 30 kg/m2

No known contraindication to either the ENG contraceptive implant or oral LNG EC using the CDC Medical Eligibility Criteria for Contraceptive Use 2016

Negative urine pregnancy test

Willing to abstain from further UPI in the 7 days following insertion

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

Desiring to avoid pregnancy for at least 12 months.

Their current preferred phone number must be functioning at the time of study entry and will be tested prior to enrollment. We will obtain preferred mode of communication (phone, text, email) and also a contact information for a secondary person.

Exclusion Criteria:

Current pregnancy or breastfeeding

Previous use of oral EC in the current cycle

Report of UPI beyond 5 days in current cycle

Vaginal bleeding of unknown etiology

Allergy to LNG or ENG

IUD or implant in-place

History of permanent contraception through sterilization or hysterectomy

Monogamous partner with a vasectomy, or

Depo-provera injection within past 15 weeks.

Design

Study Procedures

Recruitment/Participant Identification Process:

All clients who present to selected Planned Parenthood Association of Utah clinics for Emergency Contraception (EC) will receive a single-page explanation of EC options (attached in Documents section of study application) with ongoing contraception initiation: copper or LNG IUD alone, oral LNG EC + implant or other hormonal contraception, oral LNG EC alone, or oral UPA EC alone (with or without delayed initiation of hormonal contraception).

This explanation will end with an assessment of interest in a contraceptive visit, which allows us to gather information on women who refuse the counseling and opted to only access oral

EC. This information will include: age, race/ethnicity, last menstrual period, and reason for declining counseling.

Women desiring additional information about the ENG implant will then be asked if she is interested in study participation, through a consent process managed by an IRB approved member of the study team.

Those with interest in other methods, including IUDs, will receive a contraceptive visit by PPAU clinical staff.

Informed Consent:

Description of location(s) where consent will be obtained:

Consent will be obtained in a private examination room at the clinic where the patient is receiving care.

Description of the consent process(es), including the timing of consent:

Due to the nature of this study, it may not be possible for patients to return at a later time to enroll in the study. Participants will have all questions answered prior to enrollment. The research staff are experienced in interviewing and working with this population. They will be certain to take the time needed to ensure that the patient understands the study and is consenting willingly. If the woman continues to have questions, she will be offered the opportunity to discuss the study in further detail with the PI or other medical providers with extensive experience with the clinical care of IUDs and emergency contraception.

Procedures:

Screening/enrollment Visit: Subjects interested in the ENG implant will be screened for eligibility and interest in the study. Each subject will have the study explained and, if she desires to participate, she will sign the informed consent prior to any study procedures. The screening/enrollment visit will include: review of medical, surgical and social history, medications, contraceptive use, height and weight to calculate BMI <30, and a urine pregnancy test. We will collect detailed information on menstrual cycle history, last menstrual period, cycle length over the preceding six months, and time of unprotected intercourse. This will enable us to calculate the timing of UPI relative to position in the menstrual cycle should any pregnancies occur. Finally, we will insert the ENG implant with co-administration of oral LNG EC (1.5mg po X1). Participants will be given a home pregnancy test with instructions on use at 1 month. They will also have a clinic appointment made for 1 month, in case of need for in-person urine pregnancy testing or follow-up from a positive home pregnancy test.

Women who choose an IUD: Women who choose an IUD and agree to participate in this study will be asked to sign the consent document. They will then be asked to complete a questionnaire about prior sexual activity, use of contraception, pregnancies and sexually transmitted infections. Completion of this questionnaire will be the only study procedure asked of this subgroup of participants. There will be no follow-up procedures.

One-month follow-up (Phone or in-person): Four weeks after enrollment, the research staff will contact the participant per their contact preference (text, phone, etc.) and send a link to a

RedCAP survey to record the results of their home pregnancy test, assess satisfaction with the implant and record any adverse events that have occurred. If the participant is unable to complete the home pregnancy test and record results, a clinic visit will be scheduled for a urine pregnancy test. If a patient has a positive pregnancy test, she will receive an ultrasound, a blood test for b-HCG, standard pregnancy options counseling and removal of the implant will be recommended if she opts to continue the pregnancy. Participants will receive $40 for this follow-up.

Three-month follow-up (Online link or Phone):* Three months after enrollment, participants will receive a link to a RedCAP survey to assess satisfaction with the implant and adverse events. If the participant has discontinued the method, we will collect the date of discontinuation, reason(s) and current contraceptive method. If the survey is not completed within 7 days, the research staff will complete up to 3 attempts to contact the participant by each contact method for survey administration. No compensation for this call.

Six-month follow-up (Online link or Phone):* Six months after enrollment, participants will receive a link to a RedCAP survey to assess satisfaction with the implant and adverse events. If the participant has discontinued the method, we will collect the date of discontinuation, reason(s) and current contraceptive method. If the survey is not completed within 7 days, the research staff will complete up to 3 attempts to contact the participant by each contact method for survey administration. Participants will receive $20 for this follow-up.

Nine-month follow-up (Online link or Phone):* Nine months after enrollment, participants will receive a link to a RedCAP survey to assess satisfaction with the implant and adverse events. If the participant has discontinued the method, we will collect the date of discontinuation, reason(s) and current contraceptive method. If the survey is not completed within 7 days, the research staff will complete up to 3 attempts to contact the participant by each contact method for survey administration. No compensation for this call.

Twelve-month follow-up/Exit visit (Online link or Phone):* Twelve months after enrollment, participants will receive a link to a RedCAP survey to assess satisfaction with the implant and adverse events. If the participant has discontinued the method, we will collect the date of discontinuation, reason(s) and current contraceptive method. If the survey is not completed within 7 days, the research staff will complete up to 3 attempts to contact the participant by each contact method for survey administration. Participants will receive $20 for this follow-up.

*Only the 1st 100 participants agreeing to longer-term study participation will be enrolled for the 3 to 12-month visits

Electronic Health Record Data Extraction: We will use PPAU electronic health records to identify all EC encounters that occurred during the study timeframe and will record all method choices at the time of EC provision or the follow-up visit, if UPA was administered and method initiation delayed. We will also review the Planned parenthood Association of Utah records for study participants in the 1-year following enrollment who were lost to follow-up to identify any care related to ENG implant removal, continuation, or pregnancy.

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 will be maintained in individual participant binders.

Data extraction will be recorded in a study specific REDCap database.

ENG implants will be supplied via Merck. Oral LNG EC is provided at no cost from PPAU and the study team will provide the other LARC (long acting reversible contraception) methods, the copper and LNG IUD, at no cost to avoid bias in LARC preference. All devices and the oral LNG EC are FDA approved and will be maintained in their usual packaging.

The investigator will be responsible for the destruction of the supplies at the study center pursuant to the ICH/GCP Guidelines, local regulations and the investigator's institutional policies. Clinical supplies will be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. The investigator will be responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the patients, and the disposition at the end of the study.

Procedures performed for research purposes only:

Study procedures involve women who present to Planned Parenthood for emergency contraception but who are also looking for long-acting reversible contraception at the same time as emergency contraception (EC).

Study procedures include:

Enrollment survey and choice of either a Nexplanon implant plus Plan B for emergency contraception or an IUD (either hormonal or copper) for EC and continued contraception.

Individuals who chose the Nexplanon implant plus Plan B will then be asked to provide pregnancy information at one month plus satisfaction surveys at 3, 6, 9, and 12 months.

Statistical Methods, Data Analysis and Interpretation

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 violations have been identified (if appropriate), and data has been declared complete.

Variables/Time Points of Interest

The primary outcomes are 1) pregnancy rate calculated as the proportion of women with a positive pregnancy test at 1 month following the enrollment and 2) proportion of EC clients willing to initiate a same-day contraceptive implant. Secondary outcomes will be implant continuation at 6 and 12 months and timing and reasons for discontinuation.

Statistical Methods

We will calculate the one-month pregnancy rate and confidence intervals will be constructed using effective sample size adjustments for the small sample size. We will report descriptive data on the methods chosen from all EC clients during the study timeframe, as well as the responses from the informational assessment on those not interested in an ongoing contraceptive method the same day. Kaplan-Meier estimates will be constructed to estimate the proportion of patients who continue with their implant for 1 year (continuation proportion) and to estimate the proportion that have an unintended pregnancy by 1 year.

Power/Sample Size:

This study seeks to obtain point estimates to evaluate guideline-adherent care and for future study evaluations/comparisons. Guidelines allow for same-day initiation of the ENG implant with oral LNG EC, with the unstudied assumption that pregnancy rates will be equivalent. With this assumption, we anticipate a 2.5% pregnancy rate (95% CI= 1.3-4.6) based on the Glasier article estimate of pregnancy rate in the upper BMI range (25-29.9) with use of oral LNG EC alone. [5] In our recent IUD EC trial the median BMI was 25. The potential exists for higher pregnancy rates in BMI >30, thus we will exclude this population and recommend oral UPA as the preferred EC if an IUD is not desired. Because additional episodes of UPI in the same menstrual cycle following EC increase risk of pregnancy, inclusion criteria include a recommendation to avoid UPI for 7 days after enrollment.

We plan for a sample size of a maximum of 300 participants for the primary outcome. This is based on the below table demonstrating the 95% CI and margin of error for sample size and upper limit CI of 5.0. We will analyze our pregnancy rate starting at 100 participants with 1-month pregnancy outcome data and with every subsequent 50 participants. We establish stopping rules demonstrating efficacy. For example, we will stop trial enrollment if the 1-month pregnancy point estimate is <2% AND the top end of the 95% CI is <5%. This would occur if 2 (or fewer) pregnancies occurred with 1-month pregnancy outcomes for 200 participants. This would yield a point estimate of 1% and a 95% CI (0-3.8%). There is not a perceived risk of having a 1-month pregnancy rate greater than what is known for oral LNG for EC. However, we have developed a stopping point if there is an unknown interaction or effect of combined use of oral LNG and ENG implant initiation. Once we have outcome data on 100 participants, we will cease trial enrollment if the point estimate for the 1-month pregnancy rate exceeds the known upper bound of the 95% CI for women with in the upper BMI range (25-29.9) using oral LNG EC (4.6, from Glasier estimate above).