Official Title: The effect of rifampin on etonogestrel concentrations in contraceptive implant users

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Proposal Narrative

I. Hypotheses and Specific Aims:

Specific Aim:

- To evaluate the pharmacokinetic effect of rifampin on serum etonogestrel concentrations in contraceptive implant users at the dose of rifampin used for latent tuberculosis infection (LTBI) treatment (600mg per day)

- Exploratory Aim – to evaluate the effect of rifampin on serologic measures of ovulatory suppression (estradiol and progesterone) in contraceptive implant users

Hypothesis:

- We hypothesize that rifampin will have a significant pharmacokinetic effect on participants' etonogestrel levels resulting in etonogestrel concentrations at least 35% decreased from baseline measurements.

II. Background and Significance:

Rifampin is an antibiotic historically prescribed as part of a treatment regimen for active tuberculosis (TB) infection. Though active TB infections have become rarer over time in the US, it is estimated that up to 13 million people in the US may have latent TB infections (LTBIs), with even greater numbers of LTBIs worldwide[1]. In efforts to combat the persistent rate of LTBI, the US Centers for Disease Control and Prevention (CDC) released updated treatment guidelines for LTBI in 2018[1]. This recommended treatment guideline consists of four treatment regimens, varying in duration from 3 to 9 months. The CDC recommends utilization of the shorter regimens when possible to achieve higher patient compliance and infection clear rates. The second shortest duration treatment regimen (4 months) consists of daily rifampin only[1].

In addition to its antitubercular properties, rifampin is a known strong cytochrome P-450 (CYP) 3A4 enzyme inducer[2]. Similar to other strong CYP3A4 enzyme inducers (e.g. carbamazepine), rifampin can affect the serum concentrations of exogenous steroid hormones found in hormonal contraception[2]. The only published literature on the interaction between rifampin and hormonal contraception has focused on combined oral contraceptives[3]. Five studies that investigated the pharmacokinetics of combined oral contraceptives all found significant reductions in serum ethinyl estradiol and progestin concentrations with rifampin co-administration[3]. This pharmacokinetic effect is significant enough to warrant a category 3 recommendation (theoretical or proven risks usually outweigh the advantages) from the CDC Medical Eligibility Criteria (MEC) for Contraceptive Use for concomitant rifampin and combined hormonal contraceptive methods[4]. This pharmacokinetic effect is large enough to raise concerns for combined hormonal contraceptive method efficacy and recommendation of alternative methods. One of those alternative methods is the etonogestrel (ENG) implant (Nexplanon®), which has a category 2 recommendation in the CDC MEC for concomitant rifampin use[4]. However, in

the clarifications for this recommendation, the CDC MEC warns that rifampin is "likely to reduce the effectiveness" of the ENG implant, with no supporting evidence provided[4].

Our prior work found that a strong CYP3A4 inducer (carbamazepine) caused clinically significant reductions in serum etonogestrel concentrations among contraceptive implant users[5]. We found a median decrease in serum ENG of 61% (range 25-87) with 8/10 participants having serum ENG concentrations <90pg/mL after concomitant carbamazepine[5]. Though there is currently no published data on the pharmacokinetic interaction between rifampin and the ENG implant, given its similar enzyme induction properties, there is concern that the CDC MEC recommendation for rifampin and the ENG implant may underestimate the potential risk for contraceptive failure. In further support of this, our Family Planning listserv recently discussed the case of a patient with an ENG implant in place that became pregnant shortly after starting rifampin for LTBI treatment. Given the social, financial, and healthcare costs of unintended pregnancies, it is imperative that we better understand the drug-drug interaction between rifampin and the ENG implant. Especially in light of the contradictory category 2 recommendation and clarification in the CDC MEC[4], more data are needed to determine if rifampin has a significant enough pharmacokinetic effect on the ENG implant to potentially cause contraceptive failure. This information would allow healthcare providers around the world the ability to provide improved counseling to patients needing treatment for LTBI in regards to both their TB treatment regimen and their concurrent contraceptive options.

III. **Preliminary Studies/Progress Report:** There are no preliminary studies for this protocol.

IV. Research Methods

A. Outcome Measure(s):

Primary outcome:

- Serum etonogestrel concentrations measured before and after concomitant rifampin therapy

Secondary outcomes:

- Serum estradiol (E2) and serum progesteron (P4) concentrations measured before and after concomitant rifampin therapy

B. Description of Population to be Enrolled:

We aim to enroll up to 15 reproductive age (18-45 years) women in this study based on the following criteria:

- Inclusion Criteria: Healthy women, who have had an ENG implant for 12-36 months at the time of enrollment and will maintain their implant during the study without modifications.
- Exclusion Criteria (at baseline):
    - We will exclude women who are taking any known cytochrome P-450 3A4 enzyme inducers or inhibitors.
    - We will exclude women with a known allergy or insensitivity to rifampin.

    - We will also exclude women with a body mass index (BMI) <18.5, as underweight women may have altered metabolism. We will not have an upper BMI cut-off as studies have shown that overweight and obese women have equivalent metabolism and efficacy with the ENG contraceptive implant[6,7].
- Exclusions Criteria (screening laboratory testing)
    - We will also exclude women with any hepatic or renal dysfunction as determined by a comprehensive metabolic panel. For purposes of this study, liver function tests will be evaluated and evidence of hepatic dysfunction will be defined as an ALT >52 or AST >39, which are beyond the reference range of normal values used by the University of Colorado clinical laboratory. Renal function will be assessed by a serum creatinine and a value >1.2 will be evidence of renal dysfunction as this is greater than the reference range used by the University of Colorado clinical laboratory.
    - We will also exclude women with any abnormal hematology as determined by a complete blood count. For purposes of this study, abnormal hematology will be defined as a WBC, RBC, or PLT value beyond the reference range of normal values used by the University of Colorado clinical laboratory.
    - We will also exclude women with abnormal coagulation factors as determined by coagulation factor tests (PT/INR, PTT). For purposes of this study, abnormal coagulation factors will be defined as any test value beyond the reference range of normal values used by the University of Colorado clinical laboratory.

C. Study Design and Research Methods

We propose a prospective, pre and post study to evaluate the pharmacokinetic effect of rifampin on serum ENG levels in contraceptive implant users. We will enroll healthy women using an ENG implant for at least 12 months and no greater than 36 months. Our exclusion and inclusion criteria are detailed as above. Interested participants will undergo a phone screening prior to scheduling an enrollment visit. At the enrollment visit, potential participants will have their vital signs checked in the form of a pulse and blood pressure and will have their height and weight measured for purposes of calculating a body mass index. We will review each potential participants past medical history and current medications to ensure study eligibility. If interested participants meet our non-laboratory inclusion and exclusion criteria, then they will undergo informed consent in a private clinic room.

After the participant has been consented, we will perform a blood draw to obtain whole blood and serum. Appropriate blood samples will be sent to the University of Colorado Clinical Laboratory for a comprehensive metabolic panel, complete blood count, and coagulation factor testing (PT/INR, PTT). We will also obtain additional blood tubes for measurement of serum estradiol and progesterone. These tubes will be sent to the UCH Clinical Laboratory for analysis if the participant's screening laboratory testing is normal. A blood sample for serum will be centrifuged on location and the serum collected for

storage in our -80°F freezer. For participants that meet our laboratory exclusion criteria, we will ultimately measure a serum baseline ENG concentration from the serum collected at the enrollment visit. The research team will then follow-up the screening laboratory tests to determine final eligibility based on the criteria discussed above. Eligible participants will then be given the options of either returning to our clinic to pick up the study medication or have the study medication mailed to them via FedEx.

Participants will then begin a 2 week regimen of rifampin at 600mg per day. This dose is the recommended dose for treatment of LTBI and duration of 2 weeks will achieve steady state rifampin levels with adequate time for liver enzyme induction. All participants will then return at the end of the second week for a repeat blood draw. We will again obtain serum as described above for planned measurement of serum ENG concentrations. We also obtain blood samples for repeat measurements of serum estradiol and progesterone. We will also measure a serum rifampin level at the time of the second ENG blood draw to confirm compliance. Serum estradiol, serum progesterone, and serum rifampin levels will all be measured at the UCH Clinical Laboratory. At the conclusion of enrollment, all stored serum samples will be de-identified and shipped to a Merck® laboratory for serum ENG concentration measurement. Batch analysis will be performed using a liquid chromatography mass-spectrometry method that has been previously validated. Participants will serve as their own controls for this study.

All participants will be required to use either a back-up non-hormonal method of birth control or abstain from intercourse during the study and for 2 weeks after the last dose of rifampin. Rifampin has a half-life of 3-4 hours, and thus, will be eliminated within 1-2 days of the last dose, but we will allow a full 2 weeks of buffer to ensure that the contraceptive effect of the implant has reinitiated before recommending resuming unprotected intercourse.

All study visits will occur at the Comprehensive Women's Health Clinic in Lowry. This is our Family Planning site for both clinical and research visits. All consent and enrollment processes will be conducted in a private clinic room and interested participants will be allowed as much time as needed to review the consent and ask any questions regarding the consent and study procedure.

F. Data Analysis Plan:

For this study, we aim to show a decrease in serum ENG concentrations of at least 35% from baseline, which would be consistent with the effect of a moderate to strong CYP3A4 inducer based on FDA standard definitions[2]. Based on our previous cohort of 350 ENG implant users[8], we converted the median and range of serum ENG from that cohort to a mean of 137.4pg/mL with a SD of 106.6 based on Hozo et al's (BMC Med Res Methodol, 2005) formula. We then determined the assumed standard deviation of the differences in serum ENG concentrations to be 53.3 for before and after rifampin exposure based on an assumed correlation of 0.875 between these measurements. In order to find at least a 35% decrease in serum ENG concentrations (at least 48.1pg/mL decrease) with alpha level of 0.05 and power of 0.9, we will need 13 study compliant participants. Given the non-normal distribution of serum ENG concentrations, we will plan for 15 study compliant participants. We expect the discontinuation rate to be low given the short period

of treatment time (2 weeks), and so will plan for enrollment of 15 participants. If our discontinuation rate is higher than expected, then we will consider additional enrollment as needed.

We will use a paired Wilcoxon signed rank test to compare pre and post exposure serum ENG concentrations with each participant serving as their own control. We use the same analytic test for comparing pre and post exposure estradiol and progesterone levels. We will use a p-value of <0.05 as a cut-off for statistical significance. As each participant serves as her own control, we do not need to incorporate demographic factors into our analyses.

H. References:

References

- 1. Treatment Regimens for Latent TB Infection (LTBI). https://www.cdc.gov/tb/topic/treatment/ltbi.htm. Accessed July 17, 2019.
- 2. U.S. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers. https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm. Accessed 01/17/2017.
- 3. Simmons KB, Haddad LB, Nanda K, Curtis KM. Drug interactions between rifamycin antibiotics and hormonal contraception: a systematic review. *BJOG.* 2018;125(7):804-811.
- 4. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep.* 2016;65(3):1-103.
- 5. Lazorwitz A, Davis A, Swartz M, Guiahi M. The effect of carbamazepine on etonogestrel concentrations in contraceptive implant users. *Contraception.* 2017;95(6):571-577.
- 6. McNicholas C, Swor E, Wan L, Peipert JF. Prolonged use of the etonogestrel implant and levonorgestrel intrauterine device: 2 years beyond Food and Drug Administration-approved duration. *American journal of obstetrics and gynecology.* 2017;216(6):586.e581-586.e586.
- 7. Xu H, Wade JA, Peipert JF, Zhao Q, Madden T, Secura GM. Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. *Obstet Gynecol.* 2012;120(1):21-26.
- 8. Lazorwitz A, Aquilante CL, Sheeder J, Guiahi M, Teal S. Relationship between patient characteristics and serum etonogestrel concentrations in contraceptive implant users. *Contraception.* 2019;100(1):37-41.