**Official Title:** The effect of isotretinoin on the etonogestrel contraceptive implant

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Proposal Narrative

Objective: This is an exploratory pharmacokinetic study to demonstrate the effect of concomitant isotretinoin therapy on ENG contraceptive implant use.

Specific Aims:

1. To describe serum ENG levels with concomitant use of the ENG implant and isotretinoin by comparing levels before and after four and eight weeks of isotretinoin therapy, and
2. to characterize whether any reductions in serum ENG are below the level needed to maintain ovulation suppression (<90pg/mL).

This study will fill a knowledge gap regarding the pharmacokinetic effects of isotretinoin on the ENG implant so that providers can appropriately counsel users about contraceptive effectiveness.

Rationale

The ENG implant (Nexplanon®, formerly Implanon®) is the most effective form of reversible contraception available with perfect and typical use effectiveness >99%.[1] When cost is not prohibitive, up to 11% of women chose this method.[2] Little data, however, exists pertaining to drug interactions with the ENG implant, particularly with medications known to decrease the efficacy of oral contraceptives.[3] We recently demonstrated that carbamazepine, a strong cytochrome P-450 enzyme inducer, significantly decreased serum ENG levels in reproductive-aged women (average and median decrease was 60%) and the majority (80%) of the post-therapy serum ENG levels were below the threshold for ovulatory suppression (<90pg/mL) (see *Links with other projects*). These findings highlight the need for more research on drug-drug interactions that may reduce contraceptive efficacy. In particular, we must examine drugs that pose teratogenic risks given the added medical and social implications for women faced with unintended pregnancies.

Acne is a common condition occurring in reproductive aged women, about half of whom are affected and at least 10-12% seek medical treatment.[4] Isotretinoin (formerly branded as Accutane®) is commonly used for treatment of severe acne in this group; in 1999, almost 300,000 women took isotretinoin.[5]. Isotretinoin is a well-known teratogen that can result in abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, thymus, parathyroid glands, and neurodevelopmental delay without structural anomalies.[6] Because of isotretinoin's known teratogenicity, women taking this medication are required to use two forms of contraception, often including one hormonal and one barrier method. In 2006, the U.S Food and Drug Administration established the iPLEDGE Program to reduce the rate of isotretinoin-induced birth defects. The program requires a "pledge" from sexually active women to use two contraceptive methods during isotretinoin therapy. Despite this program, each year 150 affected pregnancies are reported.[7,8] A recent survey demonstrated that 20% of women on isotretinoin therapy who claimed abstinence had unprotected intercourse and 31% of contraceptive users reported using less than two forms of contraception during at least

one episode of intercourse.[8]

Isotretinoin is also a known cytochrome P-450 enzyme inducer.[9] A prior pharmacokinetic study demonstrated small reductions in serum levels of ethinyl estradiol and norethindrone (9% and 11% decreases in area under the curves, respectively) that were variable and with a trend towards an increase in pharmacodynamic ovulation measures.[10] The U.S. Centers for Disease Control Medical Eligibility Criteria (CDC MEC) currently has no safety recommendations regarding concomitant isotretinoin and hormonal contraceptive use.[11] Given the severe teratogenic risks that isotretinoin incurs, further investigation is needed to better understand drug-drug interactions between isotretinoin and hormonal contraceptives. In this study, we will describe and characterize the pharmacokinetic effect of isotretinoin on ENG levels in implant users.

Research design and methods

**Outcome Measure**: Current data suggests that a serum ENG concentration of at least 90pg/mL is needed to prevent ovulation.[12] Given that there is little pharmacologic data about isotretinoin available, we cannot reliably predict how much of an effect concomitant isotretinoin use will have on serum ENG levels in implant users. Thus, we will perform an exploratory study to describe and characterize ENG levels during concomitant isotretinoin therapy.

**Description of Population to be enrolled:**

We will enroll reproductive-aged women (ages 18-45) who are under the care of a dermatologist for treatment of acne and planning to initiate therapy with isotretinoin. These women must have chosen an ENG contraceptive implant for their primary mechanism of birth control during isotretinoin therapy under the iPLEDGE agreement.[6] The ENG contraceptive implant must have been placed at least four weeks prior to study enrollment, but in place no longer than three years. Our inclusion criteria includes the following recommendations that are followed for isotretinoin initiation:[6]

- Have a secondary form of non-hormonal contraception or abstain during isotretinoin therapy and four weeks afterwards
- Have at least two negative pregnancy tests at least 19 days apart prior to initiating isotretinoin therapy[6]
- Not currently breastfeeding
- Have normal baseline laboratory evaluation including liver function tests, basic metabolic panel, and complete blood count
- Have no known contraindications to isotretinoin
- Abstain from taking any Vitamin A supplement during the study period
- Not currently taking any know cytochrome P-450 3A4 enzyme inducers or inhibitors (see Appendix A)
- Have a BMI ≥18.5 due to concerns for abnormal metabolism and higher risk for side effects in

underweight women. We have no upper BMI limit, as pharmacokinetic and efficacy studies in overweight and obese women using the ENG implant are reassuring.[13,14]

**Study Design**

We are conducting a pre-post study to determine the pharmacokinetic effects of concomitant isotretinoin use on serum ENG levels. We will recruit potential participants via the University of Colorado research email, flyers located on campus, our Family Planning Divisional research registry, and informative postcards available at the University of Colorado Dermatology clinic and the Adolescent Medicine Dermatology clinic at the Children's Hospital of Colorado. We also plan to reach out to private dermatology clinics in the Denver metro area for purposes of advertising. The dermatologists at these sites have agreed to offer information about the study verbally and in the form of a postcard, but these providers will not be involved in the study beyond advertising purposes. Interested participants will call and speak to our professional research assistant (PRA). Eligible participants must be under the care of a dermatologist and planning to initiate isotretinoin therapy. Interested participants must also have an ENG implant in place for at least 4 weeks prior to study enrollment. The ENG implant has an initial pharmacologic burst that peaks at four days after insertion, thus a delay of at least four weeks after insertion will both allow for serum ENG levels to plateau and satisfy the iPLEDGE requirement for a month of reliable contraception prior to initiating isotretinoin therapy.[6,15]

We will invite eligible participants for a screening visit at CWHC approximately one week prior to initiation of isotretinoin therapy. We will complete informed consent. During screening, the PRA will obtain a history including current medications and supplements and palpate whether the implant is in place. Participants will take a urine pregnancy test and have their height, weight, and blood pressure measured. Interested participants who plan to initiate isotretinoin therapy routinely undergo a four-week evaluation period prior to initiation by their dermatologist. During this time, the dermatologist performs at least two pregnancy tests and a baseline evaluation of kidney and liver function. We will request medical record confirmation of these tests from interested participants and review their results to confirm eligibility. Prior to starting therapy, dermatologists enroll patients into the iPLEDGE program.[6] They are also thoroughly counseled by their dermatologist on the importance of maintaining a back-up contraceptive method or abstaining from intercourse during isotretinoin therapy and for an additional four weeks afterwards. We will then determine eligibility, and enroll participants. Enrolled participants will undergo an initial blood draw (including a back-up tube for a total of no more than 20cc of blood drawn) to measure their baseline serum ENG level. All participants will be compensated $30.00 after their initial blood draw.

After the enrollment visit, participants will initiate isotretinoin therapy under the supervision of their dermatologist. Participants' dermatologists will monitor their treatment course and adjust isotretinoin therapy as deemed appropriate per the standard treatment protocol, which we will record. After four weeks of isotretinoin therapy, participants will return for their second ENG level blood draw (no more than 20cc of total

blood drawn). After nine weeks of isotretinoin therapy, participants will return for their third and final ENG level blood draw (no more than 20cc of total blood drawn). Participants will be compensated $30.00 for each blood draw visit. No more than two blood draws will be performed in any eight week period during the study. Most patients receive isotretinoin for 16-20 weeks duration. We will call participants after they have completed their isotretinoin therapy, and up to four weeks after, to assess satisfaction with the contraceptive implant and whether there was an unintended pregnancy. They will be compensated an additional $10.00 for completion of the telephone call. We will exclude from final analysis any participants discontinued from isotretinoin therapy secondary to adverse side effects, per their dermatologist's recommendations, or based on participant preference.

At CWHC, collected ENG blood draws undergo centrifugation and the serum will be stored at -80ºC until analysis within the freezer located at CWHC. Upon completion of participant enrollment, we will remove personal identifiers, package, and ship all serum samples to Columbia University to undergo blinded, batched serum ENG measurement. ENG levels will be determined using a LCMS protocol that has been previously validated (Dr. Serge Cremers lab).[16] Samples for the entire study will be batched and run together to minimize assay variability. We will enter all data into a password-protected database via secure Internet connection (REDCap) using the participant ID numbers. The list of participant ID numbers and corresponding names will be stored separately on a password protected shared drive for the Division of Family Planning. Participants serve as their own control and we will compare their serum ENG levels at baseline to their levels after four and eight weeks of the isotretinoin therapy using paired Wilcoxon-signed Rank test.

There is no currently available literature regarding the pharmacokinetic effect of isotretinoin on the ENG implant, but we have demonstrated that a strong cytochrome P-450 enzyme inducer can reduce 80% of serum ENG levels to below the threshold for ovulatory suppression. We, therefore, plan to analyze 10 study compliant participants who complete isotretinoin therapy and all study procedures. This is a feasible number for an exploratory study, feasible for study recruitment at our institution, and consistent with similar pharmacokinetic studies of this nature (see *Links with other projects*). To account for an anticipated 25% drop-out/noncompliance rate, we will enroll up to 14 participants and we will screen up to 30 participants to account for screening failures prior to actual enrollment.

Citations


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**Appendix A**

Screening list of known CYP-3A4 Inducers and Inhibitors

Bergamottin
Butalbital
Cafestol
Carbamazepine
Chloramphenicol
Cimetidine
Ciprofloxacin
Delavirdine
Dithiocarbamate
Efavirenz
Fluoxetine
Fluvoxamine
Gestodene
Ginkgo biloba
Glucocorticoids
Isoniazid
Mibefradil
Mifepristone
Milk thistle
Modafinil
Norfloxacin
Orphenadrine
Oxcarbazepine
Phenobarbital
Phenytoin
Pioglitazone
Piperine
Quercetin
Rifabutin
Rifampin
St John's wort
Star Fruit
Troglitazone
Valerian
Voriconazole
Ziprasidone