Official Title: Pilot study of etonogestrel contraceptive implant insertion at an alternative subdermal scapular site

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I. Hypotheses and Specific Aims:

Specific Aims:

1. To assess the pharmacokinetics of the etonogestrel contraceptive implant when inserted at an alternative scapular site.
2. To gather preliminary data regarding insertion site and bleeding side effects when the etonogestrel contraceptive implant is inserted at an alternative scapular site.
3. To explore optimal patient positioning for etonogestrel contraceptive implant insertion at an alternative scapular site.

Hypotheses:

1. We hypothesize that the pharmacokinetics of the etonogestrel contraceptive implant when inserted at an alternative scapular site will be similar to the published pharmacokinetics with arm insertion.
2. We hypothesize that women with alternative scapular site insertion of the etonogestrel contraceptive implant will report similar insertion site and bleeding side effects as compared to known side effects with arm insertion.

II. Background and Significance:

The etonogestrel contraceptive implant (Nexplanon®, formerly Implanon®) remains the most efficacious hormonal contraceptive method available in the US with increasing uptake, particularly among adolescents and young women[2,3]. The contraceptive implant is inserted subdermally on the inner side of the non-dominant arm, roughly 8-10cm proximal from the medial epicondyle of the humerus (Figure 1)[4]. The manufacturer instructions originally stated that insertion should occur between the biceps and triceps muscles, while avoiding insertion deep into this sulcus[4]. However, these instructions were updated in 2018 to move the insertion site 3-5cm inferiorly over the triceps muscle and all healthcare providers trained in contraceptive implant insertion prior to October 2018 had to undergo a mandatory training module to learn about this revised insertion site[5].

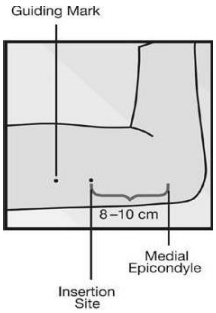


Figure 1: Manufacturer's recommended insertion site

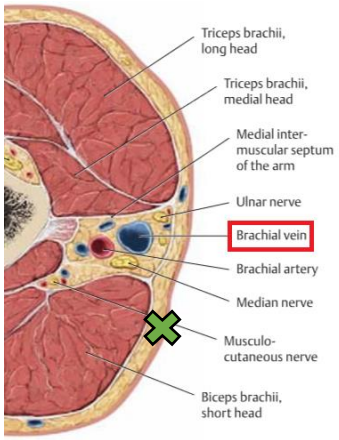


Figure 2: Arm anatomy highlighting neurovascular bundle in the sulcus. Standard implant insertion site marked in green

The etonogestrel implant insertion site was moved by the manufacturer due to rare complications resulting from the underlying vascular and neurological structures found in the sulcus between the biceps and triceps muscles (Figure 2) [6]. The basilica/brachial vein is located in this sulcus and case reports of implants embolizing into the pulmonary vasculature proved that intravascular placement of the implant was possible[7,8]. A review of the FDA Adverse Event Reporting System found a total of 38 reported cases where the etonogestrel implant had migrated to the lung/pulmonary artery, chest wall, other vasculature, and other body sites (e.g. neck, shoulder, clavicle, axilla)[8]. Though these migrations and intravascular insertions are very rare, removal of migrated implants often involves cardiothoracic surgery with significant potential morbidity and leaving migrated implants in situ has been associated with potentially life-threatening complications such as pneumothorax[7].

Additionally, insertion of the contraceptive implant deep into the sulcus between the biceps and triceps muscles can result in peripheral nerve injury at the time of removal given the high prevalence of neurovascular structures in the sulcus[6,9]. These rare injuries and migrations have become highly publicized (news reports found on nypost.com, livescience.com, health.com, etc.) and some women may not opt for our most effective hormonal contraceptive method due to the risks of deep insertion and current lack of an alternative implant insertion site.

In addition to these rare neurovascular risks, conventional insertion of the contraceptive implant may not be ideal for certain populations. Women with psychotic illnesses or decreased capacity can often benefit from contraceptive methods not requiring patient compliance (e.g. taking a pill every day), but case reports have demonstrated that an easily accessible insertion site can lead to picking or even removal attempts that may increase the risk of infection at the insertion site[10,11]. These self-removal attempts can result in significant self-harm, such as the case report of a young woman who used a sharp blade on her palpable implant during an acute psychotic episode resulting in lacerations and even implant fracture[12]. For such a case where conventional insertion was deemed not appropriate for the patient, Pragout et al reported insertion of the contraceptive implant in the right lower scapular region (Figure 3)[11]. The patient tolerated the insertion very well, had no side effects or discomfort related to the implant, and the implant remained superficial and palpable. They measured a single serum etonogestrel concentration at 4 months of implant use, which was 194pg/mL and well above the threshold for ovulatory suppression (>90pg/mL)[11,13]. A case report of 14 year old twins with global development delay and habitual skin picking also found that insertion of the implant over the scapula avoided any implant picking issues and led to improved menses for both girls[14].

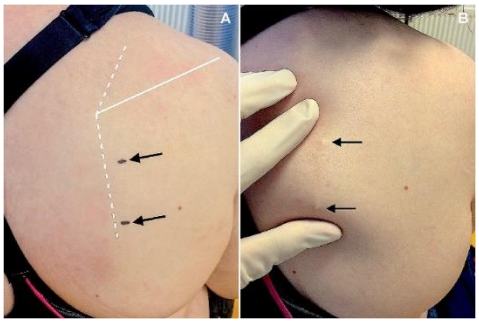


Figure 3: Subdermal scapular insertion of implant from Pragout et

This scapular subdermal insertion site is an ideal alternative insertion site for the contraceptive implant because it is distant from any danger zones containing neurovascular structures (Figure 4a) and is a less-accessible area of the body[15]. Furthermore, additional populations may benefit from an alternative implant insertion site, such as women with muscular dystrophy disorders who may have far less muscle tissue in the arm, and thereby less tissue barrier between subdermal implant insertion and the underlying neurovascular structures[16]. The scapular subdermal insertion site benefits from the bony structure immediately under the implant site, which should prevent deep implant insertion and thereby protecting any underlying neurovascular structures beneath the scapula. Furthermore, the infraspinatus fascia that separates the subdermal tissue from the underlying scapular musculature is affixed to the borders of the scapula, thereby preventing migration of the contraceptive implant beyond the borders of the scapula even should deep/subfascial placement occur (Figure 5)[1].

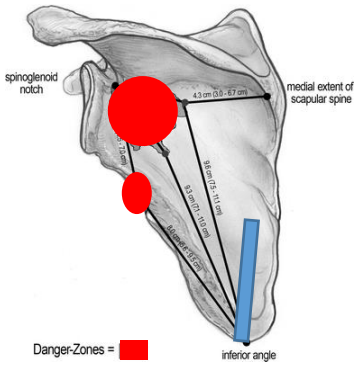


Figure 4a: Areas of neurovascular structures (designated in red) superficial to the scapula and subdermal implant insertion site (designated in blue)

To address the needs of patient populations that may benefit from an alternative insertion site for the contraceptive implant, the scapular insertion site warrants further investigation. Patients

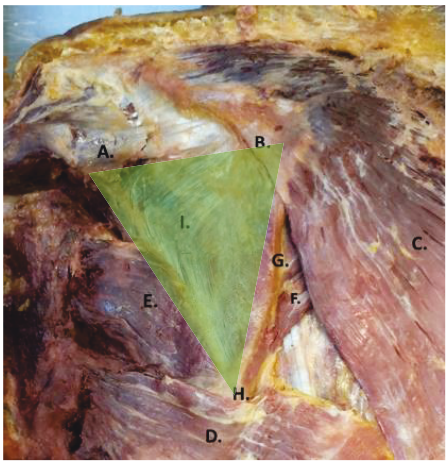


Figure 5: Infraspinatus fascia (highlighted in green); G – medial border of scapula (infraspinatus fascia insertion site)[1]

with developmental delays often require reliable contraception without patient compliance, making the contraceptive implant an ideal option for many of these patients, but arm insertion leaves the implant accessible and can result in self-induced injury such as compulsive scratching, or even implant migration or breakage due to constant manipulation[10-12]. These patients and their caregivers may greatly benefit from an alternative implant insertion site that is not easily accessible, and so the scapular insertion site would increase their very limited contraceptive options. Case reports of such insertions have demonstrated benefits among individual patients with developmental delays[11,14], but actual research is needed on this topic before wider implementation can be reasonably considered.

In this regard, more data are needed regarding the pharmacokinetic properties of the etonogestrel contraceptive implant at this alternative insertion site. It remains unknown whether one of the primary benefits of the scapular insertion site, distance from any major vascular structures, could influence the pharmacokinetics of the contraceptive implant. Pharmacokinetic changes in serum etonogestrel concentrations, as found with cytochrome P450 inducing medications, can potentially affect the contraceptive efficacy of the implant and has resulted in case reports of contraceptive failure[17]. Though the single serum etonogestrel measurement from Pragout et al[11] at four months of scapular implant use was consistent with levels found with standard arm insertion, more pharmacokinetic data are needed for longer periods of implant use to determine if the absorption rate at this alternative site maintains serum concentrations similarly to arm insertion. To address this specific knowledge gap, we propose a pilot study to establish preliminary serum etonogestrel concentration curves for placement of the contraceptive implant at this scapular subdermal insertion site and gather additional pilot safety data from a small cohort of women.

III. Preliminary Studies/Progress Report:

The only preliminary results pertinent to this pilot study come from the case report as discussed above[11].

IV. Research Methods

A. Outcome Measure(s):

Primary Outcome:

- Serum etonogestrel concentrations measured at 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months post-insertion.

Secondary outcomes:

- Insertion site side effects
- Implant-related side effects

B. Description of Population to be Enrolled:

We aim to enroll five reproductive age (18-45 years) women interested in using the etonogestrel contraceptive implant based on the following crtieria:

Inclusion criteria:

- Healthy women
- English or Spanish speaking

Exclusion criteria

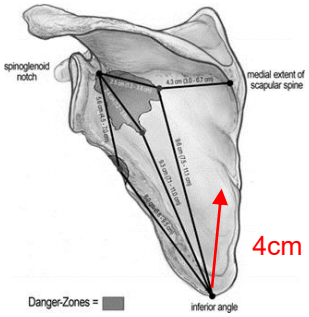
- Any contraindications to etonogestrel implant use based on the US Medical Eligibility Criteria for Contraceptive use (defined as class 3 or 4 recommendation)[18]
- Any known liver conditions that could affect drug metabolism (e.g. cirrhosis, hepatitis)
- Currently taking any medications or supplements known to be CYP3A4 inducers/inhibitors[19]
- Body-mass index less than 18.5kg/m^2 or greater than 30kg/m^2

C. Study Design and Research Methods

We will recruit five English or Spanish speaking reproductive aged women (ages 18-45) interested in using the etonogestrel contraceptive implant as their birth control method. We will exclude women with any contraindications to etonogestrel implant use based on the US Medical Eligibility Criteria for Contraceptive use (defined as a class 3 or 4 recommendation)[18]. We will also exclude women with any known liver conditions that could affect drug metabolism (e.g. cirrhosis, hepatitis) or currently taking any medications or supplements known to be CYP3A4 inducers/inhibitors[19]. We will also exclude women with a body-mass index (BMI) less than 18.5 kg/m^2 and a BMI greater than 30 kg/m^2. Underweight women may have altered metabolism that could influence the pharmacokinetic outcomes in this study. We will exclude obese women as this pilot study is also exploring the ideal positioning for scapular implant insertion (Aim 3) and increased subcutaneous tissue may affect our ability to accurately assess all bony landmarks. We will recruit participants for this pilot study using posted flyers on the University of Colorado Anschutz Medical Campus, posted flyers at our off-site Comprehensive Women's Health Center clinic, and through online advertisements.

Interested women will undergo a phone screening prior to scheduling an enrollment visit. At the enrollment visit, potential participants will have their vital signs checked and will have their height and weight measured for purposes of calculating a body mass index. We will review each potential participant's past medical history and current medications to ensure study eligibility. Participants meeting all inclusion/exclusion criteria will then undergo informed consent in a private clinic room. During the consent process, we will inform participants of the exploratory nature of this study and the potential risk of unintended pregnancy, and thus will recommend that all participants use a back-up contraceptive method or abstinence during the study. Participants will be allowed to use any contraceptive method (hormonal or non-hormonal) of their preference as long as it does not contain etonogestrel, a pro-drug for etonogestrel (e.g. desogestrel), or estrogen. Estrogen can have mild effects on the CYP3A4 metabolic system and

Figure 4b: Planned insertion site in red and total length of implant



we want to avoid any potential confounding for our pharmacokinetic outcomes[3].

After the participant has been consented, we will have the participant trial several positions to determine the ideal positioning for identifying the bony landmarks of the scapula. These positions will include movement of the shoulders anteriorly and posteriorly, placement of the arms on or off the chest wall, elevation or relaxation of the elbows, flexion or extension of the spine, and combinations of these positions. We will document the position that provided the most reliable identification of the bony landmarks and planned contraceptive insertion site. We will then insert the etonogestrel contraceptive implant (Nexplanon®) at the subdermal scapular site as described above (Figure 4b) on the participant's non-dominant side. This will entail marking of the insertion of the site with two points located on the inferior angle of the scapula. The area will then prepped with chlorhexidine in the typical fashion. We will then inject ~3cc of 1% lidocaine along the planned insertion site, as is routine for contraceptive implant insertion. Following the manufacturer's insertion guidelines (see Appendix A), we will insert the device inserter along the planned insertion site and then release the contraceptive implant. We will then palpate the implant to ensure appropriate subdermal placement. We will clean the insertion area and place a steri-strip across the insertion site. We will cover the insertion site with a sterile gauze and tape, which can be removed 24 hours after insertion.

Participants will return to clinic for nine blood draws at the following time points post-insertion: 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months. We will centrifuge blood drawn at these visits to extract serum samples. We will store these serum samples in our -80°F freezer for eventual serum ENG concentration measurement. At each follow-up visit, participants will provide urine for a urine pregnancy test and we will also assess for insertion site and implant-related side effects. We will conduct brief interviews to assess for the circumstances when participants have felt the physical presence of their implant without touching the implant itself and to inquire about any insertion site related concerns (e.g. discomfort, pain, itching). In terms of implant-related side effects, we will ask participants to report any side effects they feel may be related to the implant and we will also specifically assess for irregular/frequent bleeding, headaches, weight gain, mood changes, acne changes, libido changes, breast tenderness, or vaginal discharge. These assessments are similar to standard clinical practice for contraceptive follow-up and will focus on identifying what concerns or side effects are a priority for participants. These interviews will occur at each follow-up visit and the research personnel conducting the interview (PI, Co-I, or PRA) will document the responses of participants for categorization at the end of the study.

At the follow-up visit at 12 months, we will remove the contraceptive implants in the standard clinical fashion (see Appendix A). We will clean the area with chlorhexidine, inject 1% lidocaine at the removal site, make a 1-2mm skin incision using a scalpel, and grasp the implant using a hemostat. We will clean the removal site and place a steri-strip across the skin incision. We will then place a sterile gauze and tape over the removal site, which can be removed 24 hours later. Participants will then return to clinic in 1 week for their final study visit and an additional blood draw. We will similarly centrifuge blood from this draw and store serum for eventual etonogestrel concentration analysis. This blood draw will assess the wash-out from removal of the contraceptive implant to determine if serum concentrations are similarly close to undetectable at 1 week post-removal as found with conventional arm insertion. We will then counsel participants on their contraceptive options and provide contraception through our routine clinical practice.

After all five participants have completed study procedures, the stored serum samples will be de-identified and shipped to Columbia University to undergo serum etonogestrel concentration

analysis using a validated ultra performance liquid-chromatography mass spectrometry method[20]. This method utilizes an analytical platform comprising a triple quadrupole Waters Xevo TQ-S mass spectrometer equipped with an electrospray ionization source and integrated with a Waters Acquity UPLC controlled by Mass Lynx Software 4.1[20]. The lower limit of quantification for etonogestrel from this assay is 25pg/mL and three levels (low, medium, high) of quality controls are included with the samples to assess batch effect. The mean intra-assay precision is 3.2% and the inter-assay variability across batches is 1.8%[20,21]. We will batch analyze all samples to reduce assay variability. We will enter all pharmacokinetic and follow up data into a REDCap database, which is password protected[22]. Only the Principal investigator and research staff directly involved in this study will have access to this database. All paper consents and follow up documents will be stored in a locked cabinet in a locked, secure room.

F. Data Analysis Plan:

We will perform all statistical analyses using IBM SPSS™ statistical software. We will perform descriptive analyses for our primary pharmacokinetic outcomes and determine medians and ranges at each follow-up time point. For specific Aim 1, we will determine if the pharmacokinetic outcomes obtained during this study fall within the standard definition of bioequivalence with previously published pharmacokinetic data from arm insertion of the etonogestrel implant. Bioequivalence is defined as within 80-125% of prior pharmacokinetic results[23]. For Specific Aim 2, we will determine the frequency of any insertion site or implant-related side effects and report these as preliminary findings. For Specific Aim 3, we will report the specific characteristics of the position found to be ideal for subdermal scapular implant insertion and whether this was consistent across all participants or what variations were required.

We chose a sample size of five participants for this study based on its pilot nature and the limited funding available. Given the repeated pharmacokinetic measurements planned and the high cost of the etonogestrel contraceptive implant (~$975 per device), the per participant cost for this study restricts our enrollment to no more than five participants to stay within the funding limit. However, many landmark pharmacokinetic studies on contraception were conducted with similar sample sizes, including the study by Wenzl et al. that established the original pharmacokinetic curves for the etonogestrel implant among only eight women[13]. Thus, this sample size is appropriate for our pharmacokinetic pilot study.

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