Labor and Delivery Implant Insertion (LADII)

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**Project Summary:**

Investigating the timing to lactogenesis stage II (defined as the initiation of copious milk secretion) in women who obtain the contraceptive implant in delivery room versus the postpartum ward will add important data to the literature. If insertion in this time period is found to be without negative effects on breastfeeding the study findings would facilitate earlier insertion of the contraceptive implant, in the delivery room. Gurtcheff et al. recently analyzed time to lactogenesis in women initiating the contraceptive implant prior to medical discharge following delivery and 4-8 week postpartum and found no difference. In the proposed study, we seek to add to the literature by investigating immediate post-delivery insertion in the delivery room of the contraceptive implant versus insertion prior to medical discharge in the postpartum ward.

We propose a non-inferiority randomized controlled trial comparing time to lactogenesis stage II in healthy women with immediate insertion (0-2 hours following delivery) of the contraceptive implant in the delivery room versus in women with insertion of the contraceptive implant following delivery in the postpartum room and prior to medical discharge (24-48 hours following delivery). We hypothesize there will be no significant difference in time to lactogenesis with immediate delivery room (0-2 hours following delivery) vs. postpartum ward insertion (24-48 hours). In addition, we plan to follow women postpartum to evaluate breastfeeding continuation and exclusivity, discontinuation of the implant and any adverse events.

**Description of the Project:**

**1.1 Rationale**:
Over half of the 6.1 million pregnancies each year in the United States are reported as unintended. [1] More interventions are needed to prevent unintended pregnancies, as they are associated with higher maternal and child morbidity and mortality. [2] Infants conceived by women less than six months postpartum are at increased risk of poor perinatal outcomes such as being small for gestational age and being born preterm. [3] Additionally, both unintended pregnancy and a short inter-pregnancy interval are associated with delayed and insufficient prenatal care. [4] Gemmill et al. (2013) investigated the prevalence and correlates of short inter-pregnancy intervals in the United States. These authors documented that one third of pregnancies conceived in a nationally representative sample were within 18 months of a previous birth (n=2253). After adjusting for sociodemographic and childbearing characteristics, women were significantly more likely to have a short inter pregnancy interval if they were ages 15-19 years old. [5]

Further, pregnancies of adolescents (ages 10-18) and young women (ages 19-24) are very unlikely to be planned pregnancies. In fact, 82% of pregnancies were unplanned in the 15-19 age range. Robust data demonstrates that adolescent and young mothers are at high risk of becoming pregnant within 12 months of delivery--these mothers have a

higher risk of preterm birth, low birth weight and neonatal mortality compared to their adult counterparts.

There is evidence of adolescents who experience repeat pregnancy have poorer educational attainment and lower rates of employment than adolescents that do not have a repeat pregnancy. We also have data that young mothers who initiate LARC are less likely to have repeat pregnancies than those who decline postpartum contraception [6].

A 2015 survey of postpartum women about future pregnancy intention and contraception plans found the majority (n=237, 96.7%) of women did not desire pregnancy in the next year. [7]

Many women have already ovulated and resumed sexual intercourse by 6 weeks postpartum [8] and upwards of 40% of women do not return for postpartum care. [9] The majority of providers wait until the six week postpartum visit to initiate contraception—this delay in contraceptive uptake puts women at risk of an unintended, short interval pregnancy. An opportune time to facilitate contraception initiation is in the immediate postpartum period following delivery and prior to hospital discharge. Providing women with contraception they need during this time is convenient and cost effective for the patient, provider, and health care system. [10] In the 2015 survey of postpartum women, 42.8% (n=107) indicated that if the implant or intrauterine device could be inserted before they left hospital, they would choose these methods ($p<0.0001$). [7]

A 2009 CDC study analyzed the prevalence and types of contraception used by 43,887 women 2-9 months postpartum and found that 88% reported use of at least one contraceptive method, with 61.7% using a highly effective method, defined as: <10% of women experience an unintended pregnancy; includes sterilization, intrauterine device, shot, pill, patch, and ring. [11]

This same study demonstrated that women with no prenatal care had the lowest rates of using at least one method (76.9%) and had a low rate of using highly effective contraceptive methods (54.5%). Based on these data, the promotion of highly effective contraception, especially among women with no prenatal care, should be prioritized and immediate postpartum initiation of a highly effective method could be the solution. [11]

The World Health Organization (WHO) and the CDC have distinct recommendations with regard to early administration of the contraceptive implant. By the CDC Medical Eligibility Criteria for Contraceptive Use, the etonogestrel implant is classified as a Category 2 method for breastfeeding women at less than 1 month postpartum, indicating this is a method for which advantages generally outweigh any theoretical or proven risks. [12] However, the 5$^{th}$ edition of the WHO Medical Eligibility Criteria for Contraceptive use classifies the implant as category 2, indicating "generally use, some

follow-up may be needed" for women breastfeeding at less than 1 month postpartum. [13] These slightly different recommendations may have an impact on the availability of progestin-only methods for women in the postpartum period. More information is needed on the impact of the implant on breastfeeding immediately postpartum in order to inform improvements in service delivery and family planning interventions, both domestically and internationally.

In addition to this, a barrier to initiating progestin contraceptives in the early postpartum period is the concern of interference with breastfeeding, specifically lactogenesis. A study looking at lactation consultants' knowledge about postpartum contraception and impact on breastfeeding documented disconnect between the Centers for Disease Control (CDC) United States Medical Eligibility Criteria for Contraceptive Use (US MEC) guidance and lactation consultants' knowledge regarding the safety of immediate postpartum contraception. [14] Providing different recommendations amongst health care providers and lactation consultants may lead to confusion for patients—conflicting opinions regarding their contraceptive method may result in less women leaving the hospital without a method of contraception.

Duvan et al. (2010) showed that if women are well-informed regarding the side effects of the contraceptive implant, women find that it is an acceptable form of reversible contraception in the postpartum period. [15] The pharmacokinetic profile of the etonogestrel implant shows a peak serum concentration of approximately 1,000 pg/mL on day 4 after insertion. Thus insertion immediately postpartum should not interfere with lactogenesis, as there would still be a drop in progesterone that would allow for lactation induction to occur following delivery. [16], Appendix A

The initiation of the contraceptive implant at 4-8 weeks postpartum has been studied in breastfeeding women; no change in volume or composition of breast milk was found. [17] A study looking at growth of breastfed infants found that at three year follow up, child growth and development was no different between users of implant and copper intrauterine device (IUD). [18] Additionally, Brito et al. (2009) documented no diminished weight gain in infants of women who were exclusively breastfeeding and obtained a contraceptive implant at 6 weeks postpartum. [19] The literature demonstrates immediate contraceptive implant insertion does not alter volume of breast milk intake by newborns. Braga et al. (2015) evaluated breast milk volume when the ENG implant was inserted immediately postpartum and found no difference in the median breast milk intake by newborns between women who were randomized to have the implant inserted within 48 hours after delivery and those who obtained no method of contraception. The study also documented similar weights of newborns between both groups at six weeks following delivery, adding to safety data on effects of immediate insertion on breastfeeding. [20]

**Objectives and hypotheses:**

This is a non-inferiority randomized controlled trial:

Our objective is to determine whether time to lactogenesis stage II differs between immediate delivery room insertion (0-2 hours following delivery) and delayed postpartum insertion (24-48 hours following delivery) of the contraceptive implant in the postpartum ward prior to medical discharge. We hypothesize there will be no significant difference in time to lactogenesis stage II between the two groups.

**Design & Methodology:**

**This is a non-inferiority randomized controlled trial.**

**Peripartum women with healthy, term newborns who plan to use the contraceptive implant (etonogestrel implant, Nexplanon) for postpartum contraception and intend to breastfeed will be randomized to receive:**

- **Arm 1: Immediate delivery room insertion (0-2 hours following delivery)**
- **Arm 2: postpartum room insertion (24-48 hours following delivery)**

**The primary outcome is time to lactogenesis stage II (defined as the initiation of copious milk secretion) as documented by maternal perception by a validated tool. [21]**

Secondary outcomes include breastfeeding continuation and exclusivity, contraceptive continuation, patient satisfaction, pregnancy rates, timing and number of follow up postpartum care visits.

Data will be collected on time of exclusive breastfeeding in days, supplementation rates, side effects (irregular menstrual periods, changes in appetite, nausea, acne, headache) continuation or change of contraceptive method, dates of follow up postpartum care visits, subsequent pregnancies and user satisfaction. These data will be collected in the week following insertion, at 4-8 weeks, 3, 6, and 12 months following insertion with telephone interviews or online questionnaires.

Recruitment methods will take place in the clinical setting through chart review and provider referral. We will also use flyers placed on public announcement boards on campus and wherever permitted in the hospital.

**Study Procedures:**

Eligible women will be screened and identified via chart review, in the pre-natal obstetric clinic, and labor and delivery ward (L&D) at Stanford University by research study staff. If patients meet criteria, the treating physician will initially approach and inform patients about the study. If a patient is interested, the treating physician will notify research staff and the patient will be approached by research personnel to discuss participation. If a treating physician has identified a patient who may be eligible

for study recruitment and physician confirms that patient agrees to be contacted by phone, we will call the patient and conduct a telephone screening interview (please see attached materials) and will recruit the patient in person at their next prenatal visit or when admitted to Labor and delivery, prior to delivery.

Patients will be counseled about risks and benefits of contraceptive options and will be counseled appropriately regarding risks and benefits of subdermal contraception implant, as well as the unknown effects of early progestin administration on breastfeeding. Patients will not be eligible for the study unless they have been consented for a postpartum contraceptive implant prior active labor. If the patients meet inclusion criteria they will be invited to participate in the study and consent will be obtained. When a study patient is admitted to L&D, they will be met by research personnel and be randomized to one of the two arms. Participants will be randomized through block randomization—allocation will be sealed in an opaque envelope. The patient, provider, and research staff will be aware of arm allocation, this is not a blinded study. At this time, baseline data will be collected on patient age, gravidity, parity, breastfeeding experience on REDCap with a designated Ipad.

Trained providers will use standard protocol to place the contraceptive implant either in delivery room or in postpartum ward after delivery. We will collect information on the timing of delivery and the time of implant insertion. A card indicating date of insertion and expiry date will be given together with post insertion instructions on wound care. Participants will be monitored daily by the research staff, in the first seven days postpartum, or until lactogenesis reported, beginning at 24-hours following delivery, to determine time to lactogenesis stage II using a validated tool. [21] Patients will be asked: "Has your milk come in yet?" and "When did your milk come in?" If the patient answers yes to first question the response will be recorded to the nearest hour. Participants will be asked: "How many times have you tried to breastfeed before your milk came in? Delayed lactation will be defined as no lactation by 72-hours following delivery. Lactation failure will be defined as no lactogenesis by 120-hours following delivery. Post-discharge follow-up questionnaires will involve telephone interviews, text messaging, electronic communication as needed, until lactogenesis occurs and at 4-8 weeks, 3, 6, and 12 months. Participants will be asked about length of exclusive breastfeeding, supplementation rates, side effects, continuation or change of contraceptive use (including abstinence or withdrawal), dates of postpartum medical visits, pregnancy, satisfaction with the contraceptive implant, resumption of vaginal intercourse, and infant weight. Once the participant completes the 12 month follow up questionnaires, they will have completed the study.

**Criteria for selection of subjects:**

Exclusion criteria:

Contraindication to implant insertion such as history of breast cancer. Hypersensitivity to any components of implant. Women who are not English or Spanish speakers or fluent in either language. Women who delivery infants that are not healthy.

Inclusion criteria:

- Pregnant women who are patients of the Stanford University Obstetrics service
- Pregnant women who delivery a healthy infant, regardless of gestational age.
- Intend to breastfeed
- Desire the contraceptive implant as their method of contraception
- Agree to be randomized to delivery room vs. postpartum ward insertion

**Description of the drugs & devices to be studied:**
Not applicable.

**Follow up procedure:**
Participants will receive brief telephone follow-up, including an interview at 4-8 weeks, 3, 6, and 12 months from date of delivery.

**Criteria for discontinuation:**
Participants who experience complications during labor and delivery or whose infants have medical problems will be discontinued. Patients who change their mind about contraceptive implant use will be discontinued. Intention to treat analysis will be employed.

**Lab and other investigations:**
Not applicable.

**Data Management**
Data will be collected on REDCap software, will be coded, monitored, and verified.

**Data Analysis**
SPSS version 23 will be used for data analysis.

**Number of subjects and statistical power:**
Based on previous reports of women with uncomplicated vaginal deliveries, mean time to lactogenesis stage II is 54 hours with a standard deviation of 12 hours. [21] If there is truly no difference between immediate insertion and delayed insertion of the contraceptive implant on time to lactogenesis stage II, then 68 patients are required to be 80% sure that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will be above the non-inferiority limit of a mean difference of 12 hours (alpha 5%; SD 18). Sealedenvelope.com was used to calculate

sample size based on these parameters. A non-inferiority margin of 12 additional hours is chosen to be relevant because common medical interventions like epidural anesthesia, cesarean section, labor induction, have been to delay stage II lactogenesis by up to 12 hours. [22] To account for potential participant dropout, 82 participants will be recruited.

**Study limitations:**
This is not a blinded study; appropriate blinding would require the use of placebo implants and additional procedures. We do not anticipate our inability to blind participants and providers to impact our primary outcome of time to lactogenesis stage II.

Our recruitment will be limited to the Stanford Obstetrics and Gynecology service. Thus internal validity will not be a concern, but this clinic's population is not representative of the diversity of the female population in the United States or of women giving birth in the United States.

Based on this study's inclusion and exclusion criteria, results cannot be extrapolated to women with some medical conditions, complications, during labor and delivery, or who have infants with medical problems.

**Duration of project:**
Project completion is expected in 21 months. 9 months for recruitment, enrollment, and data collection, 12 months for follow up phone call, data analysis, and manuscript writing. Estimated Start and End date: September 2016 – June 2018.

**Project management:**
Project will be coordinated, conducted, and monitored by research staff. The research mentors will be: Kate Shaw M.D., M.S, primary mentor, and [redacted], MPH, secondary mentor.

**Links with other projects:**
Not applicable.

**Main problems anticipated:**
Our recruitment site sometimes experiences low patient volumes that may contribute to slow recruitment. It is possible that enrolled patients may experience complications during labor and delivery or after delivery in which case, patients will no longer be eligible for study. Patients may change their mind and no longer wish to participate in study. In order to mitigate these potential challenges, we will chart review in advance on a weekly basis in order to approach all eligible patients. We will also counsel and explain study thoroughly to ensure patients are able to make informed decisions regarding participation.

**Expected outcomes of the study and dissemination of findings:**

We expect to find that timing to lactogenesis stage II is not different between women who obtain contraceptive implant insertion in the delivery room versus in the postpartum ward. We hope to publish these results to contribute to body of literature that examines safety of immediate postpartum contraception, allowing for better delivery of postpartum contraception without negative effects to breastfeeding in the period of 1-2 hours after delivery.

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**Informed decision-making and confidentiality:**
Please see attached consent form in appendix A.

**Budget & Justification:**
There is no monetary cost for this study. Only human resources are required. Griselda Velasquez has a research grant that will fund living costs.

**Personnel**:

[redacted]

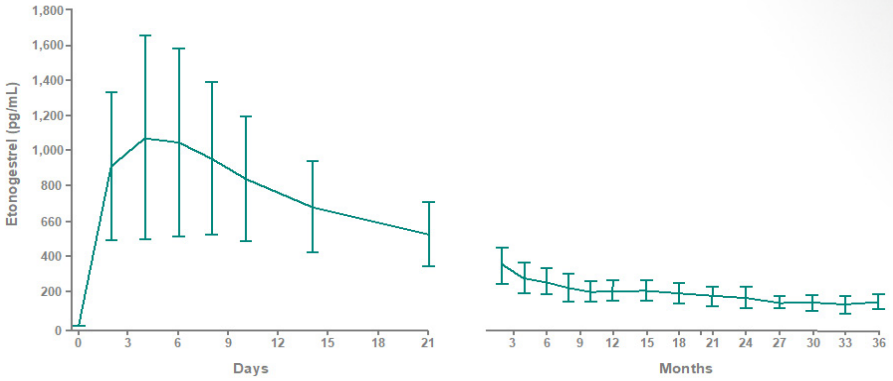
**Participant Costs:**
None. Patients will not require additional office visits or expenses. Participants will not be compensated for their time.

**Appendices**:
A: Consent Form
B: Redcap Data Collection Tool Script

**Reference Graphic:**

# Pharmacokinetic profile of NEXPLANON® (etonogestrel implant)

**Mean (± SD) serum concentration-time profile of etonogestrel after insertion of NEXPLANON during 3 years of use**

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