UC San Diego

Postpartum Progestin-Only Pill Use and Breastfeeding Study

Protocol Number: 803604

National Clinical Trial (ClinicalTrials.gov) Identifier Number: NCT04965116

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Postpartum progestin-only pill use and breastfeeding study
Study Description:	This study will assess the impact of early initiation (less than one week postpartum) and delayed initiation (4 weeks postpartum) of two types of progestin-only contraceptive pills on maternal, breastmilk, and infant outcomes. This is a placebo-controlled randomized controlled trial enrolling dyads of mothers and their newborn babies. We will explore if the type and timing of initiation of pills is acceptable to the user with minimal side effects, impacts the supply or composition of breastmilk, and/or affects infant growth.
Aims:	**Specific Aim:** To determine whether the type of progestin used (drospirenone in drospirenone-containing progestin-only pills (d-POPs) vs. norethindrone in norethindrone-containing progestin-only pills (n-POPs)) or the timing of progestin initiation (early vs. delayed) affects: **Aim 1a Maternal**: the duration of exclusive breastfeeding continuation or the rates and types of breastfeeding supplementation over 8 weeks postpartum. **Aim 1b Maternal**: the proportion of mothers using progestin-only pills at 8 weeks postpartum. **Aim 2 Milk**: the composition of breastmilk (fat, protein, carbohydrates) at 4 weeks postpartum. **Aim 3 Infant**: infant growth (weight, length, and head circumference) from birth to 4 weeks.
Study Population:	Postpartum women who delivered an infant within the previous 7 days
Description of Sites Enrolling Participants:	University of California, San Diego (UCSD)
Study Duration:	1 year
Participant Duration:	8 weeks

2 INTRODUCTION

2.1 STUDY RATIONALE

Drospirenone-containing progestin-only pills (d-POPs) may be an acceptable alternative to Norethindrone-containing progestin-only pills (n-POPs) in the postpartum period when initiated either a week or month after delivery with fewer side effects and no impact on breastfeeding, breastmilk, and infant outcomes. Providing women with more options of safe, effective postpartum (PP) contraception has the potential to reduce unintended pregnancy and short inter-pregnancy intervals, thereby decreasing maternal and infant morbidity and mortality.

2.2 BACKGROUND

Use of postpartum (PP) contraception can help women achieve their reproductive goals and prevent short inter-pregnancy intervals (IPIs). Short IPIs (<18 months between birth and subsequent pregnancy) are associated with an increased risk of maternal and infant morbidity and mortality including preterm birth. One-third of pregnancies in the United States occur after short IPIs; and approximately 70% of pregnancies in the first year after delivery are unintended. Women who receive contraception after delivery are significantly less likely to have an unintended pregnancy and short IPI.

Contraception is typically initiated around 6 weeks after delivery; however, the timing is based on historical precedent, not evidence. By 6 weeks PP, more than half of women have resumed intercourse. The CDC provides guidance that it is difficult to be “reasonably certain that woman is not pregnant” beyond 4 weeks PP unless she meets the very stringent criteria for lactational amenorrhea (LAM) which includes exclusive breastfeeding and no interval of greater than 4-6 hours between feeds. Delaying access to PP contraception beyond 4 weeks may increase the risk of undesired pregnancy and short IPIs.

Breastfeeding has many important health benefits for both mothers and infants, as well as economic and environmental benefits for families and communities. The American Academy of Pediatrics recommends exclusive breastfeeding for the first 6 months of life. Many women want to understand the effects, if any, of contraceptives on breastfeeding outcomes. Among 1,308 pregnant and PP women, 79% reported that safety during breastfeeding was an “extremely important” consideration when choosing contraception.

The natural PP decline in serum progesterone triggers lactogenesis; therefore, there is theoretical concern that use of progestin-containing contraceptives within the first weeks after delivery could inhibit initiation of breastfeeding or impact establishment of supply or composition of breastmilk. In addition, since progestins have been detected in breastmilk, there is concern about the effect of progestin exposure on early infant growth and development. Most existing studies on PP use of progestins initiated within days of delivery are small and of poor to fair quality, but the available data suggest that there is no effect on onset of lactogenesis, quantity or composition of breastmilk, breastfeeding rates, or infant growth. However, the Centers for Disease Control and Prevention (CDC) Medical Eligibility Criteria (MEC) for contraceptive use cites a paucity of high-quality data for ongoing concerns about the potential effect of progestins on breastfeeding and infant growth and their decision to categorize progestins use in the early PP period as Category 2 (advantages generally outweigh theoretical or proven risks) instead of Category 1 (no restriction). Whether progestin use affects

breastfeeding performance or infant health was identified as a priority research gap by the CDC. High-quality data on the potential effects of the timing of progestin initiation on breastfeeding are urgently needed to inform national and international guidelines on contraceptive use during breastfeeding.

A new progestin-only pill containing drospirenone has benefits compared to traditional norethindrone progestin-only pills, including less reliance on a narrow window of time for pill intake to maintain efficacy, but data on use of this type of progestin in breastfeeding are lacking. Because estrogen-containing contraceptives are contraindicated for a minimum of 21 days PP due to the risk of thromboembolism, and have been associated with decreased breastmilk supply, progestin-only contraception, including progestin-only pills (POPs) are commonly used for contraception among breastfeeding women regardless of time since birth. Approximately 16-20% of PP women who intend to breastfeed choose POPs for contraception following delivery in the U.S, approximately 500,000 women per year.

Until recently, POPs containing 0.35 mg daily of the oral progestin Norethindrone (n-POPs) have been the only available POP (Table 1). Norethindrone is a variant of progestin derived from testosterone. N-POPs do not consistently inhibit ovulation; the contraceptive mechanism of action is primarily through progestin effects on the cervical mucous and endometrium. They require daily use with a narrow window of time for intake to maintain efficacy and are associated with unpredictable vaginal bleeding patterns and acne. Fewer than half of women who intend to use n-POPs PP use the method at 3 months. Women who choose n-POPs for PP contraception are significantly more likely to have a short IPI compared to women choosing all other reversible methods.

Drospirenone is a novel progestin derived from spironolactone (Table 1). POPs containing 4 mg of oral drospirenone (d-POPs) became available for use in the U.S. in 2019. D-POPs consistently suppress ovulation and allow for a wider missed-pill window and cyclic use with hormone-free days which offer the potential to improve ease of use and to decrease irregular bleeding. Unlike norethindrone, drospirenone has anti-androgenic properties and should not exacerbate acne and may improve it. The efficacy of d-POPs among non-breastfeeding women is similar to combined estrogen-progestin pills. However, little is known about the effect of d-POPs on breastfeeding performance or PP contraceptive use, efficacy, or side effects among PP women.

Table 1: Progestin types available as progestin-only pills for contraception in the United States

Progestin	Progestin Classification	Available in U.S.	Hormone-free days, 28-day cycle	Androgen effect	Metabolized into Ethinyl Estradiol
Norethindrone	19-nor testosterone, Estrane	1970	None	Medium-high	Small amount
Drospirenone	Spironolactone	2019	4	Antiandrogenic	None

D-POPs are promoted for use while breastfeeding despite a lack of data on the effect of d-POPs on breastfeeding or infant outcomes. The package insert states, “no effects on breastfed infants are

anticipated" but the only data presented to support the safety of d-POPs among breastfeeding women is an average drospirenone concentration in breastmilk over a 24-hour period of 5.6 ng/mL. Only 11 breastfeeding women were included in the published study on d-POP efficacy in the U.S. The single other published study evaluating d-POPs and breastfeeding outcomes was conducted among only 12 women and showed that 18.13% of plasma drospirenone was found in breastmilk. High quality data are required to inform CDC guidelines on use of differing progestin types during breastfeeding.

Most previous studies have failed to show a negative effect of progestins on breastfeeding or infant growth. However, most existing studies are small, are of poor to fair quality, do not include assessments of d-POPs users and do not use validated outcome measures. Furthermore, most studies evaluating the effect of POPs on breastfeeding have initiated the method at 6 weeks PP or later. The single study specifically evaluating the effect of early initiation of POPs was not randomized and compared all progestin users (including pills, injectables, and implants) to non-hormonal contraception users. That study did not show a deleterious effect of progestins on breastfeeding, but it was limited by lack of a comparison group allowing for assessment of differences in outcomes by progestin type or by timing of progestin initiation. Other randomized studies comparing the effect of early versus delayed initiation of progestins have evaluated different delivery systems such as intrauterine devices (IUDs) and implants. There are no studies comparing breastfeeding outcomes among d-POP and n-POP users. Most studies have examined the effect of progestins on maternal, milk, or infant outcomes in isolation and have failed to evaluate the effect of progestin exposure during breastfeeding on the mother-milk-infant triad. An adequately powered, high-quality, randomized controlled trial (RCT) using validated measures of maternal, infant and milk outcomes and including d-POP users is needed to minimize the effects of bias and confounding and overcome the weaknesses in the rigor of the prior research. Our goal with this pilot study is to inform a future large-scale randomized controlled trial.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

1. There are potential risks of loss of confidentiality.
2. There is risk of stress, emotional distress, inconvenience, and possible loss of privacy associated with participating in a research study.
3. These are known risks of POPs, however they are routinely prescribed for women, both post-partum and otherwise.

2.3.2 KNOWN POTENTIAL BENEFITS

Patients may not experience a direct benefit from participation in this study. However, we hope that this study will help us determine if POPs can be provided during the early postpartum period with minimal impact on breastfeeding, infant growth and high patient satisfaction rates. There may be a benefit to women in the early initiation POP group to avoid unplanned early repeat pregnancies.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The potential benefit of early postpartum POP use outweighs the potential risks of changes to breastmilk, breastfeeding or infant growth changes.

3 OBJECTIVES AND ENDPOINTS

Aim	Variable	Description	Source
Maternal Outcomes			
1a	**Breastfeeding**	Exclusive breastfeeding: own mother's milk via breast or bottle. Predominant breastfeeding: greater than 75% of the infant's diet is their own mother's milk; the remainder of the diet is formula, donated milk, or other supplemental foods Mixed Breastfeeding: 25-75% or more of the infant's diet is their own mother's milk Predominantly supplementing: <25% diet is breastmilk No breastfeeding: infant is not consuming own mother's milk	End of weeks 2-8
1a	**Supplementation type**	Donated breastmilk, formula, other milks (cow, plant-based, nut), juice, water, cereal, other foods	End of weeks 2-8
1b	**Progestin-only pill use**	Any use, timing of initiation of POP use (assigned), type of POP (assigned), number of missed pills	End of weeks 2-8.
1b.	**Contraception use**	Sterilization (male and female), intrauterine devices, subdermal implants, oral contraceptives (combined), condoms (male and female), injectables, emergency contraceptive pills, patches, diaphragms, sponges, cervical caps, spermicidal agents, vaginal rings, withdrawal, fertility awareness, abstinence, and LAM	4 and 8 weeks
	Vaginal bleeding	Number of days of any bleeding and spotting in last month	Estimated at 4 and 8 weeks
	Satisfaction with contraception	Satisfied with method, would recommend method to a friend	4 and 8 weeks
	Pregnancy	Self-reported new pregnancy, pregnancy intendedness, whether planning to continue the pregnancy or not, and pregnancy outcome: continued, terminated, pregnancy loss	4 and 8 weeks
Milk Outcomes			
2	**Composition of breastmilk**	Fat, protein, carbohydrate (including oligosaccharide) content of milk	4-week breastmilk sample
	Maternal perception of adequate milk supply	Hill and Humenick Lactation Scale	End of weeks 2-8
Infant Outcomes			
3	**Change in infant growth**	Weight, length, and head circumference	Change between baseline and 4 weeks

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a three-arm, placebo-controlled, double-blinded randomized controlled pilot trial that includes 8 weeks of participation from enrollment to final follow-up.

We hypothesize that the type of progestin used and the timing of progestin initiation will not have clinically meaningful effects on breastfeeding continuation, supplementation, the composition of breastmilk, or infant growth and body composition. In addition, we hypothesize that the timing of progestin initiation will not have a meaningful effect on progestin-only pill (POP) continuation, but that women will be more likely to continue d-POPs compared to n-POPs. Findings from this study will support more women to use progestin-containing contraceptives to prevent unintended pregnancy in the postpartum period with a greater understanding of the safety while breastfeeding.

4.2 END OF STUDY DEFINITION

A participant is considered to have completed the study after she has completed all phases of the study including the last visit at 8 weeks postpartum.

5 STUDY POPULATION

Postpartum women delivering a baby at University of California, San Diego (UCSD) within the past 7 days will be eligible. 30 women will be enrolled. Participants will be screened for eligibility according to the below criteria using a screening checklist. If eligible and interested in participating, a consent form will be signed.

5.1 INCLUSION CRITERIA

There will be a total of 30 postpartum women enrolled in this study. Participants will need to meet the following criteria:
-Are 18 years of age or older
-Desires to use POPs for 3 months
-Speak English or Spanish
-Had a vaginal or cesarean delivery of a singleton full term (≥37 weeks) infant less than 168 hours prior
-Intends to breastfeed exclusively for 6 months

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:
-Desire another pregnancy in less than 6 months
-Do not intend to exclusively breastfeed
-Do not have access to a telephone
-Have any medical contraindication to POPs
-Have any contraindication to breastfeeding, including maternal illegal drug use, history of breast augmentation or reduction, infant with major congenital anomaly
-Cognitively impaired
-Currently incarcerated

5.3 SCREEN FAILURES

For individuals who do not meet the criteria for participation in this trial (screen failure) due to not meeting eligibility requirements, the reason will be documented. Potential participants who decline

participation will be noted and counted as well. No identifying information will be collected from screen failures.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION

Group 1: Initiation of d-POPs 120-160 hours after delivery (N=10)
Group 2: Initiation of n-POPs 120-160 hours after delivery (N=10)
Group 3: Initiation of d-POPs 4 weeks after delivery (N=10) [placebo starting 120-160 hours, continuing for 28 days]

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be randomized to their assigned group by chance with a computer-generated randomization scheme. The participant and investigator will both be blinded to the group assignment. The investigational pharmacy will be aware of the group assignment of each participant and will encapsulate and prepare the blinded medications for the the research coordinator to deliver to the participant.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If a participant chooses not to move forward with initiation of the study POPs, she will remain in the study under observation. Remaining study procedures should be completed as indicated by the study protocol. Reasons for choosing another method of contraception will be documented and the participant followed for the study duration of 8 weeks.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants may withdraw voluntarily from the study at any time. The PI or study team will not withdraw anyone from the study without specific request from the participant. Medical care will be provided by the patient's clinician as standard of care in the case of study withdrawal. Research participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if she fails to return for any scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to respond to surveys or return to the clinic for the required study visit:

- The research coordinator will attempt to contact the participant, re-send surveys and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant, including 3 telephone calls or texts. These contact attempts should be documented in the participant's study file.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

This pilot study is a placebo-controlled double-blinded RCT. We will recruit women in the third trimester of pregnancy during their routine prenatal care clinical visits and post-partum (PP) during their hospital stay. Women will not be enrolled and randomized until after delivery. All women delivering at UCSD hospitals are offered comprehensive contraceptive counseling by nurse midwives or physicians during prenatal appointments and/or after delivery before discharge from the hospital.

Enrollment Procedures:
We will assess women who indicate that they desire POPs for contraception for eligibility after they have received contraceptive counseling. Research staff will identify postpartum women who are planning on utilizing POPs as postpartum contraception via review of medical records of patients receiving inpatient obstetrical services at UCSD. Study staff will visit these potential participants during their inpatient hospital stay to present the study and administer the pre-screening eligibility form if the patient is interested in participation. While only women who intend to use POPs for at least 8 weeks will be enrolled, all participants will be told if they are unhappy with POPs at any time, the study team will facilitate timely contraceptive counseling and referral to an appropriate provider to ensure that they can switch contraceptive methods at any time if they choose.

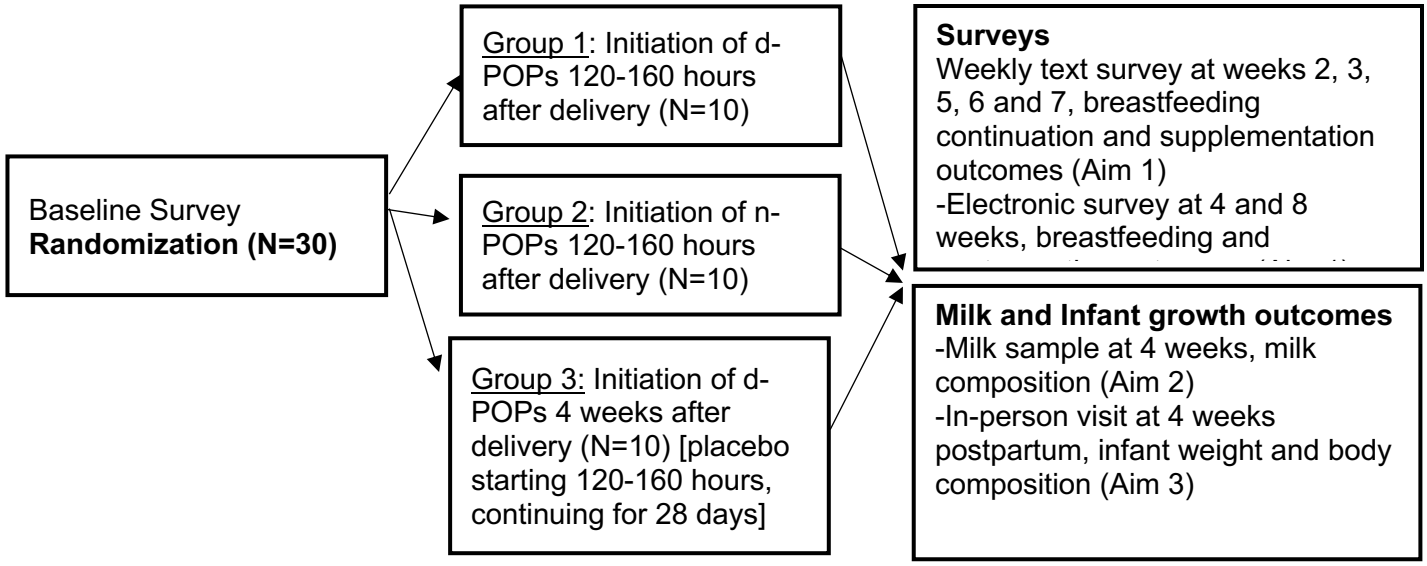
After enrollment and prior to randomization, participants will be asked to complete a brief self-administered demographic questionnaire using a private secure tablet that enters data directly into REDCap (Research Electronic Data Capture), a secure electronic data collection system. Demographic characteristics collected will include maternal age, race, Body Mass Index, gestational weight gain, parity, education, previous experience breastfeeding, previous contraceptive use history, breastfeeding intentions, delivery type and complications, infant stay in neonatal intensive care unit (and length of stay), infant birth weight, race, sex assigned at birth, and gestational age at birth. Participants will receive a gift card via text or email link for completing the survey.

Randomization:
A licensed medical provider on the clinical care team will review eligibility for the method and instruct patients on use of POPs prior to discharge from the hospital and will approve a prescription for both POPs. Participants will then be randomized to (1) early d-POPs to be initiated at 120-168 hours (5-7 days) after delivery, (2) early n-POPs to be initiated at 120-168 hours after delivery, or (3) placebo for 28 days followed by d-POPs initiated at 4 weeks (28-35 days) after delivery, at a 1:1:1 ratio (Figure 2). Study staff will then provide participants with written and verbal instructions about when to initiate the method and to take the study medications in the order dispensed. Participants, care providers, and research staff will be blinded to group assignment. Participants will be instructed on lactational

amenorrhea method (LAM), a highly effective form of contraception, and will be counseled that if they no longer meet criteria for LAM, then they may be at risk for unintended pregnancy between days 28 and 33 and should use condoms or abstain from intercourse during that time. Before day 28, the CDC Selected Practice Recommendations state that a provider can be "reasonably certain that woman is not pregnant" regardless of LAM use and after day 33 all study drugs will be effective contraception regardless of group assignment.

The research team will dispense two 28-day pill packs containing either d-POPs, n-POPs, or one placebo and one d-POPs, as determined by the randomization scheme, and labeled 1st and 2nd. For participants in group 3, the first pack will contain only placebo to facilitate delayed initiation while ensuring blinding. D-POP packs will include 24 active and 4 placebo tablets per month, and n-POP packs will include 28 active tablets, packaged in order of daily use. All d-POP, n-POP, and placebo tablets will be encapsulated by the research pharmacies to have an identical appearance.

Figure 2: Outcome Evaluation Study Design



Surveys:
Investigators will send participants hyperlinks via 5 text messages weekly at the end of weeks 2, 3, 5, 6, and 7 PP. Hyperlinks will lead to a brief questionnaire that participants can complete through a smartphone or tablet. Participants will complete a tablet-based survey in person at their 4 week visit. Participants will receive an emailed hyperlink at the end of week 8 which will lead to a longer questionnaire. A telephone survey will be available as an alternative to the digital questionnaires if desired. Survey questions will address continuation of and satisfaction with breastfeeding, the use of supplemental feeding, types of supplemental feeding being used, use of contraception, and satisfaction with contraception.

At 8 weeks PP, participants will be emailed and requested to complete a more detailed questionnaire eliciting breastfeeding continuation, supplementation amount and type, episodes of lactation support, perception of adequate milk supply, vaginal bleeding patterns, satisfaction with breastfeeding and

contraceptive use, satisfaction with contraception, infant health and well-being, and any new pregnancies and respective pregnancy outcomes if available. Additional potential confounding factors will be explored, such as use of nipple shields, pacifiers, breastmilk expression, and other medications the participant is using. Participants will receive a gift card via text or email link for each completed survey.

Both text and email questionnaires will be sent via a hyperlink that connects to a HIPAA-compliant secure platform that will input the data directly into a REDCap database. Participants who do not have smartphones or email access will be offered participation instead using phone surveys administered by study staff and gift cards will be mailed to these participants.

Breastmilk collection and analysis:
Women will attend an in-person visit at 4 weeks PP with their infant. Participants will have the option to collect a mid-feeding sample at home with all pumping materials and instructions sent to her home or collect a sterile sample at the visit using a study-provided breast pump. 10 mLs of breastmilk from the collection (either refrigerated sample brought to the visit or collected on-site) will be frozen at the site of the visit at the research site. The milk samples will be frozen at -80 degrees onsite. The lab will use liquid chromatography to assess the composition of breast milk and compare the concentrations of total fat, total protein and carbohydrates including oligosaccharides.

8.2 SAFETY AND OTHER ASSESSMENTS

A Data Safety and Monitoring Board (DSMB) is not planned for this small pilot study.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

The FDA definition of an Adverse event is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

OR

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (DE challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the

study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, by communication from the participant to the study team, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All adverse events will be reported to th UCSD IRB. The management of information that is relevant to the protection of participants including adverse events, UPRs, protocol violations/deviations, interim results and protocol modifications will be the responsibility of the PI.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

All serious adverse events will be reported to th UCSD IRB. The management of information that is relevant to the protection of participants including adverse events, UPRs, protocol violations/deviations, interim results and protocol modifications will be the responsibility of the PI.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

The UCSD IRB provide guidance to the PI on informing participants regarding AEs and SAEs as needed.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigators will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported to the IRB within reasonable timing of the investigator becoming aware of the problem.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The IRB at each site will provide guidance to PIs on informing participants regarding UPs as needed.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Comparisons will be made between groups 1 and 2 to assess differences in outcomes by type of progestin used, and between groups 1 and 3 to assess differences in outcomes by timing of progestin initiation. The primary outcome is the proportion of women exclusively breastfeeding at 8 weeks postpartum. Differences in baseline demographic characteristics and in variables between groups will be assessed using χ^2, Fisher exact, or t-tests as appropriate.

9.2 SAMPLE SIZE DETERMINATION

The sample size (N=30 in 6 months) was chosen to demonstrate feasibility to enroll 180 women in 36 months at our site during a larger multi-site trial and to successfully complete follow-up.

9.3 POPULATIONS FOR ANALYSES

The following datasets will be utilized for analysis:

- Intention-to-Treat Analysis Dataset: All participants randomized with known outcomes per the 8 week follow up survey.
- Per-Protocol Analysis Dataset: Participants who reported taking their assigned POP throughout the study period and reported follow up data on the 8 week survey.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

A survival analysis will be conducted to to assess time spent exclusively breastfeeding.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Proportions will be compared using chi-square tests. ANOVAs will be used to calculate means for analysis using all 3 groups and t-tests for any pairwise comparisons.

9.4.4 SAFETY ANALYSES

AEs and SAEs will be recorded by the study team when they become aware. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented in a table.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics such as demographic information (age, education level, race, ethnicity and employment status) will be collected. At the time of enrollment, questions will also be asked about pregnancy history, past use of contraception, use of donor milk and current perception of adequacy of

human milk supply. Means and proportions of respondents in each of the two groups will be compared to assess for success of randomization.

9.4.6 PLANNED INTERIM ANALYSES

Interim analyses are not planned during this short pilot study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator and funding agency. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and/or IRB.

10.1.2 STUDY GOVERNANCE

The name and contact information of the Principal Investigator:

Sarah Averbach, MD, MAS, Associate Professor
University of California, San Diego
9500 Gilman Drive, La Jolla, CA, 92093
858-329-4464
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10.1.3 SAFETY OVERSIGHT

Safety oversight will be monitored by the study PI.

10.1.4 CLINICAL MONITORING

Data verification will take place periodically. This will ensure data completeness and monitor safety of participants.

10.1.5 DATA HANDLING AND RECORD KEEPING

10.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

10.1.5.2 STUDY RECORDS RETENTION

Study documents will be retained for 2 years after the formal completion of the study.

10.1.6 PROTOCOL DEVIATIONS

It is the responsibility of the PI to use continuous vigilance to identify and report deviations. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

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