# PROTOCOL:

# VAGINAL PROGESTERONE FOR THE PREVENTION OF PRETERM BIRTH IN WOMEN WITH ARRESTED PRETERM LABOR (PAL)

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# A Introduction

## *A1 Study Abstract*

Preterm birth, defined as birth before 37 weeks' gestation, is a leading cause of infant death and disease. Progesterone is the single most effective intervention in the prevention of preterm birth. However, current use of this therapy is limited to certain high-risk groups including women with a history of preterm birth and women with a short cervix. This study seeks to evaluate the efficacy of this preventive therapy in another high-risk group: women with arrested preterm labor.

## *A2 Primary Hypothesis*

We *hypothesize* that administration of vaginal progesterone in women who present with preterm labor but remain undelivered after cessation of short-term therapy to inhibit contractions will result in *lower rates of preterm birth before 37 weeks* than will administration of placebo.

## *A3 Purpose of the Study Protocol*

This study protocol outlines the purposes and procedures of this randomized controlled trial.

# B Background

## *B1 Prior Literature and Studies*

Approximately 12% of births in the United States (U.S.) are preterm, defined as occurring before 37 weeks' gestation (Mathews 2012). Infants born preterm suffer from short- and long-term complications affecting multiple organ systems (Mathews 2012, McIntire 2008, Saigal 2008). In addition, approximately 67% of all deaths within the first year of life occur in infants born prematurely (Mathews 2012). Progesterone is the single most effective medical therapy in the primary prevention of preterm birth (Tita 2009); however, its use is limited to women with a history of prior preterm delivery and women found by transvaginal ultrasound to have a short cervix (Meis 2003, Fonseca 2007, Hassan 2011). An additional group of women at risk for preterm delivery is the approximately 5% of pregnant women (McPheeters 2006) who present with contractions and cervical change but have temporary arrest of preterm labor. Despite the initial arrest of labor progress, as many as 50-60% of these women will ultimately deliver preterm infants (ACOG 2012, Lyell 2008). A handful of studies, including a recent meta-analysis (Likis 2012), have found that the use of vaginally administered progesterone in women with arrested preterm labor is associated with a longer arrest-to-delivery interval and higher infant birth weight. However, concerns about the applicability of the findings to the U.S. healthcare system limit their ability to change the standard of care for this at-risk population; an adequately powered study providing Level I evidence for this practice is thus required.

## *B2 Rationale for this Study*

There is a direct correlation between gestational age at delivery and infant morbidity and mortality (Mathews 2012). Prolonging a pregnancy by even a few days or weeks can have a significant impact on a child's health. Women with arrested preterm labor are an identifiable high-risk group whose children may benefit from long-term therapy to delay delivery. If our study confirms the findings of the meta-analysis by Likis (2012) that progesterone decreased by 38% the preterm birth rate in women with arrested preterm labor, we estimate (on the basis of recent birth data [Mathews, 2012]) that this therapy may prevent as many as 40,000 preterm births annually in the U.S.

# C Study Objectives

## *C1 Primary Aim*

To evaluate the efficacy of vaginal progesterone in women with arrested preterm labor after 24 weeks' gestation to reduce their risk of preterm birth before 37 weeks.

## *C2 Secondary Aim*

None

## *C3 Rationale for the Selection of Outcome Measures*

The primary outcome is delivery prior to 37 weeks' gestation. This was selected as the primary outcome because the current definition of preterm birth is any delivery occurring prior to 37 weeks gestation. With advancing gestational age, the risks of adverse outcomes for the fetus are diminished. Infants born at term generally do not require additional therapeutic interventions and are discharged from the hospital at the time of maternal discharge without the sequelae of prematurity.

# D Investigational Agent

## *D1 Preclinical Data*

See clinical data to date.

## *D2 Clinical Data to Date*

Although not FDA approved, micronized vaginal progesterone is commonly used in practice for the prevention of preterm birth. Recently, the American College of Obstetricians and Gynecologists recommended that women with diagnosed short cervix (<20 mm on ultrasound) at 24 weeks gestation or earlier should receive vaginally administered progesterone supplementation which is routinely administered daily until 37 weeks gestation. Multiple randomized controlled trials have demonstrated the safety and tolerability of this medical therapy. Fonseca et al. performed a randomized controlled trial utilizing micronized progesterone capsules 200 mg in 250 women with a short

cervix. None of the women reported any increase in the frequency or severity of side effects such as fatigue, headaches or genital irritation. Also, no new symptoms were reported by participants after starting treatment. Arikan et al. published a randomized trial evaluating the use of micronized progesterone in women with arrested preterm labor. In this non-blinded study, no complaints or adverse effects related to the treatment were reported by participants. In a large, international multicenter randomized controlled trial that include 458 women, micronized progesterone was administered as a gel rather than a tablet. No difference in adverse events were reported in women who received progesterone and those who received a placebo gel. The most commonly reported side effects in both groups included vaginal pruritus, vaginal discharge, vaginal yeast infection and nausea. No differences in rates of congenital anomalies were found in those fetuses of women who received progesterone and those who received the placebo (RR 0.32, 95% CI 0.03-3.02). Likewise, a study specifically evaluating the safety of progesterone exposure in pregnancy found no increased risk of fetal adverse effects (Northen 2007).

### *D3 Dose Rationale and Risk/Benefits*

The progesterone that will be utilized is micronized vaginal progesterone 200 mg daily. This choice was selected because this is the dose and formulation that is routinely prescribed by Washington University/Barnes-Jewish Hospital obstetricians for the prevention of preterm birth in asymptomatic women with a short cervix diagnosed by routine ultrasound examination. In addition, this dose was also used by Fonseca et al. in their randomized controlled trial for the prevention of preterm in women with a sonographically short cervix and they reported no increase in side effects with this drug. We also believe that the use of a vaginally inserted suppository rather than a gel may be easier for women participating in the study.

## E Study Design

### *E1 Overview or Design Summary*

Randomized, double-blinded, placebo controlled trial. Women enrolled in the study will be randomized to vaginal administration of micronized progesterone 200 mg or placebo daily from time of enrollment until 36 6/7 weeks gestation. Investigators, participants, and the obstetric providers will be blinded to the allocated intervention.

As part of the study, participants have the option to provide a vaginal swab specimens for future studies evaluating the effect of vaginal progesterone on the vaginal microbiome. If the woman agrees to participant in this part of the study as well, then a swab will be collected by her obstetric care provider after enrollment but prior to study drug administration and an additional swab will be collected 2-6 weeks after randomization at a follow-up visit.

## *E2 Subject Selection and Withdrawal*

### 2.a Inclusion Criteria

- Singleton or twin gestation
- Between $24\,^{0}/_{7}$ and $33\,^{6}/_{7}$ weeks' gestation
- Initially present with regular contractions and clinical diagnosis of preterm labor but remain undelivered with 1) no further cervical change 12 hours after discontinuation of acute tocolytic therapy; or 2) be considered eligible for discharge based on attending physician judgment prior to the 12 hour period of time 3) no further cervical change after 12 hours if no tocolytic is administered
- The participant's cervix must be at least 1 cm dilated at the time of enrollment

### 2.a Exclusion Criteria

- non-English speaking,
- rupture of membranes,
- chorioamnionitis,
- non-reassuring fetal status,
- maternal indication for delivery (e.g., severe preeclampsia),
- placental abruption,
- intrauterine fetal demise,
- prenatally diagnosed major fetal anomalies,
- a cervical cerclage in place,
- previous administration of progesterone during the current pregnancy for a history of preterm birth or short cervix,
- participant is either unwilling or unable to attend follow-up study visits following hospital discharge at the Barnes-Jewish Hospital Center for Outpatient Health or the Maternal-Fetal Medicine (MFM) practice at Washington University. Enrollees will not need to receive their pregnancy care at these locations but must meet with a study coordinator every two weeks.

### 2.b Ethical Considerations

All participants in the study will be consented. Information about potential maternal and fetal risks and benefits will be reviewed. There will be no coercion involved. Neither enrollment nor refusal to participate in the study will influence a woman's obstetric care or the care of her fetus/neonate, besides the use of the allocated study drug and follow-up after hospital discharge for women for women who agree to participate.

### 2.c Subject Recruitment Plans and Consent Process

A member of the research team will approach women with arrested preterm labor to discuss possible participation. Women may be approached prior to the completed 12 hours after discontinuation of acute tocolytic therapy; however they will not be randomized until at least 12 hours after the discontinuation time unless they are considered eligible for discharge from the hospital prior to completion of the 12 hour time period. The research team member will review the goals of the study, use of the allocated study drug, plans for follow-up, and the entire consent process, and will provide the woman a copy of the consent form. The physicians and nurses caring for the patient will not be involved in the consent process, and the patient will be assured that her decision to participate in the study will not influence her care beyond the use of the

allocated study drug and follow-up if discharge from the hospital occurs before delivery. Each woman will have up to 24 hours to decide whether she would like to participate in the study. At the time of enrollment, release of records forms will also be signed by the participant to permit the investigators to obtain medical records for the participant and her infant from another institution or obstetric provider in the event that she delivers at a location other than Barnes-Jewish Hospital.

A separate section of the consent form allows the participant to agree or decline participation in the vaginal sample collections for future studies. Woman will be able to participate in the randomized controlled trial without agreeing to specimen collection.

## 2.d Randomization Method and Blinding

Participants in the study will be randomized using a computer-generated randomization scheme with 1:1 allocation to receive progesterone or placebo. The randomization scheme will be set-up by a statistician within the department of Obstetrics and Gynecology at Washington University. Research assistants not otherwise involved in the study will place pieces of papers with letters "A" or "B" into envelopes labeled with participant study numbers based on the randomized assignment. This will be completed prior to the study commencement. The envelopes will then be provided to *Katherine Vehe*, phone: 314-362-3376, in the Barnes-Jewish Hospital pharmacy who will supervise the allocation of study drugs within the pharmacy. She will decide prior to the study start the assignment of "A" or "B" to the progesterone or placebo and this will be recorded. This allocation will remain consistent throughout the study and the other members of the research team, patient care providers, and participants will be blinded to this allocation. Once a participant is given a study number, the study coordinator will contact *Katherine Vehe* who will provide the appropriate drug based on the letter contained within the envelope that corresponds to the study number.

## 2.e Risks and Benefits

There are no emotional, psychological, or social risks to the participant beyond the stress of having an increased risk for preterm birth. The cost of the study drug will be covered, so there is no increased financial burden to the participant. Both progesterone and the placebo will be placed vaginally and there is a potential risk for vaginal discharge, irritation, yeast infection, and nausea with either drug. However, data from large randomized controlled trials performed with the same medication suggests that there is minimal to no increased risk of these potential side effects (Fonseca 2007, Hassan 2011). Every two weeks, a research nurse will discuss and record any side effects reported by the participant. The participant may discontinue use of the allocated study drug at any time and continue to participate in the study. A Data Safety and Monitoring Board, which will be created before the study begins, will review the blinded results, including reported side effects when 50% of planned enrollment is achieved (120 women) and provide recommendations to the investigator regarding the safety of continuing the study. There is a very small potential risk of loss of confidentiality; however, multiple mechanisms will be used to decrease this risk, including the storage of research information in a password-protected database on a password-protected computer in a locked office, the use of research identification codes, and coding of data entered in the database.

There are no direct benefits that are expected for the participant. However, available data suggests a possible delay in delivery with the use of vaginal progesterone in this population of women. Survival increases and the risk of significant morbidity decreases with advancing gestational age. Even a few days or weeks of delaying preterm birth can be of significant benefit, as the fetus is developing every day.

## 2.f Early Withdrawal of Subjects

Participants may withdraw from the study at any time. Alternatively, participants who are unable to follow-up after discharge from the hospital or refuse to continue taking the study drug may remain in the study for the purpose of intention-to-treat analysis.

## 2.g When and How to Withdraw Subjects

Participants may withdraw from the study at any time. Participants may do this by contacting the study team or sending in a withdrawal letter.

In addition, the study coordinator will contact a participant who does not return to Barnes-Jewish Hospital/Washington University for study drug pick-up as scheduled to discuss further participation. She will call the participant at the phone number that she provided at the beginning of the study.

If a participant withdraws from the study, a member of the research team should discuss the following options:
1) Complete withdrawal from the study without the use of data collected as part of the study in analysis.
2) Continued study participation with no further follow-up visits and discontinuation of the study drug, but with the collection of information following delivery regarding the delivery timing and neonatal outcomes. This will allow intention-to-treat analysis.

Participants who withdraw from the study will also be asked to provide a reason for study withdrawal.

## 2.h Data Collection and Follow-up for Withdrawn Subjects

Even if the participant discontinues the study drug, she may continue to participate in the study and outcome data regarding delivery timing and neonatal outcomes will be collected with her permission (option 2 above).

# *E3 Study Drug*

## 3.a Description

Women in the study will be randomized to receive vaginal micronized progesterone or a similar appearing placebo.

## 3.b Treatment Regimen

A single suppository of the allocated drug will be placed vaginally each day.

## 3.c Method for Assigning Subjects to Treatment Groups

Participants in the study will be randomized using a computer-generated randomization scheme with 1:1 allocation to receive progesterone or placebo. The randomization scheme will be set-up by a statistician within the department of Obstetrics and Gynecology at Washington University. Research assistants not otherwise involved in the study will place pieces of papers with letters "A" or "B" into envelopes labeled with participant study numbers based on the randomized assignment. This will be completed prior to the study commencement. The envelopes will then be provided to *Katherine Vehe*, phone: 314-362-3376, in the Barnes-Jewish Hospital pharmacy who will supervise the allocation of study drugs within the pharmacy. She will decide prior to the study start the assignment of "A" or "B" to the progesterone or placebo and this will be recorded. This allocation will remain consistent throughout the study and the other members of the research team, patient care providers, and participants will be blinded to this allocation. Once a participant is given a study number, the study coordinator will contact *Katherine Vehe* who will provide the appropriate drug based on the letter contained within the envelope that corresponds to the study number.

## 3.d Preparation and Administration of Study Drug

Both the study drug and placebo will be compounded in the Barnes-Jewish Hospital pharmacy. The placebo will contain polyethylene glycol (PegBlend, *Fagron Pharmaceuticals*) a compound commonly used in the manufacturing of suppositories. The progesterone suppositories will contain micronized progesterone 200 mg and polyethylene glycol. These products will be contained within an opaque suppository capsule which can be placed vaginally. The drugs will be refrigerated prior to use.

## 3.e Subject Compliance Monitoring

Every two weeks regardless of whether the patient remains inpatient or outpatient the study coordinator will meet with the participant. Women who were discharged from the hospital will be instructed to bring their study drug containers to this visit and the number of remaining suppositories will be counted and the number of missed doses calculated. During these visits, compliance and side effects will be discussed. Prior to the start of the visit the participant will be asked to fill out a one-page questionnaire:

1) Have you been admitted to the hospital since our last meeting?

   A. Yes
   B. No

      If yes, reason(s) and date(s): _____
      _____

2) Have you started any new medications since our last meeting?

   A. Yes

B. No

If yes, please list them: _____

3) How many does of the study drug have you missed or forgotten to take since our last meeting?

A. Missed 10 or more
B. Missed 5 – 10
C. Missed less than 5
D. Missed none

4) Have you noticed any new symptoms since our last meeting?

A. Yes
B. No

If yes: Symptom(s): _____
Start and End Date(s): _____
Frequency: _____
Severity: _____

## 3.f Prior and Concomitant Therapy

Prior use of any form of progesterone during the current pregnancy other than that provided during the study is an exclusion criterion for study enrollment. Another criterion for enrollment is that the participant must have discontinued acute tocolytic therapy for 12 hours prior to enrollment and remained clinically stable. An exception to this is that if the participant begins to labor in the future (any time prior to 32 weeks' gestation) while enrolled in the study, magnesium sulfate may be administered for the purpose of fetal neuroprotection while the threat of preterm delivery persists. Magnesium is used for acute tocolytic therapy, but it use in this circumstance is not tocolysis but rather to decrease the risk of cerebral palsy in the offspring. Other therapy for medical or pregnancy-related indications may be prescribed by the participant's physician and be taken concomitantly.

## 3.g Packaging

Either the progesterone and placebo suppositories will be distributed to the patient's nurse (while inpatient) or study coordinator (outpatient) in a UV light protected, USP tight medicine bottle.

## 3.h Blinding of Study Drug

The research team, obstetric providers, and participant will be blinded to the study drug. The pharmacist will not be blinded to the drug and will distribute the proper allocated drug to the study coordinator and nursing staff. The placebo and micronized progesterone will be contained within identical appearing suppository capsules. Care will be taken not to include information regarding the specific drug on the medicine bottle.

### 3.i Receiving, Storage, Dispensing and Return

While the participant is an inpatient in Barnes-Jewish Hospital, the study coordinator will notify pharmacy of the new participant and the study drug will be distributed from pharmacy to the nursing staff on labor and delivery or the antepartum unit on a daily basis. The drug will be stored in the medication refrigerator on the unit until it is administered to the patient. Upon discharge from the hospital, the study coordinator will obtain a 21-day supply of the study drug from the pharmacy which will be distributed to the participant. The participant will be instructed to store the medication in a refrigerator prior to use. She will follow-up every two weeks with the study coordinator at Washington University or Barnes-Jewish Hospital outpatient offices and will be provided with the next two week supply of study drug and will bring back any leftover pills from her previous supply of drugs.

# F Study Procedures

## *F1 Screening for Eligibility*

Obstetric care providers including physicians and nurses will notify the study coordinator if a potential participant is identified. Prior to approaching the individual for possible enrollment, the study coordinator will review the patient's records to determine eligibility for the study based on the prior outlined inclusion and exclusion criteria. We will keep track of the total number of women screened, but will not record any personal information regarding women who do not meet eligibility criteria.

If the woman meets eligibility criteria, then the study coordinator will approach her for enrollment in the study. The goals of the study, the use of the allocated study drug, plans for follow-up and the entire consent will be reviewed in person with each woman and she will be provided a copy of the consent form. This discussion will occur in the woman's private hospital room. The physicians and nurses caring for the patient will not be involved in the consent process and the patient will be assured that her decision to participate in the study will not influence her care beyond the use of the allocated study drug and follow-up if discharge from the hospital occurs prior to delivery. The study coordinator may approach women prior to the completed 12 hours after discontinuation of acute tocolytic therapy to discuss the study and gauge interest in participation, but the woman will not be randomized until at least 12 hours after the discontinuation time unless the patient is eligible for discharge prior to the 12 hour time period based on attending physician judgement. Each woman will have up to 24 hours to decide whether she would like to participate in the study.

Questions that the study coordinator will specifically ask of the individual prior to enrollment in the study include:

- Are you currently taking any form of progesterone therapy?
- Have you in the past had any adverse reaction to taking a progesterone drug?
- Would you be willing and able to return to Barnes-Jewish Hospital/Washington University every two weeks for a study visit and to receive a refill on the study

drug if your physician determines that you are able to be discharged from the hospital prior to delivery?

The name and birth date of each individual invited to participate in the study will be recorded in a password protected spreadsheet stored in the password protected computer of the study coordinator along with information about whether the participant agreed to participate in the study or not. This information will ensure that the same woman is not approached for the study more than once.

We will also ask the potential participant to provide a reason for not wanting to participate in the study. Basic demographic information including maternal age, race, parity, history of prior preterm birth, and gestational age and cervical dilation at the time she was approached for study participation will be recorded from the medical record. Women who decline participation will be notified that we would plan to collect the information above and the purpose of collecting that information.

As a trial that is evaluating the use of a preventive medication in a population that is not normally offered this type of therapy, it is critical that the acceptability of the therapy within this population is assessed as part of the trial. In addition, the basic demographic data that is collected will allow the research team to assess for a possible selection bias among women who agree to participate and those who do not. This information will be stored in a secure document on the password protected computer of the investigator. All PHI data will be deleted at the completion of the study and publications resulting from this study will contain no personally identifiable information about these individuals. However, we will use this information to create a flow diagram for the study.

## *F2 Schedule of Measurements*

**I. Procedures following enrollment:**

- Randomization: Once the participant agrees to participate in the study, the study coordinator will contact the pharmacy with the participant's study identification number. The pharmacist or pharmacy technician will use the study randomization scheme to determine whether the participant will receive progesterone or placebo. This will be recorded by the pharmacist in a randomization log which will link the study number with the allocated drug. This log will not be seen by the participant, obstetric provider or any member of the research team unless requested by the Data Safety and Monitoring Board or at the completion of the study.
- Vaginal specimen swab: If the participant agrees to provide vaginal specimens, then the first specimen will be collected by her obstetric care provider in the hospital with a speculum examination prior to beginning the study drug. This specimen will be stored for future vaginal microbiome research. The swabs will be stored as part of the Women and Infants' Health Specimen Consortium.
- Data collection: Initial data collection will begin following enrollment. Information will be recorded from the participants medical record and will include:
    - Participant demographic data: age, race/ethnicity, weight, height, smoking status, drug use, marital status
    - Past medical and surgical history data

- Prior pregnancy history data: number of prior pregnancies and prior pregnancy outcomes including gestational age at delivery
- Current pregnancy data: date of first prenatal visit, use of medications during the pregnancy, infections, date of first ultrasound examination, any pregnancy complications other preterm labor, cervical length if performed as part of routine screening earlier in pregnancy
- Care during current hospitalization for preterm labor: gestational age at time of admission, medications administered including tocolytics and antenatal corticosteroids, cervical examination on admission, most recent cervical examination, complications of pregnancy diagnosed during the hospitalization, estimated fetal weight at time of admission

- Study drug distribution: While the participant remains hospitalized at Barnes-Jewish Hospital the study drug will be dispensed on a daily basis by the pharmacy to the nursing staff in the unit in which the participant is staying. The participant will be provided the drug every 24 hours and will be asked to place the drug herself with nursing instruction.
- The participant's care will not be altered based on her enrollment in the study except for taking the study drug. Decisions regarding clinical management will be determined by the obstetric care providers caring for the participant during her hospitalization. Other than collection of the vaginal swab at enrollment, no additional procedures will be performed as part of the study.

**II. Follow-up procedures:**

- Follow-up procedures will depend on whether the participant remains hospitalized until delivery or she is discharged home, which will be determined by her obstetric care providers and will not be influenced by her participation in the study.
- Inpatient:
  - The study drug will continue to be provided by the pharmacy on a daily basis and distributed to the participant by nursing staff.
  - During the follow-up visit, the study coordinator will discuss compliance with the study drug and possible side effects. The participant will fill out a one-page questionnaire form that asks questions about compliance and side effects. This information will be recorded and provided to the DSMB at the midpoint review.
  - For women enrolled in the vaginal specimen collection portion of the study, a repeat vaginal swab will be collected by the obstetric care provider 2-6 weeks after enrollment.
- Outpatient:
  - At the time of discharge from the hospital, the participant will be provided with a 21-day supply of study drug.
  - The participant's follow-up prenatal care will be determined by obstetricians caring for her during the hospitalization. Continued prenatal care by a primary obstetrician not affiliated with Washington University/Barnes-Jewish Hospital is not an exclusion criterion for the study.
  - The participant will be asked to return to Washington University/Barnes-Jewish Hospital for a follow-up study visit every two weeks. At that time, a clinical visit in the High-Risk Obstetric Clinic at the Center of Outpatient Health or with a Maternal-Fetal Medicine specialist at the Center for

Advanced Medicine will be offered to those women not receiving primary obstetric care at Washington University/Barnes-Jewish Hospital, but this will be optional for the participant if she is receiving care at a different location with an obstetric care provider. The date and time of study visits will be coordinated with the study coordinator.

- At each study visit, the next two week supply of study drug will be provided to the participant by the study coordinator. The participant will bring back any leftover pills. The study coordinator will obtain the study drug from the pharmacy at Barnes-Jewish hospital where the compounding is occurring prior to each study visit.
- During the follow-up visit, the study coordinator will discuss compliance with the study drug and possible side effects. The participant will fill out a one-page questionnaire form that asks questions about compliance and side effects. This information will be recorded and provided to the DSMB at the midpoint review.
- For women enrolled in the vaginal specimen collection portion of the study, a repeat vaginal swab will be collected by an on-site obstetric care provider or PI 2-6 weeks after enrollment.

**III. Delivery follow-up**

- The following data will be collected following delivery:
  - Delivery data: gestational age at delivery, indications for delivery, mode of delivery, maternal complications antepartum or postpartum including placental abruption, rupture of membranes, infection, other
  - Infant outcomes: birth weight, sex, Apgar scores, cord gas results if performed, type of nursery admission, respiratory distress, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and discharge status
    - Collected infant data will be limited to the hospitalization at the time of birth.

## *F3 Safety and Adverse Events*

### 3.a Safety and Compliance Monitoring

Every two weeks, a study coordinator will discuss and record any side effects reported by the participant. The participant may discontinue use of the allocated study drug at any time and continue to participate in the study. A Data Safety and Monitoring Board will be created prior to the study. The Data Safety and Monitoring Board (DSMB) will meet and be provided interim results and data regarding reported adverse events after 50% of planned enrollment is achieved (120 women enrolled). The data will be presented in a blinded fashion with regards to the drug exposure of each group. At the request of the DSMB, the study will be unblinded for further review. It is at the discretion of the DSMB to request early cessation of the trial. During conduct of the study, any severe adverse events will be immediately reported to the DSMB and Human Research Protection Office at Washington University.

## 3.b Medical Monitoring

i **Investigator only-** N/A

**ii Independent expert to monitor-** N/A

**iii Institutional Data and Safety Monitoring Board**

The Data Safety and Monitoring Board (DSMB) will meet and be provided interim results and data regarding reported adverse events after 50% of planned enrollment is achieved (120 women enrolled). Members of the DSMB include: Jeffrey Peipert, MD, PhD; Emily Jungheim, MD, MSCI; Jenifer Allsworth, PhD.

**iv Independent Data and Safety Monitoring Board-** N/A

## 3.c Definitions of Adverse Events

An adverse event will be defined as any undesirable experience which occurs while taking the study drug, whether or not the event is attributable to taking the drug.

## 3.d Classification of Events

All adverse events reported by the participant or her physicians will be recorded as part of the study. They will be further investigated if necessary and categorized by their relationship to the study drug, severity, and expectedness.

**i Relationship**

*Unlikely to be related to the study drug*: These include events that have not been previously described to be associated with the study drug; events that have a temporal relationship with study drug administration which makes causation highly unlikely; known biological mechanisms for the event suggest that the likelihood that the study drug caused the event is low.

*Possibly related to the study drug:* These events are not previously reported to be associated with the study drug, but the temporal relationship between study drug administration and the event and a plausible biological mechanism suggest that there is a possible relationship between the study drug and the event.

*Likely to be related to the study drug:* These events have been previously reported in prior studies evaluating the use of vaginal progesterone (vaginal irritation, vaginal discharge, vaginal infection, headache, nausea). Of note, however, the side effects recorded in prior studies have not significantly differed among those women who received progesterone and those who received placebo.

**ii Severity**

*Mild:* Vaginal irritation, infection or discharge; headache, nausea

*Severe:* Allergic reaction, congenital anomaly, maternal or fetal death, a life-threatening event or disability

### iii Expectedness

*Common*: A common event occurring in pregnancy regardless of the probability of its relationship with the study drug (i.e.; vaginal irritation, infection, or discharge; headache, nausea, vomiting).

*Rare:* A rare event in pregnancy regardless of the probability of its relationship with study drug (i.e.; allergic reaction, congenital anomaly, death or disability).

## 3.e Data Collection Procedures for Adverse Events

Every two weeks, a study coordinator will discuss and record any side effects reported by the participant. In addition, the participant will fill out one-page questionnaire form with questions regarding study drug compliance and possible side effects.

## 3.f Reporting Procedures

All adverse events will be reviewed by the Data Safety and Monitoring Board (DSMB) at the midpoint meeting. Any severe event will be reported the Human Research Protection Office at Washington University and the DSMB immediately.

## 3.g Adverse Event Reporting Period

All severe adverse events will be reported to the Human Research Protection Office and the DSMB members immediately for review. Any other adverse event will be reviewed by the DSMB at the midpoint of the study (50% enrollment). Participants can report adverse events at any time during enrollment in the study and up to six weeks postpartum.

## 3.h Post-study Adverse Event

Adverse events can be reported by participants up to six weeks postpartum. It is highly unlikely that any new events after that time period are related to participation in the study.

# *F4 Study Outcome Measurements and Ascertainment*

*Primary Outcome:* Delivery before 37 weeks' gestation

*Secondary Outcomes:*

- Delivery prior to 34 weeks' (evaluated among women enrolled ≤ 31 6/7 weeks' gestation)
- Delivery within two weeks of randomization
- Total number of days of pregnancy prolongation
- Infant birth weight
- Neonatal intensive care unit admission
- Chorioamnionitis
- A composite neonatal outcome comprising neonatal death, respiratory distress syndrome, bronchopulmonary dysplasia, severe (grade III/IV) interventricular hemorrhage, necrotizing enterocolitis, and sepsis.

The outcomes of interest will be ascertained from the participant's medical record and her infant's medical record during the hospitalization at the time of birth.

# G Statistical Plan

## *G1 Sample Size Determination and Power*

We plan to enroll 120 patients, with a 1:1 allocation to treatment and placebo. This sample size is adequate to detect a one-half reduction in the primary outcome, delivery before 37 weeks, assuming an alpha of 0.05, 80% power, and a baseline risk of preterm birth of 60% in the population of women with arrested preterm labor (Lyell 2008). A recent query of admissions to Barnes-Jewish Hospital revealed that 730 women were evaluated for threatened preterm labor each year during the last 3 years. Although we suspect that <50% of women will meet inclusion criteria, we estimate that the study will be completed within 2 years.

## *G2 Interim Monitoring and Early Stopping*

The Data Safety and Monitoring Board (DSMB) will be provided interim results and data regarding reported adverse events after 50% of planned enrollment is achieved (120 women enrolled). The data will be presented in a blinded fashion with regards to the drug exposure of each group. At the request of the DSMB, the study will be unblinded for further review. It is at the discretion of the DSMB to request early cessation of the trial. During conduct of the study, any severe adverse events will be immediately reported to the DSMB and HRPO.

## *G3 Analysis Plan*

All analyses will be performed using the intention-to-treat principle. Outcomes will be compared among women allocated to progesterone therapy and women who received placebo.

## *G4 Statistical Methods*

Baseline characteristics of women randomized to progesterone will be compared with those of women randomized to placebo. Rates of delivery before 37 weeks' gestation will be compared among the groups using the Chi-square test. A secondary analysis of women enrolled ≤31 $^{6}/_{7}$ weeks' gestation will evaluate rates of delivery before 34 weeks. Additional outcomes that will be evaluated (by using Chi-square test for binary outcomes and the Student t-test for continuous outcomes) include delivery within two weeks of randomization, total number of days of pregnancy prolongation, infant birth weight, neonatal intensive care unit admission, chorioamnionitis, and a composite adverse neonatal outcome comprising neonatal death, respiratory distress syndrome, bronchopulmonary dysplasia, severe (grade III/IV) interventricular hemorrhage, necrotizing enterocolitis, and sepsis. Length of time from enrollment to delivery will be analyzed using Kaplan-Meier curves and the Cox proportional hazards model.
All analyses will be performed using the intention-to-treat principle.

Microbial sequencing will be performed on the vaginal swabs using well established 16s RNA sequencing procedures at the Genome Institute at Washington University.

Sequenced data will be processed to compare the vaginal microbiome in those who received the placebo to those who received vaginal progesterone.

We will use a multivariate model of species abundance distribution (SAD) or ranked abundance distribution (RAD) of vaginal microbiomes obtained from taxonomical assignment of 16S rRNA genes samples, with Dirichlet-Multinomial (DM) distribution and its generalizations. SAD/RAD is classified as a multivariate community descriptor of intermediate level of complexity providing more information than univariate community descriptors such as species richness, Shannon evenness, and Simpson diversity. To compare case and control groups we will apply the two sample RAD-mean test comparison. We will also apply a logistic regression model to predict PTB as a function of the vaginal microbiome.

### *G5 Missing Outcome Data*

Women with missing primary outcome data, delivery before 37 weeks' gestation, will be excluded from analysis. However, information regarding missing data will be reported in the manuscript.

### *G6 Unblinding Procedures*

After the final participant in the study has delivered, the study will be closed. At that time, the randomization log maintained by the pharmacists during the study which links the participant identification number to the allocated study drug will be released to the research team. The study drug information for each participant will be added to the study database for analytic purposes.

## H Data Handling and Record Keeping

### *H1 Confidentiality and Security*

- All conversations with participants regarding enrollment in the study and the consent process will occur in a private hospital room. Follow-up visits as an outpatient will be conducted within the privacy of an office or examination room.
- All data collected on participants for the purpose of the study will be stored in a password-protected database on the password-protected computer in an investigator's locked office. Information stored in the database will be coded and the key for the code will be stored in a separate location.
- Research identification codes will be utilized in this study to link participant information in the study database. These research identification codes will be unrelated to participant name, date of birth, medical record number, or any other form of personally identifiable information. The spreadsheet linking the participant name with her research identification code will stored in a separate database on a password protected computer. This spreadsheet will be destroyed at the completion of the study.
- Vaginal swabs collected from women who agree to provide these biospecimens for future research will be labeled using the study research code so that the sample is de-identified. The swabs will be stored as part of the Women and Infants' Health Specimen Consortium.

## *H2 Training*

A thorough review of study procedures will be reviewed with the study coordinator prior to beginning enrollment in the study.

## *H3 Case Report Forms and Source Documents*

N/A

## *H4 Records Retention*

The de-identified database will be maintained for future research. Only women who consent to the collection of vaginal swab specimens will have biospecimens stored for future research. Data regarding whether a specimen was collected from a particular woman will be recorded in the study database.

## *H5 Performance Monitoring*

N/A

# I Study Monitoring, Auditing, and Inspecting

## *I1 Study Monitoring Plan*

The Data Safety and Monitoring Board will evaluate interim results and reported adverse events. The members will meet at the midpoint of the study when 50% enrollment has been achieved (120 women).

## *I2 Auditing and Inspecting*

Study records including databases will be well-maintained and organized. If auditing or inspection of the study is requested by organizations with the appropriate authority, the required information will be provided.

# J Study Administration

## *J1 Organization and Participating Centers*

Washington University School of Medicine & Barnes-Jewish Hospital

## *J2 Funding Source and Conflicts of Interest*

Thrasher Early Career Award (PI: Heather Frey, MD)

## *J3 Committees*

Data Safety and Monitoring Board

### *J4 Subject Stipends or Payments*

None

### *J5 Study Timetable*

Start date: 4/1/13
End date: 5/7/18

## K Publication Plan

Following completion of the trial and data analysis, a manuscript will be submitted for publication in a peer-reviewed journal.

## L Attachments

### *L1 Tables- N/A*

### *L2 Informed consent documents*

See attached

### *L3 Patient education brochures- N/A*

### *L4 Special procedures protocols- N/A*

### *L5 Questionnaires or surveys*

See attached.

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