Vaginal versus intramuscular progesterone for prevention of recurrent spontaneous preterm birth

(VIP Trial)

Aim: To determine if vaginal progesterone for the treatment of prior spontaneous preterm birth can reduce the occurrence of recurrent preterm birth over intramuscular progesterone

Background:

Preterm birth is one of the leading causes of neonatal morbidity and mortality. One of the most significant risk factors for spontaneous preterm birth is a history of a prior spontaneous preterm birth. This high risk population is thus an important target for intervention. Intramuscular progesterone (17 hydroxyprogesterone caproate) is the only FDA approved medication for the prevention of reccurent preterm birth in women with a prior spontaneous preterm birth. It was studied in a randomized controlled trial (see reference Meis 2003 attached and ACOG practice bulletin number 130 attached).

Vaginal progesterone is not FDA approved for the prevention of recurrent preterm birth, but has been found to beneficial in this regard. Da Fonseca et al (2003) found that vaginal progesterone reduced the risk of both preterm birth (<37 weeks) and early preterm birth (<34 weeks) when compared to placebo in women with a prior spontaneous preterm birth (see attached reference de Fonseca 2007). In contrast, O'Brien et al (2007) did not find that vaginal progesterone significantly reduced the rate of recurrent preterm birth compared to placebo (see attached O'Brien 2007).

A recent meta-analysis of three randomized trials comparing vaginal to intramuscular progesterone for the prevention of recurrent preterm birth in women with a prior spontaneous preterm birth found that vaginal progesterone was superior to intramuscular progesterone in prevention of preterm birth <34 weeks and <32 weeks (see attached Saccone 2016).

ACOG has provided a practice bulletin for the prevention of preterm birth. Given the data presented above, they recommend "progesterone supplementation starting at 16-24 weeks of gestation to reduce the risk of recurrent spontaneous preterm birth" but do not specify the dosage or route of progesterone administration. Given the presence of trials demonstrating efficacy for both intramuscular and vaginal progesterone in the prevention of recurrent preterm birth they provide a table (See Table 1, relevant trials highlighted) with possible formulations of progesterone for the prevention of preterm birth in women with a prior preterm birth.

Methods:

This is a prospective randomized controlled trial comparing vaginal progesterone (200mg suppository daily) and intramuscular progesterone (250mg intramuscular weekly) for the prevention of recurrent spontaneous preterm birth in women with a history of prior spontaneous preterm birth.

Patients:

Pregnant women with singleton pregnancies are eligible to enroll in the trial if they were ≥18 years old with an estimated gestational age less than 24 weeks and had a prior spontaneous preterm birth of a singleton pregnancy between 16 0/7-36 6/7 weeks and have not already initiated progesterone therapy for preterm birth prevention (ie after 16 weeks gestation; first trimester use is not a contraindication).

Patients are also required provide consent, demonstrate an understanding of the purpose of the study, and agree to the study protocol.

Exclusion criteria include: a history of an adverse reaction to progesterone; a contraindication to progesterone treatment; placenta previa or accreta; major fetal anomaly diagnosed on ultrasound or known chromosomal disorder; multifetal gestation; preterm labor, premature rupture of membranes, or clinical chorioamnionitis, at the time of enrollment

The patient may choose to withdraw from the study at any time. Treatment for prior preterm birth will continue with a progesterone agent as recommended by the patient's primary obstetric provider. Participation in the interventional trial by the investigator may happen if the investigator deems that participation is detrimental to the health of the patient or the pregnancy. Patients who meet criteria but decline to participate in the trial will be verbally consented to have their outcomes followed in an observational cohort.

Randomization and treatment groups

Patients will be randomized in a 1:1 scheme. Patients, obstetric care providers, and study investigators will not be blinded as to allocation. The vaginal progesterone group will be prescribed 200mg vaginal progesterone suppositories to be taken daily starting at 16 0/7 – 23 6/7 weeks, and continued daily until 36 6/7 weeks' gestation or delivery. The intramuscular progesterone group will be prescribed 250mg intramuscular progesterone to be administered weekly starting at 16 0/7 – 23 6/7 weeks, and continued weekly until 36 6/7 weeks' or delivery.

Drug therapies

17 hydroxyprogesterone caproate 250mg weekly intramuscular from 16 weeks -36 weeks

This medication is FDA approved for the purpose of prevention of recurrent preterm birth. Common side effects include irritation at injection site, urticaria, pruritis, nausea, increased appetite, changes in mood.

Micronized progesterone 200mg vaginal suppository daily from 16weeks- 36 weeks

This medication is not FDA approved for the purpose of prevention of recurrent preterm birth and meets all the criteria for IND exemption by the FDA:

_X_ The drug product is lawfully marketed in the United States.

_X_ It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

_X_ It is not intended to support a significant change in the advertising for the product;

_X_ It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

_X_ It is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and

_X_ It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7].

Common side effects include: vaginal discharge, irritation, breast pain, constipation, cramping, emotional lability, nausea/vomiting, fatigue, headache, decreased libido, increased appetite, abdominal distension, arthralgia, dyspareunia

Study Protocol

Screening and Enrollment

Patients with a prior spontaneous preterm birth of a singleton pregnancy between 16 0/7-36 6/7 weeks will be screened at gestational age less than 24 weeks. Gestational age is as determined by last menstrual period and ultrasound biometry before 24 weeks. Aside from route of progesterone therapy, patients will otherwise be managed as is standard of care including the recommendation for cervical length screening between 16 0/7- 23 6/7 weeks. Patients with a cerclage for any indication will remain in the study.

Patients meeting criteria are screened and enrolled by study personnel and investigators (coordinators, nurse practitioners, residents, fellows, or attendings) during prenatal care at the institution during regularly scheduled visits, consultation with Maternal Fetal Medicine, or obstetric ultrasound visit, prior

to 24 weeks. If desired, the patient may take the consent home to review it with family/friend, discuss the trial with their primary obstetrician/nurse practitioner/ midwife, and return at a later date to sign the consent with study personnel. The time limit for consenting will be up to 24 weeks gestation or starting another progesterone agent, whichever occurs first. Patients who consent will then be randomized after 12 weeks to receive either vaginal progesterone or intramuscular progesterone to be started between 16 0/7-23 6/7 weeks. Treatment will be continued until 36 6/7 weeks or delivery, whichever occurs first.

Children are not included as they are not significantly impacted by a prior preterm birth history and does not warrant additional risk if they are pregnant and <18 years of age. Imprisoned women and women with cognitive impairment will not be approached. Students or employees may be approached for the study. To reduce any possible coercion, the consent will be reviewed, and encouraged to take home with and review with someone else prior to consenting. Whenever possible, the consent will be signed with study personnel not directly related to the teaching, performance, or medical care of the patient. The patient may sign on the same day if she chooses to.

Subject fees

There is no reimbursement schedule associated with the study. Travel and medication costs will not be reimbursed, as they are part of standard treatment for routine prenatal care and prior spontaneous preterm birth. The patient's insurance company will be billed for the cost of the progesterone treatment, and both treatment methods (intramuscular and vaginal progesterone) are recommended modalities by ACOG. The patient will be responsible for any co-pays associated with medications. If insurance declines to cover the medication, though unlikely given recent experience, or the patient does not have insurance, she will be responsible for the cost of the medication. There are no additional tests/examinations that are being done solely for research purposes that would be billed to the insurance company.

Interim Contacts

Each patient will be interviewed using a predefined questionnaire every 4 weeks during routine prenatal visit or by phone call to assess medication compliance and adverse effects/events by a trained study personnel or investigator.

Preterm Labor or Preterm Premature Rupture of Membranes

If a patient develops preterm labor during the study period, she will be managed per the primary obstetric provider with the recommendation being to continue study medication until delivery. If a patient is diagnosed with preterm premature rupture of membranes, study medication will be discontinued.

Data Collection

Data to be collected from each patient include demographic characteristics, BMI, smoking status, substance abuse history, obstetric history (including number and timing of prior spontaneous preterm births, and number of prior full term deliveries), antenatal complications (including hypertensive disorder of pregnancy, gestational diabetes, preexisting hypertension or diabetes, intrauterine growth restriction), delivery outcomes (gestational age, mode of delivery), neonatal outcomes (Apgar scores, birth weight, admission to neonatal intensive care unit, neonatal morbidity), and medication satisfaction, adherence, and side effects. Demographic data will be collected through a combination of interview with the patient and the medical record. Delivery and neonatal outcomes will be assessed through the paper or medical record. Compliance will be assessed through a questionnaire.

Observational Cohort

Women who do not consent to participate in the study will be asked for verbal consent to collect data only in order to make sure their characteristics are similar to the study cohort. Collected data will include demographic information, obstetric history, medical, social, and gynecological history, and current pregnancy outcomes. 150 women will be verbally consented to be in the observational cohort, 50 at Thomas Jefferson University Hospital, 50 at Baystate Medical Center and 50 women at George Washington University Hospital.

Risk/Benefit Assessment

The risks associated with participation in the interventional trial are thought to be minimal, as both intramuscular and vaginal progesterone are both in use for the treatment of prior spontaneous preterm birth. Potential side effects/adverse events of each drug will be reviewed with the patient during the consent process. The patient will be instructed that progesterone treatment would be started regardless of participating in the trial or not, and she would receive the same care if declining participation. There may be not benefit from trial participation, but may identify a superior method to administer progesterone in future pregnant women, leading to a societal benefit.

The risk of loss of confidentiality exists in both the interventional and observational cohort. This risk is minimized by storing data on a secure online database (REDCap), using non-identifiable Study ID at the primary data collection site, and keeping all identifiable information (hard copy consents) in locked cabinets in locked offices.

Outcome Measures

Primary outcome is the incidence of preterm birth <37 weeks.

Secondary outcomes

- Maternal outcomes:
    - Incidence of preterm birth <34 weeks and <28 weeks
    - Gestational age at delivery
    - Incidence of short TVU CL <25mm
    - Mode of delivery
    - Maternal mortality
- Neonatal outcomes:
    - 5 minute APGAR score,
    - Intensive care unit admission,
    - Birthweight
    - Perinatal mortality up to 28 days of life
    - Composite neonatal morbidity (respiratory distress syndrome, grade III or IV intraventricular hemorrhage, culture proven sepsis, neonatal enterocolitis, and perinatal mortality up to 28 days of life)
- Medication related outcomes:
    - Medication side effects
    - Satisfaction with medication (5 point Likert scale)
    - Medication adherence defined as:
        - Vaginal progesterone:
            - Overall adherence: #days used/#days of treatment x 100
            - Non-adherent: ≥4 days between doses
        - Intramuscular progesterone:
            - Overall adherence: #weeks used/#weeks of treatment x 100
            - Non-adherent: ≥10 days between doses

Planned subgroup analysis for the primary outcome as well as the secondary outcomes of preterm birth <34 weeks and <28 weeks of patients with a CL<25mm versus CL≥25mm, with a history indicated cerclage vs not, and for those started on progesterone 16-20 weeks versus 20-24 weeks.

Statistical Analysis

Based on a two sided significance of 5% and a power of 80% for the primary outcome, as well as incidence of recurrent PTB 36% with IM progesterone (Meis 2003), and 50% decrease with vaginal progesterone, power calculation estimated at least 95 patients in each arm. Assuming a 15% loss to follow up, **112 patients are needed in each group**; if there is an additional ~5% loss due to exclusions that come up or other inability to randomize after consent, a total of 230 women will need to be consented to reach goal randomization.

Randomization and data collection will be done using REDCap (see section below).

Statistical analysis will be performed with SPSS 23.0

Baseline characteristics and outcome measures will be compared using student t-test for continuous variables, chi-square test for categorical variables, and Kaplan Meier survival curve for gestational age of delivery. $P<0.05$ is considered significant.

Sites

This will be a multi-center trial with the primary site being Thomas Jefferson University Hospital, and the other sites being Baystate Medical Center,George Washington University, Virginia Commonwealth University, and Ohio State University. We anticipate that 80 women will be consented from Thomas Jefferson, 80 women from Baystate, 10 women from George Washington, 50 from Ohio State University, and 10 from Virginia Commonwealth University. It is possible additional sites will be added as the trial progresses. We anticipate 5 years for completion of trial including data analysis.

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Interim Analysis/Data Safety Monitoring Board

Interim analysis will be performed after the first 112 women (50% recruitment) randomized women deliver to assess for maternal mortality and neonatal mortality as part of data and safety monitoring.

Chi square analysis will be performed with a p< .001 considered significant. Interim analysis will be under the oversight of the Data Safety Monitoring Board which includes a neonatologist (Dr. Dave Carola), Maternal Fetal Medicine Dr. Stuart Weiner), from Thomas Jefferson University. Interim safety analysis statistics will be conducted by Jordan Levine (Alexendria Health LLC, 678-907-7730, Email: Jordan@alexandria.health). The following deidentified information will be used for interim safety analysis: Study ID, randomization group number (1 or 2), Maternal mortality (Y or N) and Perinatal mortality (Y or N). None of the participants have any relation with the ongoing trial design or eventual analysis.

Adverse events, protocol deviations, and unanticipated events will be reported within 48 hours to the principle study investigator at each site who will then report them to the study PI Rupsa Boelig within 48 hours. Serious adverse events will be reported to the IRB. Participating sites will be notified if any protocol changes must be made due to unexpected AE's or SAEs within 7 business days. Monthly contact by phone or email between the primary site (Thomas Jefferson) and other sites will occur to discuss study progress, recruitment, study protocol and any of potential trial issues. If new data becomes available during the course of the trial that may affect current or past trial participants, a study investigator or coordinator will contact the patient. This will be documented in the REDCap database via Thomas Jefferson University.

In addition to an interim analysis for maternal and neonatal mortality, we will also review adverse events, protocol deviations, unanticipated events, and enrollment progress at each site and collectively every 6 months.

Data Collection and Security

Data collection will be done using REDCap database hosted by Thomas Jefferson University. Only individuals who are included as investigators or study personnel will be granted access to the database. **The REDCap database will NOT include any protected health information;** patients will be identified by a unique Study ID. There will be a separate secure database at each site linking Study ID with patient identification. User access will be granted only by the PI Rupsa Boelig. Investigators and research personnel will only have access to data entered by their respective sites, with the exception of study PI Rupsa Boelig who will have access to all the data. When study personnel/investigators are no longer part of the institution or study, Rupsa Boelig will be notified and their access to the database will be immediately discontinued.