Progesterone for the Prevention of Miscarriage and Preterm Birth in Women with First Trimester Bleeding: PREEMPT Trial

Introduction

First trimester bleeding has been associated with miscarriages and preterm births. Miscarriages are estimated to occur in 20-25% of pregnancies and preterm births are said to occur in 12% of births in the United States. The well described effects of these events include maternal morbidity and psychological distress as well as neonatal morbidity and mortality in those pregnancies that achieve a viable gestational age. Preterm infants are at greater risk for developing respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, severe neurological deficits and other disorders. In addition, preterm delivery is a leading cause of health care costs in the neonatal intensive care unit, and throughout the life of surviving infants.

First trimester bleeding is a well-established risk factor for miscarriage and prematurity. In fact, amongst women with a live intrauterine pregnancy, bleeding in the first trimester is associated with a 15% to 25% risk of miscarriage - a four-fold increase in the risk as compared to women with no first trimester bleeding. Among those pregnancies that do not result in miscarriage, the risk of prematurity is associated with a 70% increase in the relative risk as compared to women with no first trimester bleeding.

The use of progesterone has been suggested as a possible agent that may reduce the rate of miscarriage and prevent prematurity in high risk individuals. Although there is biological rational and clinical suggestion that progesterone may reduce rates of miscarriage in women with first trimester bleeding, there is an important lack of conclusive and scientifically sound evidence to support or refute the use of progesterone in the prevention of miscarriage. Similarly, there are no studies evaluating the effect of progesterone on the prevention of preterm birth in women that are at high risk on the basis of first trimester bleeding. As such, a trial is needed to recommend to clinicians the use or non-use of progesterone in women with first trimester bleeding for the prevention of miscarriages and preterm birth.

Study Objective

The objective is to evaluate the role of vaginal progesterone on the reduction of miscarriage and preterm birth in women presenting with first trimester bleeding. The ultimate aim is to reduce the very high rates of these events in pregnant women that present with first trimester bleeding.

Study Design

We will address our objective through a multi-site double-blind, randomized controlled trial with a one-to-one treatment-to-placebo randomization. Both subjects and investigators will be blinded to the treatment that is given.
Study Methods

See the following diagram that outlines the steps of this study.

Study subjects must meet the following inclusion criteria:

1. Live intrauterine singleton pregnancy with documented fetal cardiac activity.
2. Gestational age <14 weeks by crown-rump length on ultrasound
3. Presence of a perigestational (subchorionic) hemorrhage on ultrasound.

Women identified as meeting these criteria will be approached by an individual from their circle of care (primary care provider, treating nurse etc.) who will ask them whether they agree to let the research nurse discuss the study with them. If the patient agrees, the care provider will refer the patient to the research nurse, who will then approach the patient to discuss the study and implement the informed consent process. After the patient has provided consent to participate in the study, the research nurse will perform a preliminary evaluation for study eligibility and if inclusion / exclusion criteria are met, the patient will be randomized to either the experimental group (i.e. micronized progesterone 200mg suppository administered vaginally at bedtime until 34 completed weeks of pregnancy) or the placebo group (i.e. similar appearing suppository containing vehicle alone administered vaginally at bedtime until 34 completed weeks of pregnancy). At the first baseline visit the subject will be provided enough treatment packs to last her until her second visit, which is between 18 and 20 weeks. The participant will be given a package containing the allocated compound with information on use and potential side effects as well as study information including contact numbers, emails, and website for reporting of adverse events and outcomes. Interventions will be prepackaged and labeled with unique site-specific identifying numbers.

There will be an initial phone call placed to participants 2 days following their enrollment to welcome them to the study and to answer any questions or concerns they may have. The first follow-up phone call will take place at 14 weeks for evaluation of adverse events and pregnancy outcomes. The first post-recruitment visit will take place at the hospital of recruitment for Montreal Sites and at the Karma Medical Clinic for subjects recruited at that clinic. This visit, which will take place at 18-20 weeks following the patient’s scheduled ultrasound visit, will involve an evaluation of adverse events, pregnancy outcome, suppository count and documentation of ultrasound report findings. Participants will also be provided with a new supply of their allocated study treatment to last them until the end of their 34th week of pregnancy. Three additional follow-up telephone calls will take place at 26 weeks, 32 weeks and 37 weeks for evaluation of adverse events and pregnancy outcomes. A final postpartum evaluation will take place at the hospital following delivery for evaluation of maternal and neonatal outcomes. If this is not possible the final evaluation will take place over the phone 2 days following delivery. The postpartum evaluation will be corroborated with a chart review of both mother and baby 6 weeks following delivery. In cases of miscarriage, there will be a post-miscarriage follow-up phone call and chart review. The chart reviews will take place at the hospital.
**PREEMPT Trial**

**PATIENT FOLLOW-UP**

- **6-14 weeks**
  - **Patient recruitment**
    - Baseline questionnaire administered by study nurse
  - Study nurse supplies enough treatment packs to last until 18-20 week visit

- **2 days post randomization**
  - Study nurse welcome phone call

- **14 weeks**
  - Follow-up phone call from study nurse
  - Schedule next follow up visit during ultrasound

- **18-20 weeks (ultrasound visit)**
  - Follow-up visit during ultrasound by study nurse
  - Study nurse supplies enough treatment packs to last until the end of 34 weeks of pregnancy