Study Protocol and Statistical Analysis Plan

Title: Impact of a higher dose on the pharmacokinetics of 17-alpha hydroxyprogesterone caproate in obese women

NCT number: NCT03433040

Document date: IRB approved Protocol version 7 (3/2/2021)

Impact of a higher dose on the pharmacokinetics of 17-alpha hydroxyprogesterone caproate in obese women

Short title: 17OHP-C dosing among obese women

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Study sponsor: Lumara will be providing the study drug

Table of Contents

Abbreviations

17OHP-C	17 hydroxyprogesterone caproate
BMI	Body mass Index
mg	milligram
PTB	Preterm birth
USF	University of South Florida
TGH	Tampa General Hospital

Specific Aims

Prospective studies have shown that 17 hydroxyprogesterone caproate (17OHP-C) significantly decreases rates of preterm birth (PTB). Low levels of plasma 17OHP-C are associated with increased risks of spontaneous PTB. Emergency data suggest 17OHP-C may be less efficacious in obese women. Since obesity is associated with lower levels of plasma 17OHP-C, we hypothesize that higher doses of 17OHP-C may help to prevent spontaneous PTB among obese women. We propose a prospective study including a randomization of obese women with the following specific aims:

Primary Aim: Determine if a higher weekly dose of 17 OHP-C in obese women results in a higher maternal plasma levels compared with the standard 250mg weekly dose.

Hypothesis: A 500mg weekly dose of 17OHP-C will produce higher maternal plasma levels in obese compared to the standard 250 mg dose.

We will randomly assign obese women with a prior history of spontaneous PTB to 250 mg or 500 mg weekly doses of 17OHPC, and compare mean plasma levels of 17OHP-C in obese women receiving 500 mg to obese women receiving 250 mg as well as non-obese women receiving 250 mg.

Secondary Aim: Determine the relationship between maternal 17-OHPC levels and gestational age at delivery.

Hypothesis: Higher doses of 17OHP-C will be associated with high gestational age of delivery in obese women.

We will compare the mean gestational age at delivery of obese women receiving 250 mg to obese women receiving 500 mg as well as non-obese women receiving 250 mg.

B. Background

PTB continues to be the leading cause of neonatal morbidity and mortality in the United States, affecting 9.57% of all births in 2014. [1, 2] The impact of PTB is far reaching. Consequences of PTB include numerous detrimental short and long-term outcomes for the premature infant, [3-6] impaired maternal and paternal psychological health, [7, 8] and steep personal and societal costs. [9-13] Several strategies have been

introduced to decrease rates of PTB. In addition to nationwide campaigns aimed at reducing iatrogenic preterm deliveries, [14] national organizations have issued protocols outlining appropriate candidates for 17 alpha hydroxyprogesterone caproate (17OHP-C), vaginal progesterone, and cerclage – all of which have been shown to decrease rates of PTB among specific populations.[1, 15, 16]

Among women with a history of a spontaneous PTB, 17OHP-C has been shown in a randomized trial to decrease the risk of a subsequent PTB by 33%. In this study including 463 women, the number needed to treat to prevent one PTB prior to 37 weeks was only 5 to 6 women. [17] In addition to effectively reducing the recurrence of PTB, mathematical modelling has demonstrated that administration of 17OHP-C to women with a prior spontaneous PTB could lead to future cost savings.[18, 19] The individual and societal benefits of 17OHP-C are clear. However, questions remain about optimal dosing of 17OHP-C among obese women. As the prevalence of obesity in the United States exceeds 35%, optimizing interventions to prevent PTB in this population has significant public health implications.

Obesity causes several physiological changes than can impact medication pharmacokinetics. Some changes include increased blood volume and increased cardiac output which can lead to varied distribution patterns and potentially a change in medication absorption.[20, 21] Caritis et al. demonstrated that body mass index (BMI) was inversely correlated with trough plasma 17OHP-C concentrations and the area under the plasma concentration versus time curve. These data suggest that higher dosing may be needed for obese patients.[22] A similar conclusion was reached in a secondary analysis of a Maternal-Fetal Medicine Unit Trial. Among 443 women, treatment with 17OHP-C in obese women or with a weight of > 165 pounds did not appear to decrease the rate of PTB.[23] Moreover, additional studies have shown that low plasma 17OHP-C levels [24] and a maternal pre-pregnancy BMI of ≥ 25 kg/m^2 are associated with higher rates of spontaneous PTB.[25]

Conversely, other retrospective studies report that spontaneous PTB rates among normal weight as compared to obese women are similar suggesting that current 17OHP-C dosing guidelines are sufficient.[26] Literature supporting optimal dosing of 17OHP-C for obese patients is lacking and current clinical studies report conflicting information.

C. Study Design

Prospective three arm study of women with a prior spontaneous PTB. Non-obese women will receive the standard 250 mg weekly dose of 17 OHP-C while obese women will be randomly assigned to the standard (250 mg) or higher dose (500 mg). The resulting three groups will consist of:

1. Normal weight women on 250mg 17OHPC
2. Obese women on 250mg 17OHPC
3. Obese women on 500mg of 17OHPC

a) Subjects

Pregnant patients receiving prenatal care at these University of South Florida (USF) and Washington University affiliated locations will be eligible:

- Genesis Healthpark
- South Tampa Center
- Washington University (Barnes Jewish Hospital) in St. Louis

b) Inclusion / Exclusion Criteria

Inclusion Criteria

- Pregnant women, with a singleton gestation
- Ages 18 – 55
- Able to read and write in English and / or Spanish
- History of spontaneous PTB
- Obesity (≥ 30 kg / m^2) vs non-obese groups (18 – 29.9 kg / m^2) defined by first documented body mass index at an office visit
- Gestational age between 12 weeks, 0 days and 24 weeks, 6 days of gestation
- An ultrasound before 24 + 6 weeks gestation to confirm dating and to rule out major fetal anomalies
- Willing to have weekly injections at the physician's office
- The newborn will be enrolled on the mothers consent for chart review only

Exclusion Criteria

- Multifetal gestation
- Known fetal anomaly
- Current progesterone treatment
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
- Current or history of thrombosis or thromboembolic disorder
- Current anticoagulation
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy

- Cholestatic jaundice of pregnancy
- Liver tumors, benign or malignant, or active liver disease
- uncontrolled hypertension (controlled hypertension is eligible)A seizure disorder
- Current or planned cervical cerclage
- Plan to deliver elsewhere

c) Research Design and Methods

Initial Enrollment: Pregnant patients receiving prenatal care at one of the USF affiliated sites or Washington University in St. Louis sites who report a history of a PTB will be approached by the research nurse. The research nurse will explain the study, review inclusion/exclusion criteria with the patient, and invite interested potential study candidates to sign a medical records release so that records from the previous PTB can be reviewed. If the medical records confirm the birth of a previous PTB was of a live born singleton gestation between the gestational ages of 20 weeks and 36 weeks and 6 days then the patient will be invited to participate in the study. At that time the informed consent form will be thoroughly reviewed with the patient, and if the patient desires to enroll, she will provide informed consent to enroll in the study. Consecutive women with normal BMI or obese women meeting the inclusion criteria will be approached to avoid selection bias.

Randomization: will occur at the time of enrollment. The randomization will be computer generated. Randomization envelopes indicating the randomization arm will be prepared ahead of time and the next consecutive envelope will be used at time of enrollment.

Preparation of study drug: Participants in the 250 mg of 17OHP-C arm will receive 1cc weekly injection of the study drug while the obese women receiving 500 mg of 17OHP-C will receive 2cc weekly injection during the study period. The clinical investigators will not be blinded to the study arm of participant [a) to track which patients receive which dose and b) so that the dose can be given to the treating physician should an adverse event occur], but the lab performing the pharmacokinetics studies will be blinded.

Administration of study drug: Administration of study drug will be performed by clinic staff in the office to ensure medication compliance. Although the patients will be enrolled into the study from as early as 12 weeks in preparation for the intervention, study medications will not be started until at least 16 weeks. The medication will be administered from between 16+0 weeks and 24 +6 weeks until 36 + 6 weeks gestation or until in preterm labor with advanced dilatation/delivery.

If the participant has already received the first prescription but has not yet taken any doses they would still be eligible to participate. They would not be able to return the medication to the pharmacy or

donate the medication. They could use their medication and then the remainder of the medication would be provided by the study.

Timeline of study visits: At the enrollment visit, a maternal blood draw to determine baseline 17P levels will be completed. Participants will then have the weekly visits with their obstetric care provider for the administration of the 17OHP-C injections, with the dose determined by the study arm to which they were allocated. They will also continue to have their scheduled prenatal care with their obstetric provider.

In addition to the routine prenatal care there will be Pharmacokinetic studies as described below.

Pharmacokinetic studies: Sampling schedule in order to investigate the pharmacokinetics of 250 mg 17OHP-C weekly as compared to 500 mg 17OHP-C weekly in obese women as well as 250 mg in non-obese women will be performed as follows:

- Using principles described by Caritis et al., four completed weeks of 17OHP-C therapy is required prior to sampling anticipating that steady state will be achieved by this time point.
- Follow-up sampling will be performed at these three time points:
- Sample #1: 20 – 22 weeks gestation
- Sample #2: 27 – 29 weeks gestation
- Sample #3: 34 – 36 weeks gestation

The blood draws will occur immediately before the weekly injection in order to obtain trough 17-OHPC levels.

Blood will be stored for future analysis into the use of 17OHP-C and preterm birth. The blood stored for future research will not contain any identifying information and will only contain the individual patient randomization number and the time (gestational age) when it was drawn.

Data Collection: Socio-demographic data of all enrolled subjects will be collected. These will include: maternal age, height, weight and body mass index (BMI), smoking, alcohol, socioeconomic status, ethnicity, parity and coexisting maternal medical disorders, previous and current pregnancy information, concomitant medications, and ultrasound examinations. While having the injections the site of the injection administration will be collected, and date and time of administration.

Following delivery information from the delivery will be collected (pregnancy complications, type of labor, mode of delivery, delivery complications, gestational weight at delivery, birth weight, Apgar scores, cord blood gases, nursery admission and discharge information). Newborn outcome (respiratory distress, intraventricular hemorrhage, hypoglycemia, necrotizing enterocolitis, periventricular leukomalacia, seizures) and including any neurological assessment will also be collected.

d) Outcomes

a. Primary Outcome: Mean trough levels of 17-OHPC in the three groups.

b. Secondary outcomes of interest:

- mean 17OHP-C plasma concentrations,
- average peak concentration (Cmax)
- half-life of 17OHP-C
- absorption, metabolism, volume of distribution, apparent clearance of 17OHP-C
- Gestational age at delivery
- Preterm birth <37, 34, 32, 28 weeks

e) Data analysis

a. Sample Size Calculation:

We estimate the sample size for the study based on the primary aim and a number of assumptions:

- Trough concentrations (before next dose) for analysis[28]
- Mean trough in normal weight women=11.0ng/mL (sd 5.0)[28]
- Mean trough in obese women receiving 250mg =6.4 ng/mL (sd 4.0); assumed to be the dose below which efficacy is suboptimal[28]
- Mean trough in obese women receiving 500mg =11.0 (sd 5.0); double dose assumed to return concentration to that for 250mg dose in normal weight women
- Alpha=0.05/2=0.025 (Bonferroni correction for 2 comparisons [normal 250mg vs obese 250mg and obese 500mg vs obese 250mg])
- Beta=0.02, Power=0.80
- Drop out rate=10%.

Sample size:

Based on the above assumptions we will enroll a total of 63 women with a prior history of spontaneous PTB (21 non-obese women, and 42 Obese women randomly assigned to 250 mg (n=21) or 500 mg (n=21) of weekly 17 OHP-C.

The breakdown of enrollment between University of South Florida affiliated sites and the Washington University in St. Louis affiliated sited is:

USF - 28 participants (6 non-obese women, and 22 Obese women randomly assigned to 250 mg (n=11) or 500 mg (n=11)

Washington University in St. Louis – 35 participants (15 non-obese women, and 20 Obese women randomly assigned to 250 mg (n=10) or 500 mg (n=10)

b. Data Analyses

The Student's t-test or Wilcoxon rank sum test will be used to compare levels of 17OHP-C and other continuous outcomes in obese women on 250 mg to obese women on 500 mg and to non-obese women on 250 mg. Categorical outcomes will be compared using the chi-squared or Fisher's exact test as appropriate.

Because this is a pilot study, the primary criterion for significance ($p<0.05$) will not be adjusted for multiple comparisons, in order the avoid missing a potentially significant effect. However, the secondary criterion will be $P<0.025$ (adjusted for the 2 comparisons).

f) Feasibility

a. *Potential Pitfalls*: There is the potential to lose women to follow up due to the prospective design of the study. Several methods to improve study enrollment will be employed. First, 17OHP-C free of charge to the patients will be an incentive for enrollment. Second, the use of dedicated study staff will provide long-term continuity, and with whom the patient will develop rapport.

b. *Training*: Before enrolling patients, all study staff will be trained on the study protocol, inclusion criteria, exclusion criteria, specimen collection, data collection and entry.

c. *Leadership*: Successfully completing a prospective randomized trial is a challenging task. The experienced leadership of Dr. Charles Lockwood, Dr. Anthony Odibo and Dr. Tuuli will ensure that obstacles encountered during the course of the trial are addressed in a constructive manner to continue moving forward with the project in a timely manner.

g) Timeline

Our goal is to complete the study within 1.5 years (18 months) including time to obtain the needed IRB approval, finalize protocol, recruit and start data analysis.

Study Timeline

Project Period (months)	**0 - 3**	**4 - 16**	**16 - 18**
Protocol development & IRB			
Subject recruitment			
Data collection & management			
Data analysis			
Drafting of manuscript & reports			

h) Ethical Aspects of the Proposed Research

a. Human subjects' protection: All investigators will have completed Human Subjects' Protection training and their certification will be current. Investigators will explain the research and participation in the study in clear and simple language to ensure it is thoroughly understood by potential participants. Patients will be informed that they do not have to participate in the research, and their choice will not affect or alter their clinical care. This will be reinforced when informed consent is signed. Patients will be informed that they can withdraw their consent to participate at any time. A patient's capacity to understand and provide informed consent will be assessed when consent is obtained. If an investigator assesses that a patient does not understand the research or her decision, or the patient appears to be coerced, the investigator will make further assessments and discuss the situation with the PI to develop a management plan.

b. Potential risks:

    a. While every effort will be made to ensure protection of confidentiality, breach of confidentiality is a potential risk. To minimize this risk, a master list will be maintained linking the study ID to the patient data. This list will be doubly password protected (the computer and the file). The data will be also be in a double password protected file (the

computer and the file). Only members of the research team will have access to the research information.

b. Blood draw: there may be some discomfort, bruising and /or minor bleeding at the site of the needle insertion. There is a very small risk of infection at the blood draw site and occasionally there may be light headedness, nausea and feeling faint.

c. Intramuscular injection: there may be some redness, swelling, slight bleeding and minimal pain at the injection site. Rarely there may be swelling or inflammation.

d. 17 OHP-C: injection site irritation (pain, rash, irritation, nodules, generalized swelling, hypersensitivity, warmth), allergic reactions (hives, urticarial, pruritus, facial swelling), digestive problems (nausea, diarrhea, vomiting), urinary tract infection, fever, fatigue, hot flashes, headaches and dizziness, respiratory problems (dyspnea, chest infection), depression and anxiety, decreased glucose tolerance, fluid retention, jaundice, and deep vein thrombosis/ pulmonary embolism.

c. Potential benefits

a. The potential benefits of enrolling in the study include free administration of a drug that has been shown to decrease the risk of PTB by 33%.

b. Additionally, for the patients in the 500 mg 17 alpha hydroxyprogesterone caproate group, there is the potential benefit that it may decrease the rate of PTB more than the current regimen.

d. Costs and Compensation: Women will receive free 17OHP-C as part of the protocol to enroll in this study.

e.

i) Safety Monitoring Plan

A safety monitoring plan will be established to review data from both recruitment sites. Washington University in St Louis will form their own monitoring plan to review the study on an ongoing basis.

At USF, the study PI and the study coordinator will review the data on an on-going basis, including paying special attention to women enrolled in the study with a diagnosis of depression to ensure that this does not worsen.

The PI at USF and Washington University in St Louis will follow up on a regular basis reviewing the enrollment and any safety issues.

On a 6 monthly basis, there will be a conference call between members of the study team at USF and members of the study team at Washington University in St Louis**.**

We will pay specific attention to edema, jaundice, blood sugar, and blood pressure.

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Addendum 1

Summary Table of Studies with dosing differences.

Author *Journal* Year	Patient Population	HPC Dosage and administration	Adverse Effects
Levine *West J Surg* 1964	30 women with h/o ≥ 3 miscarriage	**500 mg per week** at enrollment < 16 weeks to 36 weeks GA	*"No significant undesirable manifestations occurred in the mothers, and the babies showed no evidence of hormonal effects."*
Hauth *AJOG* 1983	168 active-duty military women randomized to HPC or placebo (78 women declined to participate, but were assessed)	**1,000 mg per week** 16-20 weeks GA	No significant differences in maternal outcomes, perinatal mortality or infant morbidity, except the group that declined to participate had a statistically significantly lower rate of pregnancy-induced HTN
Facchinetti *AJOG* 2007	60 women with PTL randomized to HPC or observation	**341 mg 2x/week** between 25-33 weeks GA	*"None of the women reported adverse events that were linked apparently to the treatment."*
Rozenberg *AJOG* 2012	188 women with PTL randomized to HPC (or not)	**500 mg 2x/week** between 24-31 weeks GA	*"No increase in either congenital anomalies or other potential adverse effects was observed among mothers or infants exposed to 500 mg of 17P repeated twice weekly, compared with controls."*
Senat *AJOG* 2013	165 women with twin pregnancy with short cervix randomized to HPC or not	**500 mg 2x/week** between 24-31 weeks	Statistically significant increase in the rate of PTB < 32 weeks in HPC group; no other statistically significant difference between 2 groups