IRB-HSR PROTOCOL

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB-HSR On-line training and the IRB-HSR has been notified.
6. That all personnel working on this protocol will follow all IRB-HSR Policies and Procedures as stated on the IRB-HSR Website http://www.virginia.edu/vprgs/irb/ and on the School of Medicine Clinical Trials Office Website: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training , experience or credentialing to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
10. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
19. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time.
20. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.
21. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study.

22. No data/specimens may be taken from UVa without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.
23. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Investigators Experience

Dr. McCartney (Principal Investigator) has 12 years of experience performing clinical research in the field of reproductive neuroendocrinology. He has extensive experience with frequent sampling protocols, procedures of the Clinical Research Unit, and LH pulse analysis—both in adolescent girls and adult women. He was/is intimately involved with GCRC protocols JCM001 (successfully completed) and CRM001 (IRB-HSR# 13368; ongoing), which are very similar to the protocol proposed herein.

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

Department Chair

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol.
The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator

Brief Summary/Abstract

The rapidity with which progesterone slows LH (and by inference GnRH) pulse frequency in women is unclear. We hypothesize that progesterone slows LH pulse frequency within 10 hours. We propose to assess this further with a randomized, cross-over, placebo-controlled study. Regularly cycling women without hyperandrogenism will be admitted to the Clinical Research Unit on cycle day 5-9 (mid-follicular phase) for a frequent sampling study. Beginning at 0900 h, blood for LH, FSH, estradiol, progesterone, and testosterone will be obtained over a 10-hour period. Either oral micronized progesterone (100 mg p.o.) suspension or placebo will be administered at 0900 h. During a subsequent menstrual cycle, subjects will undergo another study identical to the first except that oral progesterone will be exchanged for placebo or *vice versa* in accordance with a crossover design. The primary endpoint of interest is LH pulse frequency; we will compare LH pulse frequency after progesterone administration to LH pulse frequency after placebo administration.

Background

Through this study, we seek to assess the validity of an important assumption in our overall hypothesis regarding how cyclic ovulation is established during puberty—namely, that progesterone acutely reduces luteinizing hormone (LH) pulse frequency.

Gonadotropin-releasing hormone (GnRH) stimulates LH and follicle-stimulating hormone (FSH) synthesis and secretion from the same gonadotrope cell; nonetheless, LH and FSH levels change differentially throughout ovulatory cycles, with FSH predominance in the early follicular phase and LH predominance in the late follicular phase. These variations in gonadotropin secretion result in part from different patterns of pulsatile GnRH stimulation, with high GnRH pulse frequencies favoring LH synthesis/secretion and low GnRH pulse frequencies favoring FSH synthesis/secretion (1). Thus, an ability to reduce GnRH pulse frequency is important for the normal cyclic patterns of LH and FSH.

Progesterone appears to be the primary effector of GnRH pulse frequency slowing. GnRH pulse frequency slows coincident with progesterone increases in the luteal phase, and administration of progesterone to women during the follicular phase also slows GnRH pulse frequency (2). Progesterone's ability to slow GnRH pulse frequency appears to require the permissive presence of estradiol, possibly reflecting estradiol's ability to induce hypothalamic progesterone receptors (3). However, the rapidity with which progesterone suppresses GnRH pulse frequency in women remains unknown.

Changes of GnRH pulse frequency are also seen during puberty. Specifically, early puberty is marked by relatively high LH (and by inference GnRH) pulse frequency at night, with slowing of LH pulse frequency during the day. The cause(s) of these diurnal changes in GnRH pulsatility is (are) unclear, but diurnal changes of sex steroids, which also occur during this time, may play an important role. Overnight increases of testosterone and estradiol occur in pubertal boys and girls, respectively. Estradiol infusion in peripubertal girls (4), in addition to infusions of either testosterone (5, 6) or estradiol (7) in peripubertal boys, mitigates nocturnal increases in LH pulsatility. Moreover, in contrast to diurnal changes of LH and estradiol in normal pubertal girls, age-matched girls with gonadal dysgenesis exhibit elevated LH pulse frequencies at all time periods (8, 9). Thus, diurnal changes of sex-steroids may direct diurnal changes (i.e., daytime slowing) of GnRH pulse frequency during puberty.

Since progesterone is the primary effector of GnRH pulse frequency slowing in adult women, and given that progesterone increases ~2.3-fold overnight in early pubertal girls (10), *we have hypothesized that progesterone is a major effector of diurnal (daytime) GnRH pulse frequency slowing in peripubertal girls*. We have considered the possibility that diurnal changes of progesterone during puberty could alter GnRH pulse frequency in "real-time," with morning increases of progesterone "immediately" suppressing GnRH pulse

frequency. However, the rapidity (over hours to days) with which progesterone slows LH pulse frequency in normal women remains unknown. *This is a critical point: for the above hypothetical model to be viable, these sex steroids would have acute actions, effecting GnRH pulse frequency changes over hours rather than days.*

To address this issue, our group first performed a study in adults (11). Eight normally cycling women were pretreated with transdermal estradiol patches and then admitted to the GCRC. (Pre-treatment with estradiol was given to ensure adequate hypothalamic progesterone receptors.) We administered a single dose of progesterone at 1800 h and monitored changes (before vs. after progesterone) of LH pulse characteristics. Each subject also underwent a GCRC admission where placebo was administered at 1800 h. The 10-hour mean progesterone concentration increased from 0.6 ± 0.1 ng/ml before progesterone (0800-1800 h) to 3.9 ± 0.3 ng/ml after progesterone administration (2200-0800 h). LH pulse frequency decreased significantly after both progesterone and placebo administration, with no significant difference between progesterone and placebo. (These changes after progesterone and placebo actually reflect sleep-wake differences, which have been previously described.) Also of interest, progesterone markedly and significantly increased both LH pulse amplitude and mean LH in this study—a reflection of progesterone positive feedback. We concluded that in estradiol-pretreated women in the late follicular phase, *nocturnal* LH pulse frequency is not acutely (within 12 hours) influenced by progesterone administration.

The apparent absence of rapid progesterone-induced slowing of LH frequency in the adult study above is in contrast to animal studies, which suggest a rapid (within 2-6 hours) decrease in LH and GnRH pulse frequency after progesterone administration. For instance, in ovariectomized but estradiol-replete ewes, progesterone dramatically suppresses GnRH pulse frequency over 12 hours; this effect appears to begin within 2 hours and is blocked by the progesterone-receptor antagonist mifepristone (12). Similarly, in bovine females, changes in LH pulse frequency are observed within 6 hours of altered progesterone concentrations (13).

Of great interest, several lines of evidence suggest the possibility that sleep-related LH frequency is resistant to negative feedback by progesterone, but that LH frequency while awake may remain rapidly suppressed by progesterone (14). For example, a recent study by our group (15) was performed to evaluate the effect of progesterone on LH pulse frequency in early to mid-pubertal girls. We studied 18 non-obese, non-hyperandrogenemic Tanner 1-3 girls. Frequent sampling was performed from 1900 to 0700 h. Five subjects received oral progesterone (25-50 mg at 1600 and 2000 h), while the remainder did not. In contrast to controls, girls receiving progesterone exhibited no LH pulses during waking hours, while nighttime (2300-0700 h) LH frequency was similar. Based on this study, *we concluded that exogenous progesterone acutely (within 3-7 hours) suppresses daytime, but not nocturnal, LH pulse frequency in early to mid-pubertal girls, suggesting that GnRH pulse frequency is differentially regulated by progesterone depending on sleep status*.

In support of the above notion, two studies by Loucks and colleagues suggest that dietary restriction slows daytime—but not nighttime—LH pulse frequency in the late follicular phase (16, 17). This suggests that daytime and nighttime LH frequency may be differentially affected by experimental maneuvers.

On the basis of the above, we considered the possibility that *daytime* (or non-sleep-associated) LH frequency is acutely responsive to changes in P concentrations in women, even though nighttime frequency is not. This formed the basis for IRB-HSR 13368, which involved a protocol identical to that in reference 11 (including estradiol-pretreatment and study in the late follicular phase) except that the timing of the sampling and progesterone (and placebo) administration is altered by exactly 12 hours (i.e., progesterone and placebo are administered at 0600 h instead of 1800 h). This study was designed to test whether or not progesterone suppresses *daytime* LH pulse frequency within 10 hours in estradiol-pretreated women in the late follicular phase. Preliminary data to date suggests that daytime LH frequency may not be acutely altered by progesterone, although we again see that LH pulse amplitude and mean LH increases markedly within 4 hours of progesterone administration. This latter phenomenon is a reflection of progesterone positive feedback,

which occurs in the setting of gonadotrope priming with high estradiol concentrations (18-20). Indeed, this phenomenon is important for the full expression of the midcycle (preovulatory) LH surge.

The data from IRB-HSR 13368 are important in their own right, and this study will continue until completion. However, we are now concerned that this study (IRB-HSR 13368) may possibly include two separate but related confounding factors: (a) estradiol pretreatment and (b) study in the later follicular phase. That is, we are likely studying the effects of progesterone in a hormonal milieu that is similar to the preovulatory phase of the menstrual cycle. Thus, we may be primarily assessing the acute positive feedback effects of progesterone—which may occur only in the setting of high (preovulatory) estradiol concentrations—rather than the acute negative feedback effects of progesterone. For this reason, we now propose a protocol to assess the acute effects of progesterone on LH pulse frequency *in the midfollicular phase in women who have not received pretreatment with exogenous estradiol*.

This study is important for a more thorough understanding of normal female reproductive neuroendocrine physiology. Perhaps more importantly (from our perspective), it is imperative that we fully assess the validity of this important assumption in our overall hypothesis regarding how cyclic ovulation is established during puberty.

Hypothesis to be Tested

We hypothesize that administration of progesterone to normally cycling adult women during the follicular phase will result in a demonstrable suppression of LH (and by inference GnRH) pulse frequency within 10 hours.

Study Design: Biomedical

1. Will controls be used?

This is a cross-over study, so subjects will serve as their own controls.

2. What is the study design?

Double-blind until data analysis (progesterone concentrations are measured, which will disclose whether progesterone or placebo was given).

3. **Does the study involve a placebo?** Yes.

►IF YES, provide a justification for the use of a placebo

LH secretory characteristics can be influenced by various factors such as time of day, stress, etc. Thus, defining LH secretory characteristics in the absence of progesterone is important for valid inference regarding the effects of progesterone.

Human Participants

Ages 18-30 y
Sex Female only
Race All races
Subjects- see below
1. Provide target # of subjects (at all sites) needed to complete protocol.

We aim to complete study on 12 subjects.

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

A 33% completion rate (for both admissions) is expected.

3. How many subjects will be enrolled at all sites? Up to 36

4. How many subjects will sign a consent form under this UVa protocol? **Up to 36**

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

- Subjects will be healthy women with regular menstrual cycles and no evidence of hyperandrogenism.
- Subjects will be 18-30 years old; we use a cutoff age of 30 years because age-related alterations in the hypothalamic-pituitary-ovarian axis is uncommon before age 30 years.
- Subjects will be willing to strictly avoid pregnancy (using non-hormonal methods) during the time of study and must be willing and able to provide informed consent.

2. List the criteria for exclusion

- Pregnancy
- Lactation
- History of allergy to progesterone
- BMI < 18 kg/m^2 or > 30 kg/m^2 (underweight and obesity can affect hypothalamic-pituitary-ovarian function)
- Excessive exercise, defined as routine and current engagement in either (a) moderate exercise (e.g., brisk walking) exceeding 14 hours per week or (a) vigorous exercise exceeding 7 hours a week.
- Clinical hyperandrogenism (primarily hirsutism)
- Abnormally elevated free testosterone or DHEAS concentration
- A previous diagnosis of diabetes, a fasting glucose ≥ 126 mg/dl
- Abnormal TSH (subjects with adequately treated hypothyroidism, reflected by normal TSH values, will not be excluded; or, for a new diagnosis of hypothyroidism, further study will at the least be delayed pending appropriate treatment) (confirmed on repeat)
- Abnormal prolactin (confirmed on repeat)
- Evidence of Cushing's syndrome by history or physical exam
- History of venous thromboembolism, breast/ovarian/endometrial cancer
- We will exclude women with any other cancer diagnosis and/or treatment (with the exception of basal cell or squamous skin carcinoma) unless they have remained clinically disease free (based on appropriate surveillance) for five years.
- Women with anemia (hematocrit < 36% and hemoglobin level < 12 g/dl) will be treated with iron for a maximum of 2 sequential months before the 1st admission and/or before the 2nd admission. If they remain anemic after 2 sequential months of ferrous gluconate (325 mg bid), they will then be excluded from further participation in the study.
- Women with a significant history of cardiac or pulmonary dysfunction (e.g., known or suspected congestive heart failure; known or suspected coronary atherosclerosis; asthma requiring systemic intermittent corticosteroids; etc.) will be excluded.

- Women with liver enzymes, alkaline phosphatase, or bilirubin > 1.5 times upper limit of normal (confirmed on repeat) will be excluded, with the exception that mild bilirubin elevations will be accepted in the setting of known Gilbert's syndrome.
- Abnormal sodium or potassium concentrations (confirmed on repeat); bicarbonate concentrations <20 or >30 (confirmed on repeat)
- Women with abnormal renal function (i.e., serum creatinine > 1.4) will be excluded (confirmed on repeat)
- Due to the amount of blood being drawn in the study, subjects with body weight < 110 pounds will be excluded from the study

3. List any restrictions on use of other drugs or treatments.

Being a study of the acute effects of progesterone on the hypothalamic-pituitary unit, subjects must not take hormonal medications (e.g., oral contraceptives) or other medications known to affect the reproductive axis for 60 days prior to the study and during the study.

Biomedical Research

1. What will be done in this protocol?

Interventions in this research study are not expected to directly benefit the volunteers, and all interventions (e.g., collection of blood, data, administration of progesterone) are being done solely to answer a research question and generate generalizable knowledge.

Studies under this protocol will be performed in normally cycling women from 18 to 30 years old. After informed consent is obtained, all potential subjects will undergo a screening history and physical exam. Subjects will need to fast for a minimum of 8 hours prior to screening blood draw. After informed consent is obtained, blood tests (≤ 16 cc) will be drawn at approximately 0800-1000 h as follows: LH, FSH, progesterone, estradiol, total testosterone, sex hormone binding globulin (SHBG), DHEA-S, beta-hCG, TSH, prolactin, CBC, chemistry and liver panels, and fasting insulin. BOD POD® will be used to measure total fat mass, fat free mass, and percent body fat. Waist and hip circumference will be measured.

If a low hematocrit and hemoglobin with a low or low-normal MCV (i.e., likely related to iron deficiency) is seen on screening labs, we will offer 1 month of iron treatment (ferrous gluconate 325 mg bid) with a subsequent recheck of hematocrit and hemoglobin. If hematocrit and hemoglobin are still low, we will offer 1 more month of iron treatment (ferrous gluconate 325 mg bid) with a subsequent recheck of hematocrit and hemoglobin. Only volunteers with a hematocrit ≥ 36% or a hemoglobin ≥ 12 g/dl (after a maximum of two sequential months of iron treatment) will be allowed to proceed with frequent blood sampling. Women with anemia will be treated with iron for a maximum of 2 sequential months before the first admission. If they remain anemic after two sequential months of ferrous gluconate (325 mg bid), they will then be withdrawn from the study.

This study follows a crossover design, with assessment of the acute effects of progesterone and placebo (individually) on LH (GnRH) pulsatility (namely frequency); subjects will be randomized to receive either progesterone or placebo during the first admission, with subsequent admission occurring during a subsequent cycle.

One to 3 days before a scheduled admission, subjects will come to the CRU for an outpatient blood draw for beta-HCG (1 cc). If 30 days have elapsed between (a) the most recent hemoglobin and hematocrit and (b) the scheduled overnight admission, a hemoglobin and hematocrit will also be drawn at this time (1 cc). Note: a hematocrit ≥ 36% or hemoglobin ≥ 12 g/dl in the month before overnight admission is required to participate in

the scheduled inpatient (frequent sampling) protocol. If three months have elapsed between (a) the subject's most recent safety labs and (b) the first CRU admission, a chemistry and liver panel will also be obtained at this time.

On cycle day 5-9 (mid-follicular phase), women will undergo a 10-h sampling study in the Clinical Research Unit (CRU). Subjects will come to the CRU no later than 0700 h (2 h prior to the start of sampling).

> NOTE: If not performed 1-3 days before the admission, we will perform beta-HCG, hemoglobin/hematocrit (as needed), and safety labs (as needed) on admission to the CRU.

Beginning at 0900 h, blood will be obtained through an indwelling i.v. forearm heparin lock over a 10-h period as follows: LH every 10 min (1 ml); progesterone every 30 min for 4 h, then every 2 h (1.5 ml). In addition, the following assays will be run in the same blood samples as progesterone: FSH, estradiol, and testosterone every 2 h. SHBG will be measured once at 0900 h.

At 0900 h (immediately after the first blood draw at 0900 h), either oral micronized progesterone suspension (100 mg p.o.) or placebo suspension will be administered (according to randomization). With exogenous progesterone, we aim to achieve mean plasma progesterone concentrations 4-8 ng/ml.

> NOTE: The randomization will be balanced (1:1 ratio), with an equal number of (a) subjects receiving progesterone during the first admission and (b) subjects receiving placebo during the first admission.

Subjects will not be allowed to sleep during the admission. We will ask women to eat only the food provided by the CRU staff.

At the completion of sampling (1900 h), volunteers will be discharged on oral iron (325 mg BID).

The second inpatient admission will be scheduled during a subsequent cycle. One to 3 days before the scheduled admission, subjects will come to the CRU for an outpatient blood draw for beta-HCG (1 cc). If 30 days will have elapsed between (a) the most recent hemoglobin and hematocrit (obtained after the first admission) and (b) the scheduled inpatient admission, a hemoglobin and hematocrit will also be drawn at this time (1 cc). If three months have elapsed between (a) the subject's most recent safety labs and (b) the second CRU admission, a chemistry and liver panel will also be obtained at this time.

On cycle day 5-9 (mid-follicular phase), women will undergo a 10-h sampling study in the Clinical Research Unit (CRU). Subjects will come to the CRU no later than 0700 h (2 h prior to the start of sampling).

> NOTE: If not performed 1-3 days before the admission, we will perform beta-HCG, hemoglobin/hematocrit (as needed), and safety labs (as needed) on admission to the CRU.

Subjects will undergo another frequent sampling study identical to the first, except that oral progesterone will be exchanged for placebo or *vice versa* in accordance with the crossover design. In this way, we will be able to standardize LH pulsatility after progesterone administration to LH pulsatility after placebo administration.

If the subject does not have hematocrit ≥ 36% or hemoglobin ≥ 12 g/dl at the start of or shortly before the second CRU admission (i.e., within 30 days, as long as the measurement was after the first admission), we will offer 1 month of iron treatment (ferrous gluconate 325 mg bid) with a subsequent recheck of hematocrit and/or hemoglobin. If hematocrit and hemoglobin are still low, we will offer 1 more month of iron treatment (ferrous gluconate 325 mg bid) with a subsequent recheck of hematocrit and hemoglobin. Only volunteers with hematocrit ≥ 36% or hemoglobin ≥ 12 g/dl will be allowed to proceed with the second admission. No more than 2 months of iron treatment will be given between the first and second CRU admissions.

The study will end after the second CRU admission. Subjects will be asked to continue oral iron supplementation for at least 30 d after this last overnight admission.

2. Will any of the NON-RADIOLOGIC treatments/ procedures be done for research purposes only? yes
All procedures are being done for research purposes only

►**IF YES, (*examination(s) are performed for research) check one of the following two options:***

_X____The examination(s) utilize(s) the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.

- The PI takes full responsibility for the identification of incidental findings:
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.**
- A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic**.**

3. Will any RADIOLOGIC treatments/examinations be performed for research purposes only? No

4. **Will you be using viable embryos?** No

5. Will you be using embryonic stem cells? No

Family History/Pedigree

1. What kind of information is being sought?

Family history of disorders that have a genetic component and may impact the reproductive axis (e.g., PCOS, infertility, metabolic-related disorders such as diabetes and metabolic syndrome, etc.)

2. What identifiers will be recorded with the info (e.g. names, initials, relationship such as mother, father, brother, sister, random number)? Relationship

3. Does any of the information sought potentially expose the subject or a family member to additional risk? No

Specimens: Will not be used for Genetic Research or Banking

Specimen Information

1. Describe the type of specimen to be used:

Blood (and possibly urine for pregnancy test)

2. Will the specimen be obtained BEFORE a subject has signed a consent form? No

3. Will you be using discarded specimens? No

►IF NO, and taking a blood sample, will blood be taken more than 2 times/week? Yes

►IF NO, and taking a blood sample, check the option(s) below which match the subject population.

__X__ healthy, non pregnant adults who weigh at least 110 pounds.

__ X __ Amount will NOT exceed 550 cc in an 8 week period

Specimen Labeling

1. What information/ HIPAA identifiers will be on the specimen label when it is given to the study team (from clinical labs or other source outside the study team) and/or what information will you put on the specimen?

Name, medical record number, CRU protocol number, time (date and clock hour) drawn

2. If the specimen is given to the study team with information on the label will you delete any of the information on the specimen label?

No

►IF YES, list the information that will be deleted.

3. Will any additional data be linked to the specimen by way of a code? No

4. Will the analysis on the specimen be done soon (within 24 hours) after it is collected?

We anticipate that samples obtained outside of the CRU admissions (e.g., during the screening visit) will be analyzed by UVA Clinical Labs or Ligand Assay Core will typically be run within 24 hours. Samples obtained during CRU admissions will be spun/separated/frozen for later analysis in the Center for Research in Reproduction's Ligand Core.

Specimen Shipping

1. Do you plan to ship any specimens outside of UVA? No

Data and Safety Monitoring Plan

If you have any questions completing this section call 982-4311, 924-8660 or 243-9847 for assistance
A Sponsor is defined as entity that will receive data prior to publication.

1. Definition:

1.1 How will you define adverse events (AE)) for this study?

__X__An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **even if the event is not considered to be related** to the investigational drug/device/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subjects.

1.2 How will you define serious adverse events?

__**X**__A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

__**X**__Any serious psychological and emotional distress resulting from study participation (suggesting need for professional counseling or intervention).

1.3 What is the definition of an unanticipated problem?

Do not change this answer

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

1.4 What is the definition of a protocol violation?

Do not change this answer

A protocol violation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the IRB-HSR prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or UVa staff. These protocol violations may be major or minor violations.

Additional Information: see the IRB-HSR website at http://www.virginia.edu/vpr/irb/HSR_docs/Forms/Protocol_Violations_%20Enrollment_Exceptions_Instructions.doc

1.5 If pregnancy occurs how will this information be managed?

__**X**__ Other – Subjects are counseled to take measures to avoid pregnancy during the study, and the likelihood of pregnancy will not be altered by these study procedures. Pregnancy cannot be considered an adverse event or unanticipated problem related to any of the study procedures. Pregnancy would be considered a protocol violation (on the part of the study volunteer).

1.6 What is the definition of a Protocol Enrollment Exception?

__**X**__NA- No outside sponsor

1.7 What is the definition of a data breach?

Do not change this answer

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

2. Identified risks and plans to minimize risk

2.1 What risks are expected due to the intervention in this protocol?

Expected Risks related to study participation.	**Frequency**
Risks of venipuncture	
Discomfort	_X__Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Bruising	_X__Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Infection	____Occurs frequently ____Occurs infrequently ____Occurs rarely __X_Frequency unknown, but likely to be very rare
Blood clot at the site of intravenous catheter insertion	____Occurs frequently ____Occurs infrequently _X__Occurs rarely ____Frequency unknown
Risks of frequent blood draws	
Mild anemia	____Occurs frequently ____Occurs infrequently ____Occurs rarely __X_Frequency unknown
Risk to fetus	____Occurs frequently ____Occurs infrequently ____Occurs rarely __X_Frequency unknown – Extremely unlikely, as endogenous progesterone concentrations are normally very high during pregnancy, and we are administering one

	small dose of progesterone.
Risks of progesterone	
Fluid retention	____Occurs frequently ____Occurs infrequently ____Occurs rarely __X_Frequency unknown - Can occur with long-term, higher dose progestin administration, but very unlikely to occur after one small dose of progesterone.
Sleepiness	____Occurs frequently ____Occurs infrequently ____Occurs rarely - __X_Frequency unknown - Unlikely to occur after one small dose of progesterone.
Mood swings	____Occurs frequently ____Occurs infrequently ____Occurs rarely __X_Frequency unknown - Can occur with long-term, higher dose progestin administration, but very unlikely to occur after one small dose of progesterone.
Mild vaginal bleeding	____Occurs frequently ____Occurs infrequently ____Occurs rarely __X_Frequency unknown - often occurs after longer-term, higher dose progestin administration, but very unlikely to occur after one small dose of progesterone.
Risks of iron supplementation	
nausea	____Occurs frequently __X_Occurs infrequently ____Occurs rarely ____Frequency unknown
constipation	____Occurs frequently __X_Occurs infrequently ____Occurs rarely ____Frequency unknown
dark stool	__X_Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Risk for early termination of study participation if subject becomes pregnant	Subjects are not expected to have any alteration of fertility as a result of study medications. Therefore, sexually active subjects may get pregnant during this protocol. If the volunteer becomes pregnant, the study and all study medications will be discontinued.

Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol

2.2 List by bullet format a summary of safety tests/procedures/observations to be performed.

- Risks of venipuncture will be minimized by using proper sterile technique
- Risk of anemia will be reduced in the following manner: Most importantly, blood withdrawal will be carefully limited to < 550 cc over an 8 week period of time. Specifically, 16 cc will be withdrawn during screening visit, and approximately 155 cc will be withdrawn during each CRU admission (this includes up to 0.5 cc of blood wastage per blood draw). Thus, overall blood withdrawal for the entire protocol will be approximately 325 cc. Also, hemoglobin and hematocrit will be measured and reviewed within 30 days before each CRU sampling study. Only volunteers with hematocrit ≥ 36% or hemoglobin ≥ 12 will be allowed to proceed with the frequent sampling study.
- A history and physical will be performed at screening. Women with disorder that could be exacerbated by mild anemia will be excluded: known or suspected congestive heart failure; known or suspected coronary atherosclerosis; asthma requiring systemic intermittent corticosteroids; etc.
- We do not believe that this study poses any risk to a fetus. Nonetheless, risk of fetal exposure to study drugs will be reduced by having a serum pregnancy test obtained and reviewed prior to each overnight sampling study. If the volunteer is pregnant, the study and all study medications will be discontinued.
- A single small dose of progesterone is not expected to increase the risk of venous thromboembolism or cancer. Nonetheless, we will exclude women with a history of venous thromboembolism or breast/ovarian/endometrial cancer.
- Risk from iron supplementation will be reduced by instructing subjects to take their iron tablets with food and a full glass of water. They will be told to include whole grains and fruits and vegetables in their diet for fiber.
- A comprehensive metabolic panel will be performed at screening. Women with liver enzymes, alkaline phosphatase, or bilirubin > 1.5 times upper limit of normal (confirmed on repeat) will be excluded, with the exception that mild bilirubin elevations will be accepted in the setting of known Gilbert's syndrome. Women with abnormal renal function (i.e., serum creatinine > 1.4) will be excluded. Women with abnormal sodium, potassium, or bicarbonate concentrations (confirmed on repeat) will be excluded.
- If three months have elapsed between (a) the subject's most recent safety labs and (b) an overnight admission, a CBC, chemistry and liver panel will be obtained prior to the overnight admission (or on admission) to exclude anemia and any other exclusion criteria.
- Subjects will have frequent (at least every 10 minutes) contact with CRU nursing personnel and will be asked to report any unusual symptoms occurring during the protocol.

2.3 Under what criteria would an INDIVIDUAL SUBJECT'S study treatment or study participation be stopped or modified

__**X**__At subject, PI or sponsor's request

Protocol-determined criteria for study withdrawal include pregnancy and persistent anemia despite iron supplementation. The PI could also withdraw a subject if it is felt that continuation would be unsafe. The subject may withdraw at any time and for any (stated or unstated) reason.

__**X**__Treatment would be stopped if the subject had a serious adverse event deemed related to study, or study drug will be increased if the subject tolerates dosing *insert details:*_

Specifically, treatment would be stopped if the subject had a serious adverse event deemed related to study.

2.4 Under what criteria would THE ENTIRE STUDY need to be stopped.

These are called stopping rules for early termination of the entire study.
List criteria regardless of whether the study is sponsored or not.
Be sure to include any criteria for which the UVa PI would halt the study at UVa.

__**X**__Per IRB, PI, DSMB, or sponsor discretion

2.5 What are the criteria for breaking the blind/mask?

__**X**__Other: *specify*

The treatment allocation would be unblinded if a serious adverse event occurs during study. Given that progesterone concentrations are measured, treatment allocation will be effectively unblinded once a participant completes study and blood samples are analyzed.

2.6 **How will subject withdrawals/dropouts be reported to the IRB prior to study completion?**

__**X**__IRB-HSR continuation status form

3. Adverse Event / Unanticipated Problem Recording and Reporting

3.1 Will all adverse events, as defined in section 1.1, be collected/recorded? No
►IF NO, what criteria will be used?

__**X**__Only adverse events deemed related/possibly related to study

3.2 How will adverse event data be collected/recorded? *Check all that apply*

__**X**__Paper AE forms/source documents

__**X**__Spreadsheet *(paper or electronic*)

3.3. How will AEs be classified/graded? C*heck all that apply*

__**X**__Mild/Moderate/Severe

__X__Serious/Not serious *Required for all protocols*

3.4 What scale will the PI use when evaluating the relatedness of adverse events to the study participation?

__**X**__The PI will determine the relationship of adverse events to the study using the following scale:

Related:	AE is clearly related to the intervention
Possibly related:	AE may be related to the intervention
Unrelated:	AE is clearly not related to intervention

3.5 When will recording/reporting of adverse events/unanticipated problems begin?

__**X**__After subject begins study drug/ device placement/intervention /study-related procedure/specimen collection

3.6 When will the recording/reporting of adverse events/unanticipated problems end?

__**X**__End of study drug/device/intervention/participation

3.7 How will Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches be reported? Complete the table below to answer this question

Type of Event	**To whom will it be reported:**	**Time Frame for Reporting**	**How reported?**
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Protocol Violations (*The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.)* Or Enrollment Exceptions	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*

Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- UVa Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Phone- (434) 924-7166

UVa PI HELD IND			
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibly related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA	Annually	IND annual report

4. How will the endpoint data be collected/recorded.

__**X**__Source documents

__**X**__Database: *specify*

5. Data and Safety Oversight Responsibility

5.1. Who is responsible for overseeing safety data for this study ?

__**X**__DSMB/ DSMC- *If your study is NIH funded, check with the center to determine if they require a DSMB for this study.*

5.2. What is the composition of the reviewing body and how is it affiliated with the sponsor?

Members of the study team may NOT also be members of the DMSB.

_____Information may be found in the UVa Cancer Center Institutional DSMP

__x___Other- *specify* William Evans, MD; Mark DeBoer, MD; Guofen Yan, PhD. This DSMB was established to oversee studies on NIH R01 grant. The listed individuals have no direct affiliation with the NIH and do not directly participate in these studies.

5.3. What items will be included in the aggregate review conducted by the PI?

__**X**__All adverse events

__**X**__Unanticipated Problems

__**X**__Protocol violations

__**X**__Audit results

_____Application of dose finding escalation/de-escalation rules *These should be outlined under 2.4.*

__**X**__Application of study designed stopping/decision rules

_____Early withdrawals

__**X**__Whether the study accrual pattern warrants continuation/action

____Endpoint data

_____Other: (*specify*) _____

5.4 **How often will aggregate review occur?**
For additional information on aggregate review see:
www.virginia.edu/vpr/irb/hsr/continuations.html#aggreview

__**X**__Annually

5.5. How often will a report, regarding the outcome of the review by the DSMB/DSMC, be sent to the UVa PI?

A copy of these reports must be sent to the IRB if applicable as soon as they are received by the PI. Do not wait until the next continuation to submit them to the IRB.

__**X**__Once a year

_____Other: *specify*

5.6. How will a report of the information discussed in question 5.4 OR 5.5 be submitted to the IRB?

__**X**__Part of IRB-HSR continuation status form

Payment

1. Are subjects being reimbursed for travel expenses (*receipts /mileage required***)?** No

2. Are subjects compensated for being in this study? Yes

2a. What is the maximum TOTAL compensation to be given over the duration of the protocol?

$225

2b. Explain compensation to be given.

Subjects will receive $75 for each completed inpatient admission, and a $75 bonus for completing all CRU admissions and outpatient visits in the study.

2c. Is payment pro-rated (*e.g. some compensation is given even if subjects do not complete the entire study)?*

Yes, subjects completing only one inpatient CRU admission will receive $75.

3. Is money paid from UVa or State funds (including grant funds) or will items such as gift cards be distributed through UVa?Yes

3a. How will the researcher compensate the subjects?

__**X**__ Check issued to participant via UVA Oracle or State system

3b. Which category/ categories best describes the process of compensation?

__**X**__ All compensation will be made via check issued to participant via UVA Oracle or State system

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?

There will likely be no direct benefits for the participant as a result of this study. A panel of laboratory testing will be performed (e.g., at screening), and abnormalities requiring medical evaluation are occasionally discovered in this manner.

We believe that the risk of participating in this study is minimal, but the information obtained may help to further elucidate the mechanisms involved in modulation of the GnRH pulse generator in health and disease. The information obtained via this study will be critical to obtain while pursuing our hypotheses regarding the development of ovulatory cycles during puberty and the emergence of neuroendocrine abnormalities in adolescents destined to develop PCOS. These hypotheses may be used in developing therapeutic interventions for hyperandrogenemic adolescents, a condition felt to represent a forerunner of PCOS.

2. Analyze the risk-benefit ratio.

The mechanisms by which cyclic ovulation is established at puberty are incompletely understood. Polycystic ovary syndrome (PCOS), the most prevalent reproductive disorder in young women, typically manifests at puberty, and it is very likely that the genesis of PCOS occurs at puberty. Enhanced understanding of normal neuroendocrine function during puberty and how these normal processes go awry in PCOS will be essential to design rational treatment strategies for PCOS. These studies may further elucidate the mechanisms involved in modulation of the GnRH pulse generator in adults (and by inference in peripubertal adolescents). Again, we believe that the risks involved to individuals in this study are minimal and that the potential benefits to medical knowledge are substantial.

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APPENDIX: Sponsor

Sponsor Information

This study is supported by funding from the University of Virginia's Department of Endocrinology and Metabolism.

.APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- *Finders fees will not be paid to an individual as they are not allowed by UVa Policy*
- *All recruitment materials will be approved by the IRB-HSR prior to use. The advertisements will be submitted to the IRB after the protocol has been approved.*
- *Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.*

Clinical Privileges

The following procedures will be followed:

- *Investigators who are members of the clinical staff at the University of Virginia Medical Center must have been granted clinical privileges to perform specific clinical privileges whether those procedures are experimental or standard.*
- *The IRB cannot grant clinical privileges.*
- *Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.*
- *Personnel on this protocol will have the appropriate clinical privileges in place before performing any procedures required by this protocol.*
- *Contact the Clinical Staff Office- 924-5871 for further information.*

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVa other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- *No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.*
- *No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.*

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at http://www.hhs.gov/ohrp/policy/populations/index.html

APPENDIX: Drug Information

1 What is the drug name, manufacturer and IND# if available?

In this protocol, we will use a micronized progesterone suspension (FDA IND number 64,126), which is formulated by the UVAHS research pharmacy. This IND was required solely because it is formulated/constituted by our investigational pharmacy. The progesterone used to formulate the suspension (i.e., Progesterone USP, micronized, for prescription compounding [NDC 39822-6000-3] Mfg: Spectrum Chemicals) is FDA approved.

2. If IND application has been submitted to the FDA, who is the Principal Investigator on the IND?

John C. Marshall, MD, PhD

3. What is the phase or stage of this study?
e.g. Phase 1,2 or 3, pivotal, pilot, post-marketing

This study is not being performed to evaluate the effectiveness of micronized progesterone as a therapeutic agent, so we do not feel that any of these phases/stages apply to this study.

APPENDIX: Recruitment

Recruitment includes identifying, review of records to determine eligibility or any contact to determine a potential subjects interest in the study.

1. **How do you plan to identify potential subjects?**
   To "identify" a potential subject refers to steps you plan to take to determine which individuals would qualify to participate in your study. This does NOT include steps to actually contact those individuals.
   If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being identified by the given method.
   Check the methods you plan to utilize:

a. ____ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or quality improvement.
DHHS: Study team requests Waiver of Consent to identify potential subjects.
HIPAA- *Allowed under Preparatory to Research*

b. ____ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.
DHHS: Study team requests Waiver of Consent to identify potential subjects.
HIPAA- *Allowed under Preparatory to Research*

NOTE: The information from which you are obtaining potential subjects must also have an IRB protocol approval.

IRB# _____
If obtaining information from the Clinical Data Repository (CDR) insert IRB # 10797.

c. ____ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients knowledge.
DHHS: Study team requests Waiver of Consent to identify potential subjects.
HIPAA- *Allowed under Preparatory to Research*

d. ____ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating.
DHHS: *NA*
HIPAA: *Allowed under Health Care Operations*
If this choice is checked, check 3d-INDIRECT CONTACT below.

e. **_X_** Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.
If this choice is checked, check 3d- INDIRECT CONTACT below.
DHHS & HIPAA: *NA*

f. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.
IRB# of registry/ database: _____
DHHS & HIPAA: *NA*

g_**X**__ Other- *explain*

We may offer this study as an option for some subjects who responded to advertisements for other studies (e.g., IRB-HSR 13368).

If item # a, b or c is checked above and if this protocol involves the use of protected health information you confirm the following to be true:
The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes. No PHI will be removed from the UVa covered entity during the review. The PHI that the researcher seeks to use or access is necessary for the research purposes.

2. How will potential subjects be <u>contacted?</u>

To "contact" a potential subjects refers to the initial contact you plan to take to reach a potential subject to determine if they would be interested in participating in your study. This may include direct contact by such methods as by letter, phone, email or in-person or indirect contact such as the use of flyers, radio ads etc.

If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being contacted by the given method.

Check the methods you plan to utilize:

a.____Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients.

Note: Letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

DHHS/HIPAA: Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

b.____Potential subjects will be approached while at UVa by a person who is NOT a member of their health care team.

DHHS & HIPAA: Study team requests a Waiver of Consent and a Waiver of HIPAA Authorization to contact potential subjects.

You should share the following information with the potential subject:

1. *Your name*
2. *Who you are:* ***physician, nurse etc***. at the University of Virginia.
3. *Why you want to speak with them*
4. *Ask if you have their permission to explain the study to them*
5. ***If asked about how you obtained their information use one of the following as an option for response.***
   - ***DO NOT USE THIS RESPONSE UNLESS YOU HAVE OBTAINED PERMISSION FROM THEIR UVa PHYSICIAN:***
     Your doctor, Dr. ***insert name*** *wanted you to be aware of this research study and gave us permission to contact you.*
   - *We obtained your information from your medical records at UVa**.***
     Federal regulations allow the UVa Health System to release your information to researchers at UVa, so that we may contact you regarding studies you may be interested in participating. We want to assure you that we will keep your information confidential.

IF THE PERSON SEEMS ANGRY, HESITANT OR UPSET, THANK THEM FOR THEIR TIME AND DO NOT ENROLL THEM IN THE STUDY. YOU MAY ALSO REFER THEM TO THE IRB-HSR AT 924-9634.

c.____Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team ARE health care providers of patients.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects

HIPAA: *Allowed under Health Care Operations.*

d._**X**__ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and patient contacts study team.)

DHHS & HIPAA: *NA*

3. Will any additional information be obtained from a potential subject during "prescreening"?

Yes

Pre-screening *for IRB purposes is the term used to describe activities PRIOR to obtaining Informed Consent and may not include any research procedures.*

Pre-screening of potential subjects over the telephone or in person is generally performed to determine their initial eligibility for, and, interest in a study and is a common strategy in the recruitment process.

Questions appropriate for pre-screening address the specific inclusion/exclusion criteria for the study and other issues of suitability, for example, an individual's ability to come to the research site multiple times.

It is not appropriate at this point in the process (i.e. prior to obtaining informed consent/enrollment) to gather information that is not directly related to assessing eligibility and suitability (e.g. obtaining complete medical histories, obtaining blood specimens for lab tests).

IF YES, *submit any documents that will be used to collect pre-screening information so that the IRB may confirm what questions will be asked.*

NOTE: To comply with HIPAA regulations only the minimum necessary information may be collected at this time. This means that only questions pertaining to the Inclusion and Exclusion Criteria may be asked.

IF YES,

DHHS study team requests a Waiver of Documentation of Consent for Pre-screening questions.

HIPAA- covered under Health Care Operations

IF YES, Will any of the questions involve health information?

Yes

IF YES, will you collect HIPAA identifiers with the health information?

Yes

IF YES, which HIPAA identifiers will be recorded?

Name, MR#, date of birth, age, postal address, telephone number, email address (if applicable)

Do you confirm that health information with HIPAA identifiers will not be shared outside of UVa until a consent form is signed or only shared in a de-identified manner?

Yes

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?**

Yes

For example: come to the first visit fasting, stop taking medications that may be an exclusion criteria, change diet. As this is still part of pre-screening one is not allowed to gather information that is not directly related to inclusion/exclusion criteria or other issues of suitability (e.g. is person able to come to UVa for multiple visits)
NOTE:

- *Only those members of the study team with a DEA# (license to prescribe drugs) are allowed to determine if a potential subject may be asked/informed to stop taking a drug which is an exclusion criteria.*
- *It is recommended that the potential subject notify their health care provider if they plan to stop a prescription drug.*

►**IF YES, explain in detail what you will ask them to do**.

Tips to Study Team

- *You must document their verbal consent in the study records.*
- *If a subject is asked to stop taking a drug, document the date and name of the person on the study team giving the verbal order to stop medications (again- must be a person with a DEA#) .*

DHHS- Study team requests the use of Verbal Consent (Waiver of Documentation of Consent) for minimal risk screening procedures.
HIPPA- Covered under Health Care Operations

We will request that subjects come to the screening visit while fasting for at least 8 hours. We will tell potential subjects that only subjects who have taken no hormonally-active medications

for 2 months prior to the screening visit (and 3 months prior to inpatient study) will be eligible for participation. However, we will strongly recommend that potential subjects do not stop medications without first consulting with their personal physicians.

5. How will the consenting process take place?

- *Describe the setting for the consent*
- *How much time will the consenting process take?*
- *How much time will pass between obtaining written consent and initiation of study procedures? How will you assess subject understanding?*
- *See Protocol Examples: Consenting Process for examples of how to answer this question.*

Potential subjects will be given a consent form (via mail or e-mail) to read at their leisure. If the potential subject desires to be involved in the study, a consent and screening visit will be scheduled. At the beginning of this visit, the study (including procedures, risks, alternatives) will be discussed and any questions will be answered. If the potential subject decides to enter the study, they will then sign the consent form, and study screening procedures will begin thereafter.

6. Will subjects sign a consent form for any part of the study?

Yes

7. Will the study procedures be started the same day the subject is recruited for the study?

Yes, if day of recruitment equates to day of enrollment.

►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.

When a potential subject contacts us (in response to advertisements), they are sent a copy of the consent form by mail or email. Subjects are instructed to carefully review the consent form, and are encouraged to ask any questions prior to scheduling a screening visit. Thus, by the time a consent/screening visit is scheduled, subjects have been given time to consider the study and formulate questions about the study. At the screening visit, subjects are lead through a discussion of the consent form. Subjects are given the opportunity to ask any additional questions during this portion of the screening visit. After the study team has read through the entire consent form with the subject, they are then given the opportunity to sign the consent form if they are ready to do so. They are also given the option to decline to enroll in the study, or take more time (minutes, hours, days, etc. – as long as needed) to review the consent form before making a decision regarding enrollment. If the subject decides to enroll in the study on the day of the screening visit (most participants have historically chosen this option), then we will proceed with the study procedures (namely, screening procedures) outlined above. Note that the procedures occurring on that day (i.e., screening procedures) carry minimal risk, and subjects may withdraw from the study at any time.

►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.

Please see answer immediately above.

8. Do you need to perform a "dry run" of any procedure outlined in this protocol? No

APPENDIX: Pharmacy-Investigational Drugs/Biologics

1. What is the name of the investigational drug/biologic?

Micronized progesterone

2. Where will the subjects be seen for the administration/dispensing of the drug?

__**X**__ Inpatient Unit: *specify:*_____
A single dose of micronized progesterone solution will be administered in the CRU

3. What dose will be utilized in this study?

A single dose of 100 mg.

Note that progesterone is a naturally-occuring sex-steroid produced by the ovaries (primarily) and adrenal glands. Moreover, we administer a single dose, and achieved peak concentrations are much less than those observed in the normal luteal phase.

4. What will be the frequency of dosing in this study?

Single dose at 0900 during the frequent sampling admission

5. What will be the duration of dosing in this study?

Single dose

6. What route of administration will be utilized? Oral

7. Will drug need to be prepared by the UVa Investigational Drug Service (IDS)?

__**X**__ YES
_____ NO- Drug will be prepared and/or administered per package insert

►*IF YES, complete the following information under 7a-7d.*
If you need assistance completing this section contact the Investigational Pharmacists at 982-1048

7a. Concentration

__**X**__ Standard
_____ Non- Standard- *specify*

7b. Diluents

__**X**__ Standard
_____ Non- Standard- *specify*

7c. Stability after prepared

__**X**__ Standard
_____ Non- Standard- *specify*

7d. Special storage requirements
__**X**__ Standard
_____ Non- Standard- *specify*

8. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)? No

9. Does the protocol provide provisions for dose titration, dose reductions, and or re-challenged (if drug is stopped), etc.? No

10. How will missed doses be handled?

Since the single dose is given by CRU nurses on a well-defined schedule, missed doses should not be an issue.

11. Will a comparator (active or placebo) be utilized in the protocol?

Yes

►IF YES, comparator is:
_____ Active FDA approved drug: *provide name and dose of drug*
__**X**__ Placebo*: describe*

The UVAHS research pharmacy provides a solution that is identical to the micronized progesterone suspension, with the exception that progesterone is not included.

12. Does this study involve research on a drug, biologic, supplement or food additive?

No. This study is not being performed to evaluate the effectiveness of micronized progesterone as a therapeutic agent. Instead, progesterone is being used as a physiological probe (i.e., to answer questions about normal physiology).

►IF YES, is this study investigator initiated?

If yes, answer questions # 13 and 14
If no, answer question # 13 only.

13 Are you using a drug/supplement/ food additive in a manner not approved by the FDA?

In this protocol, we will use a micronized progesterone suspension (FDA IND number 64,126), which is formulated by the UVAHS research pharmacy. This IND was required solely because it is formulated/constituted by our investigational pharmacy. No risk is expected on the basis of the way the progesterone suspension is made (and minimal potential risk is associated with progesterone administration).

The progesterone used to formulate the suspension (i.e., Progesterone USP, micronized, for prescription compounding [NDC 39822-6000-3] Mfg: Spectrum Chemicals) is FDA-approved.

IF YES, answer questions 13a-13f
You may reference the non-IRB protocol to answer these questions.

13a. Describe pertinent animal data that is available regarding the toxicity/safety of this drug.

N/A

13b. Describe pertinent human data that is available regarding the toxicity/safety of this drug.

As described above, the IND was required solely because the micronized progesterone is formulated/constituted by our investigational pharmacy. No risk is expected on the basis of the way the progesterone suspension is made (and minimal potential risk is associated with progesterone administration). The progesterone used to formulate the suspension is FDA-approved. There are no published data regarding the safety of this specific formulation of micronized progesterone suspension, but our group has used this formulation successfully in numerous clinical research protocols. Adverse events that we have observed with longer term use of micronized progesterone solution (i.e., three times a day dosing for a week) include mild somnolence and irregular menstrual bleeding: these are known to be possible side effects of micronized progesterone.

13c. Have there been any human deaths associated with this drug?

To our knowledge, no.

13d. In how many humans has this drug been used previously?

Various forms of micronized progesterone (e.g., Prometrium®) are FDA-approved. It is used clinically for a number of indications, including dysfunctional uterine bleeding, prevention of endometrial hyperplasia, luteal support, etc. We do not know how many women have used this drug, but the numbers are substantial.

13e. If this protocol will be used in children describe any previous use of this drug with children of a similar age range. N/A

14. Do the following criteria apply?

_____ The investigation is intended to be reported to FDA as a well-controlled study in support of a new indication for use or intended to be used to support any other significant change in the labeling for the drug;

_____ If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is intended to support a significant change in the advertising for the product;

_____ The investigation does involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

If Not checked- explain why you believe the risk to subjects is not increased:

As described above, the IND was required solely because the micronized progesterone is formulated/constituted by our investigational pharmacy. No risk is expected on the basis of the way the progesterone suspension is made (and minimal potential risk is associated with progesterone administration). The non-progesterone ingredients of the suspension are innocuous. The progesterone used to formulate the suspension is FDA-approved. The progesterone (in the micronized progesterone) is chemically identical to progesterone made by ovaries, and the achieved concentrations will be less than that observed in the luteal phase of the normal menstrual cycle. Our group has used this formulation successfully in numerous clinical research protocols.

_**X**_ The investigation will be conducted in compliance with the requirements for institutional review set part in part 21CFR56 and with the requirements for informed consent set forth in part 21CFR50 ; and *This item must be checked.*

_ **X** _ The investigation will be conducted in compliance with the requirements of 21CFR312.7 (Promotion and charging for investigational drugs)
This item must be checked.

15. Is this a post-marketing study? No

APPENDIX: Privacy Plan for Studies With Consent

1. Answer the questions below (1a-1e) to describe your/central registry's plan to protect the identifiable data from improper use and disclosure.

1a. How will data be stored?

__**X**__ Data, which may include health information, or other highly sensitive data will be stored with HIPAA identifiers.

1b. Will specimens be stored at UVa?

If YES, the following security precautions will be implemented:

- Specimens will be kept in a locked freezer/ or locked room
- __**X**__ Access to the freezer/room will be limited to authorized personnel. Specimens with HIPAA identifiers will never be shared outside of UVa without the written permission of the subject.

1c. Will any of the data be stored electronically at UVa?

►IF YES, will it include any HIPAA identifiers with health information or other highly sensitive data?

►IF YES, where will it be stored?

__**X**__ a Health Systems Computing Services (HS/CS) managed server that is configured to store data regulated by HIPAA.

1d. Will any of the data be stored in hard copy format at UVa (*e.g.- on paper*) ? yes

►IF YES, where will it be stored?

__**X**__ case report forms will be stored in a secure area with limited access.

1e. The following procedures will also be followed.

- Only investigators for this study and clinicians caring for the patient will have access to the data. They will each use a unique log-in ID and password that will keep confidential.
- Each investigator will sign the University's Electronic Access Agreement forward the signed agreement to the appropriate department as instructed on the form.
  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.
- UVa Institutional Data Protection Standards will be followed http://itc.virginia.edu/security/dataprotection. Identifiable data is classified as "Highly Sensitive", de-identified data is classified as "Moderately Sensitive".
- If identifiable data (*data with health information and HIPAA identifiers*) is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's "Electronic Storage of Highly Sensitive Data Policy". Additional requirements may be found in the Universities Requirements for Securing Electronic Devices.
- If identifiable health information is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.
- The data will be securely removed from the server, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy.
- The data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Policy.
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and UVa Institutional Data Protection Standards .
- The data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data *is:*
-personal information that can lead to identify theft if exposed or
-health information that reveals an individual's health condition and/or history of health services use.

PHI- *a type of Highly Sensitive Data, is health information combined with a HIPAA identifier*

- LIMIT- Limit the HIPAA identifiers to the minimal amount needed- e.g. use initials instead of name, use a code instead of initials, limit amount/type of health information collected, and collect and share only those items you state you will in this protocol.
- SECURE- Secure Highly Sensitive Data
  - Because single-use electronic devices and media, such as desktops, laptops, memory sticks, CDs, smartphones etc., can be easily lost or stolen, the University strictly limits the circumstances under which Highly Sensitive Data may be stored on them. In accordance with the University's Electronic Storage of Highly Sensitive Data Policy, you must obtain written approval from your Department AND VP or Dean prior to moving data to single use devices or media by using the Highly Sensitive Data Storage Request Form.
    - *You additionally are responsible for applying all security safeguards covered in that policy, including but not limited to password protecting and encrypting any document on a single access electronic device.*
    - *If you use your smartphone to send email and your phone is not managed was not purchased and/or set up for you by the Health System, you cannot send Highly Sensitive Data via email.*
      - *In addition, do not use Outlook Web to send your email if it contains sensitive data.*
      - *Also, you are not allowed to auto forward your email to outside email systems like Gmail or Yahoo.*
      - *Do not save any email attachment containing Highly Sensitive Data to a single use device.*
    - *You are allowed to access Highly Sensitive Data stored on the University or Health Systems network via a VPN, however you cannot download any of the information onto your desktop or laptop.*
    - *Store files containing Highly Sensitive Data on a network drive specifically designated for storing this type of data, e.g. high-level security servers managed by Information Technology Services or the "F" and "O" managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive.*
    - *If data will be collected and/or viewed via a website, it is critical that the website and associated data file are set up in a highly secured manner. Do not attempt without assistance from:*
      University Side: ITCmicrosystems@virginia.edu
      Health System: Web Development Center: (434-243-6702)
  - Encrypt any electronic file containing Highly Sensitive Data that is not on a network drive specifically designated for this purpose. . *See encryption solutions guidance.*
  - Password protect any electronic device containing Highly Sensitive Data.
  - Lock up hard copies of Highly Sensitive Data.
- PROTECT- Protect Highly Sensitive Data
  - Do not leave a hard copy file open on your desk when not using it and secure your computer when not attended.
  - Have discussions in private.
  - If you lose Highly Sensitive Data, you must report it in accordance with the Information Security Incident Reporting Policy.

- Do not share Highly Sensitive Data with those not on the study team or those who do not have a need to know.
- Do not share with sponsor unless subject has already signed a consent form or IRB has approved waiver of consent.
- If faxing Highly Sensitive Data
  - Verify fax numbers before faxing, and use fax cover sheets with a confidentiality statement.
  - If printing to a central printer, ensure that names and identifiers on the documents are given to the correct patient.
- Highly Sensitive Data may not be stored in a Drop Box.
- If you plan to store data in the Cloud, you must consult with UVa Information Technology Services (ITS) to verify all essential security measures are in place. If you have a contract to use the cloud, the contract must include required security measures as outlined by ITS.
- DO NOT email health information with name, medical record number or Social Security number to or from an email address that does not have an *HS in the address. May use subject initials if within the UVa HIPAA covered entity: The "UVA HIPAA covered entity" includes the hospital, health system, School of Medicine School of Nursing and the VP for Research Office.
- Be aware: PHI collected without consent/ HIPAA authorization will NOT be allowed to leave UVa in an identifiable form unless the disclosure is tracked with Health Information Services.
- Any Highly Sensitive Data sent outside of UVa (e.g. to sponsor) that was obtained under a consent must be encrypted and password protected.
- If your electronic device is sent outside of UVa for repair, all institutional data, whether Highly Sensitive or not, must be either encrypted or removed.
- If transporting Highly Sensitive Data in paper format from one UVa building to another, take the following steps to protect it:
  1. Put paper inside a closed container such as a briefcase, or sealed envelope to limit the chance of a losing a piece.
  2. Do not leave Highly Sensitive Data unattended in a public area if it is not locked up.
- When the study is complete, all electronic files containing Highly Sensitive Data must be stored on a network drive specifically designated for that purpose. They may not be stored on a single use device such as a CD.

- STOP, THINK and BE CAREFUL-
  - If this was your Highly Sensitive Data how would you want it protected?
  - There are significant monetary fines to the individual and the institution for loss or misuse of sensitive data.
  - Your job may also be on the line.

2. Describe your/central registry's plan to destroy the HIPAA identifiers at the earliest opportunity consistent with the conduct of the research and in accordance with any stipulations in the research sponsor contract and UVa records management guidelines.

__**X**__The HIPAA identifiers (except full dates and or address information if needed) will be destroyed as soon as all publications are complete.
This wording would allow the researcher to keep HIPAA identifiers until all queries/ request for additional information from publisher are addressed

3. **Do you confirm that you will not reuse the identifiable data (HIPAA identifiers or health information) or disclose any of this information to any other person or entity except as outlined in this protocol, except as required by law, for authorized oversight of the research study, or use it for other research unless approved by the IRB-HSR?** Yes

This means that after the study is closed at UVa:

- *You cannot contact the subject by any method (you cannot call them, send a letter, talk to them in person about the study, etc) without additional IRB approval*
- *You cannot use the data for any research that is not already described in your IRB protocol without additional IRB approval (if you change your hypothesis you must modify your protocol)*
- *You cannot share your research data with another researcher outside of your study team without additional IRB approval*
- *Any health information with HIPAA identifiers will be shredded or discarded by using recycling bins for confidential material found in clinic settings. For large item disposal of confidential material contact Environmental Services at 2-4976 or University Recycling at 2-5050.*

TABLE A: HIPAA Identifiers (Limited Data Set)

1. Name
2. Postal address information, other than town or city, state, and zip code
3. Telephone numbers
4 Fax numbers
5. Electronic mail addresses
6. Social Security number
7. Medical Record number
8. Health plan beneficiary numbers
9. Account numbers
10. Certificate/license numbers
11. Vehicle identifiers and serial numbers, including license plate numbers
12. Device identifiers and serial numbers
13. Web Universal Resource Locators (URLs)
14. Internet Protocol (IP) address numbers
15. Biometric identifiers, including finger and voice prints
16. Full face photographic images and any comparable images
17. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)