

Parents' or Guardians' Permission for Your Child to Be in a Research Study

In this form "you" means the person (your child) who is being asked to be in this study. As the parent or guardian, you are being asked to give permission for your child to be in this study.

1. Participant's Name _____

2. Medical Record # _____

What is the Purpose of this Form?

This form will help you decide if you want to be in the research study. You need to be informed about the study, before you can decide if you want to be in it. You do not have to be in the study if you do not want to. You should have all your questions answered before you give your permission or consent to be in the study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will get a copy of this signed form.

Why is this research being done?

Background

Below is a list of terms and information to help you understand why we are doing this study.

- **Hormone:** A substance made in the body that is sent directly out into the bloodstream to increase or decrease the function of certain organs, glands, or other hormones.
- **Puberty:** The time that the body is growing and changing from a girl into a woman and boys are growing and changing into men.
- **Gonadotropin releasing hormone (GnRH):** GnRH is a hormone made in a part of the brain called the hypothalamus. GnRH tells the pituitary gland to make LH and FSH (see below).
- **Testosterone:** Testosterone is a hormone that plays an important role in boys growing and changing into men. Although testosterone levels are much higher in men and boys, healthy girls and women make some testosterone too.
- **Luteinizing hormone (LH):** LH is a hormone made in a gland underneath your brain called the pituitary. LH is needed for puberty.
- **Follicle Stimulating Hormone (FSH):** FSH is a hormone made in a gland underneath your brain called the pituitary. FSH is needed for puberty.
- **Progesterone:** A hormone made by the ovaries. Progesterone is important for a lot of things. For example, progesterone helps control GnRH release from the hypothalamus.
- **Ovary:** Small oval organ in the pelvis that makes hormones (such as progesterone and testosterone) and eggs.

Gonadotropin-releasing hormone (GnRH) is a hormone from the brain. GnRH causes a gland called the pituitary to secrete two hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

- GnRH is produced in pulses from the brain, and this causes the pituitary to release LH and FSH in pulses.
- LH and FSH control the production of female hormones (such as estrogen and progesterone) and the development of eggs by the ovary.
- Progesterone and estrogen then decrease the number of GnRH pulses produced by the brain (and therefore the number of LH pulses from the pituitary).
- The ability to decrease GnRH pulses seems to be very important for normal menstrual function in adult women.

The purpose of this study is to learn more about how GnRH and LH pulses are controlled during puberty.

- In this study, we will aim to discover the effect of 7 days of estrogen and progesterone on GnRH pulses in girls in early and mid puberty.
- The information gathered in this study will hopefully allow us to learn more about how menstrual cycles are normally established in girls during puberty. Ultimately, if we understand these normal processes, we may be able to better understand abnormalities of puberty.

In this study, we will use the drugs progesterone and estradiol. The progesterone syrup that we use is made in the UVA Investigational Pharmacy. The progesterone used to make the syrup is approved by the Food and Drug Administration (FDA) but there are no specific data regarding human toxicity and safety of the UVA Health System progesterone syrup. Over 35 girls have taken the progesterone syrup as made by the UVA pharmacy and there have not been any unexpected side effects. The use of estradiol and progesterone are considered to be experimental in this study.

You are being asked to be in this study, because you are a normal girl in early to mid-puberty, with normal levels of testosterone in your blood.

Up to 16 people will be in this study at UVA.

How long will this study take?

The study involves a total of 3 outpatient visits and 2 overnight admissions. The screening visit will last about 1 hour. The other 3 outpatient visits will last 15 minutes. The 2 overnight admissions will last 14 hours each. The study will last 1 week (not including the screening visit).

What will happen if you are in the study?

All study tests, procedures, and exams are being done specifically for research purposes.

SCREENING (will take approximately 1 hour to complete):

If you agree to participate, you will sign this consent form before any study related procedures take place. Before you can start in the study, there will be a screening period. You will have tests and procedures during this time to make sure you are eligible and it is safe for you to participate. These include the following:

- Review of your medical history
- Physical exam and vital signs (blood pressure, heart rate, etc.)
- We will also check to see how far along into puberty you are. To do this, we will do a quick breast exam.
- Standard blood tests (less than 2 tablespoons of blood) to check: salts, sugars, blood counts, liver function, kidney function, pregnancy test, and a variety of hormones. We will ask that you not have anything to eat or drink except for water for 8 hours before having this blood work drawn.

If one or more of your blood tests are abnormal, we may ask you to return to the Clinical Research Unit (CRU) or alternate UVA clinic so we can repeat the abnormal blood test. The repeat test will generally occur within one month and will help exclude lab error. If repeat lab tests are still abnormal, you will not be able to continue in the study.

If the tests at this screening visit show that your blood counts are borderline, we will ask that you take 1-2 iron tablets per day (based on her weight) for 60 days and then return to the CRU or clinic to recheck you blood counts to ensure that it is safe for you to take part in the study.

If these tests show you are eligible, you will return to the GCRC to begin the study. You may be asked to do the overnight portion of the studies in a different hospital unit or in a hotel. If you are unable to begin the study within 30 days, you will need to come back to have your blood counts checked prior to the first admission. If you are unable to begin the study within 90 days, all of the screening blood tests will need to be repeated before taking part in the study. We will ask that you starting taking 1-2 tablets of iron per day (based on your weight) to prevent low blood counts during the study. You will take these for a total of 30 days.

STUDY TESTS AND PROCEDURES:

Day 0 - Admission #1 (will take approximately 14 hours to complete):

- You will be admitted to the CRU, alternate UVA hospital unit, or hotel at about 5:00 pm on the day of the admission. If the overnight visit occurs at a hotel, your parent or guardian may stay with you but it is not required, as long as two CRU staff members are at the hotel with you. Whether or not a parent or legal guardian is required to stay during the overnight admission will be discussed when your admission is scheduled.
- During your overnight stay, you will wear an actigraph. It looks like a watch and it is worn on your wrist. The actigraph will help us know when you are awake and when you are asleep.
- An intravenous (IV) line will be placed in your arm. An IV is a small flexible tube that is inserted into a vein using a needle. Once the tube is in place, the needle is removed and replaced with a cap that allows blood to be drawn or medication or fluid to be given. This means you will only have the needle stick you in the arm once

- A medicine, called EMLA cream, may be applied to the skin prior to the IV insertion to try to make it hurt as little as possible..
- We will do a urine pregnancy test. If you are pregnant, you will not be able to continue in the study.
- Starting at 7:00 PM, blood samples will be taken by a nurse every 10 minutes. Each of the blood draws will be no more than 1/2 of a teaspoon
- You will be given dinner at standard CRU mealtimes. You will not be able to eat or drink anything except water from 11:00 pm until 7:00 AM.
- A formal "lights out" will take place at 11:00 pm. At this point the lights and the television will be turned off to allow you to sleep.
- At 6 AM, the nurses will stop taking blood every 10 minutes.
- At 7 AM, the nurses will take one final blood sample.
- After the blood draws are complete at 7:00 AM, you will be served breakfast.
- The nurse will take out the IV and you will be able to go home.
- A total of 7 tablespoons of blood will be drawn during this admission.
- Before you go home from the overnight admission, you will be given a supply of estrogen (estradiol) pills and progesterone syrup with instructions on how to take them.

Day 1 - Start estrogen and progesterone:

- Estrogen and progesterone are natural hormones. The amount of these hormones given in this study is similar to the amounts that are produced by girls' bodies as they develop.
- The estrogen pills should be taken by mouth once a day for seven days.
- The progesterone syrup should be taken by mouth three times a day at 7:00 am, 3:00 pm, and 11:00 pm for seven days. If your school schedule makes it difficult to take the syrup at 3:00 pm, please discuss this with the study doctor and we will adjust the dosing schedule. Usually, this will mean that instead of taking the syrup at 3:00 pm, you will take it immediately upon arriving home from school.
- The progesterone needs to be refrigerated and should be shaken well before you take it.
- When you take the progesterone syrup, you should also eat a small snack such as peanut butter crackers and juice or a half of a sandwich and 2% milk. It is important that the snack is eaten as it helps the medicine get absorbed.

Day 3 & 5 - Outpatient Blood Draws (will take approximately 15-30 minutes to complete):

- Three days and then five days after the admission, you will return to the CRU or clinic for an outpatient blood draw at 5:00 pm. This appointment should take no longer than 30 minutes.
- A small amount will be drawn (less than 1/3 teaspoon) to make sure the estrogen and progesterone are being absorbed into the blood stream.
- On Day 5, we will check your red blood cell counts. If they are too low, you will not be able to continue with the second admission.

Day 7 - Admission #2 (will take approximately 14 hours to complete):

- After seven days of taking the estrogen and progesterone, you will return to the CRU, hospital unit, or hotel for the second overnight inpatient admission. You will bring your estrogen and progesterone bottles and any unused medicine to the admission and give them to the nurses.
- The second admission will be identical to the first inpatient admission.
- A total of 7 tablespoons of blood will be drawn during this admission.
- At the end of the second admission, you will:
 - stop taking the estradiol and progesterone
 - keep taking the iron supplements if you have not yet take a full 30 days of the iron.

FOLLOW UP:

- If possible, we would like to follow-up with you 3, 6, and 12 months after the study. This may be done by outpatient visits or phone calls and will include questionnaires and interviews. We would also like to take a small amount of blood (less than 1 tablespoon) at this time to measure hormone levels. These visits are optional.

Study Schedule table:

Day of Study	Type of Visit	Estradiol	Progesterone
	Screening visit.		
Day 0	Admission #1 Overnight with frequent blood draws		
Day 1		X	x
Day 2		X	x
Day 3	Blood draw	X	x
Day 4		X	x
Day 5	Blood draw	X	x
Day 6		X	x
Day 7	Admission #2 Overnight with frequent blood draws	X	x

If you want to know about the results before the study is done:

The study leader will tell you, during the study, of any results that are important to your health. That information is important for you to know, because it may help you decide whether you want to continue being in this study. We cannot tell you any other information until the results have been studied. At that time you can ask for more information.

If we take any blood or tissue:

The blood we take will be tested to measure salts, sugar, blood counts, kidney function, liver function, pregnancy tests, and a variety of hormones.

- A total of 15 tablespoons of blood will be drawn during the study.
- After the study is complete, any left over blood/tissue will be thrown away. It will not be stored for any future testing.

What are the risks of being in this study?

Risks and side effects related to the study procedures, drugs, and interventions include:

Likely

- Iron supplements can cause dark or black bowel movements.

Less Likely

- Estradiol and progesterone can cause nausea, fluid retention/swelling, breast tenderness, and moodiness/irritability.
- After you stop taking the estrogen and progesterone, you may have some menstrual bleeding if your own body was ready to start a period within a few months. If you do have a period, you may continue to have periods.
- Iron supplements can cause nausea and constipation.
- Frequent blood draws may result in mildly low red blood cell counts (mild anemia). Mildly low red blood cell counts usually do not cause symptoms in healthy girls, and the body is able to rapidly build red blood cells to bring the counts back to normal within 1-2 months.

Rare but serious

- Frequent blood draws could lead to significantly low red blood cell counts (significant anemia) if precautions were not taken to avoid this.
- Significantly low red blood cell counts can cause fatigue, lightheadedness, and shortness of breath, particularly with exercise. In order to prevent low red blood cell counts, we will give you iron supplements to make sure that your body has the necessary building blocks to make new red blood cells.
- We will check the red blood cell levels during the screening and before each overnight admission. If the level is too low, we will not continue the study. We carefully limit the amount of blood drawn to an amount that is safe for someone of your size.
- Long-term (over months to years) use of estrogen has been associated with the formation of blood clots in the deep veins of the body. This risk is similar to the risk of taking birth control pills.
- Long-term (5 years) use estrogen and progesterone in postmenopausal women is associated with a slightly increased risk of heart disease, stroke, and breast cancer. However, there is no evidence that the use of estrogen and progesterone as given in this study would increase these risks in young girls.

Do not share the study drug with anyone. It is prescribed only for you and could hurt someone else. Keep it out of reach of children and people not able to read or understand the label.

Risks of having your blood drawn:

Having blood drawn may cause:

- ✓ pain (common),
- ✓ a bruise (sometimes),
- ✓ fainting or passing out (not very often), and
- ✓ infection (rare).

If the people doing the study are exposed to your blood or body fluids in a way that could give them a disease, your blood may be tested. The tests might check for:

- ✓ hepatitis,
- ✓ HIV (Human Immunodeficiency Virus), or
- ✓ other infections.

You and the person exposed would be told the test results. However, your name would be kept private. If your test is positive for hepatitis or HIV, we will tell you how to find counseling. You may want help in understanding what the results mean for you.

Risks of taking blood with a catheter:

Sometimes the catheter stops working. In order to get the blood we need, we may have to stick you with another needle.

A caution about giving too much blood:

Because of the amount of blood being taken, you should not give blood for other reasons for 8 weeks. For example, avoid giving blood at a blood bank or in another research study.

Risks of EMLA numbing cream:

Common Risks are:

- Temporary redness or paleness of the skin
- Mild itching, burning, or swelling
- Change in skin temperature, which may cause mild discomfort

Rare Risks are:

- Skin discoloration
- Severe allergic reaction
- EMLA overdose (lightheadedness, nervousness, confusion, dizziness, drowsiness, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression, low blood pressure, cardiac arrest).

Risks for women:

If you are pregnant now, or get pregnant during the study, please tell us. Being in this study might hurt your unborn baby, so you will not be able to join or stay in the study. Also, you should be sure you do not get pregnant for 1 month after the study. Use an effective method of birth control during this time. If you have questions about birth control, please ask the study leader.

Other unexpected risks:

You may have side effects that we do not expect or know to watch for now. Call the study leader if you have any symptoms or problems.

Could you be helped by being in this study?

You will not benefit from being in this study. However the information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?

The only choice is not to be in this study.

Will you be paid for being in this study?

You will be paid a \$75 Simon Mall Visa gift card per inpatient admission. In addition you will receive a \$50 bonus, also in the form of a gift card, for completing the medication regimen and outpatient blood draws. Therefore, if you complete the entire study you will receive a total of \$200 in gift cards.

If you do not finish the study, but complete one overnight admission, you will be paid \$75. If you are admitted for an overnight admission, but the study leader says you cannot continue, you will be paid the full amount for the admission.

You should get your payment at the final overnight admission. The income may be reported to the IRS as income.

If you owe money to any Virginia state agency, the state can use the money you earn in this study to pay those debts. These state agencies include the UVa Medical Center, VCU Medical Center or a college or university. The money may be withheld to pay back debt for such things as unpaid medical bills, taxes, fines, child support. Even if this happens, the money you earn may be reported to the IRS as taxable income.

Will being in this study cost you any money?

The following procedures/tests which are being done solely for research purposes will be provided to you at no cost: lab tests, study drugs (estradiol, progesterone, iron supplements) outpatient visits, and hospital admissions.

You or your insurance company must pay for any tests or care given beyond what is required in this study. In addition, you and your health plan may also have to pay for other drugs or treatments that are given to help you control any side effects. You will have to pay for any costs not covered by your health plan.

What if you are hurt in this study?

If you are hurt as a result of being in this study, we have no plans to pay you for lost wages, disability, or discomfort. If you are hurt in the study in a way that is unexpected (meaning *in a way that is not listed in the risks part of this form*), your insurance company may pay for your treatment. If they do not pay, University of

Virginia will treat you free of charge. If you have questions about what will be covered if you are hurt in the study, talk to the study leader. You do not give up any legal rights by signing this form.

What happens if you leave the study early?

You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include

- a) Your study physician is concerned about your health
- b) You do not follow your doctor's instructions
- c) The study sponsor closes the study for safety, administrative or other reasons

If you decide to stop being in the study, we will ask you to please notify Dr. John Marshall in writing. We also request that you will return any unused medicine and medicine bottles.

Please send notification to PO Box 800391, Charlottesville, VA 22908. Please note that any information already obtained will continue to be used unless you request in writing that we not use your information.

How will your personal information be shared?

The UVa researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address, date of birth, social security number
- Your medical records and test results that relate only to this study

Who will see your private information?

- The researchers to make sure they observe the effects of the study and understand its results
- People or committees that oversee the study to make sure it is conducted correctly
- People who pay for the study, including people at the National Institutes of Health
- Tax reporting offices (if you are paid for being in the study)
- People who evaluate study results, which can include government agencies that provide oversight such as the Food and Drug Administration (FDA)

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

What if you sign the form but then decide you don't want your private information shared? You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation. UVa researchers will do everything possible to protect your privacy.

IRB-HSR#14100

Assessment of the sensitivity of the hypothalamic GnRH pulse generator to estradiol and progesterone inhibition in early pubertal girls (JCM026)

The information collected about you will be kept confidential by UVa as required by the federal Privacy Rule. Your information will not be released outside of UVa unless it is permitted by law.

A copy of this consent form will be put in your medical record. (This is not the same as the record of this research study.) This means that everyone who is allowed to see your records will be able to find out that you are in this study. This is done so your regular doctors will know what drugs or treatment you are getting in the study. If you have other health problems during the study, they will be able to treat you properly.

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: John Marshall
Internal Medicine, School of Medicine
Box 800391
Charlottesville, VA 22908
Telephone: (434)924-2431

What if you have a concern about a study?

You may also report a concern about a study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22908
Telephone: 434-924-2620
Fax: 434-924-2932

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB-HSR Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

Conclusion

Please check one of the following:

_____ You agree to be contacted after this study is done for follow up information.

_____ You do not agree to be contacted after this study is done for follow up information.

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you understand the information given to you about the study and in this form. If you sign the form it means that you agree to join the study.

By signing below you confirm you have the legal authority to sign for this minor.

_____ PARENT/GUARDIAN (SIGNATURE)	_____ PARENT/GUARDIAN (PRINT)	_____ DATE
---	-------------------------------------	---------------

_____ PARENT/GUARDIAN (SIGNATURE)	_____ PARENT/GUARDIAN (SIGNATURE)	_____ DATE
---	---	---------------

If you are unable to obtain parental consent from both parents, explain why not:

By signing below you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

_____ PERSON OBTAINING CONSENT (SIGNATURE)	_____ PERSON OBTAINING CONSENT (PRINT)	_____ DATE
--	---	---------------

_____ TRANSLATOR (SIGNATURE)	_____ TRANSLATOR (PRINT)	_____ DATE
------------------------------------	--------------------------------	---------------

If a translator was used to explain this study to a potential subject, the translator must sign and date this line.