COMIRB
APPROVED
For Use
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Principal Investigator: **Dr. Nanette Santoro**
COMIRB No: **15-1052**
Version Date: **05-October-2020**
Study Title: **Reprometabolic Syndrome Mediates Subfertility in Obesity (Aim 1b)**

You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you do not understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about the impact of the food we eat on our reproductive hormones. You are being asked to be in this research study because you are a female with a "normal" body mass index (BMI) between 18 & 25. This study involves the use of a drug called GnRH, but it is not being used as a treatment and is not approved for this use.

Other people in this study

Up to 120 people from your area will be enrolled in this study. Up to 20 people will participate in this section of the study, completing the same activities as you, as outlined in this consent.

What happens if I join this study?

If you join the study, you will be asked to come in for 11 study visits. Depending on the length of your cycles, your participation will last up to 6 months. As part of your participation, you will be asked to consume only meals provided by this study for 30 days (see below in visits 2-5 section for more information). These meals will be high in fat but will not increase your calorie intake and should not result in weight gain.

Visit 0 (Screening): *This visit will take approximately 2 hours.*

- You were asked to fast (no food or drink) for 12 hours prior to this visit. This is because we will conduct a fasting lipid panel, which is a routinely ordered test that uses your blood to assess your risk of developing heart disease.
- We will record your weight and height to calculate your BMI.
- About 5 teaspoons of blood will be taken from a vein in your arm for blood tests routinely ordered to help determine your general health status.
- You will have an examination of your skin, head, mouth, and neck as well as your heart and stomach.
- You will have someone listen to your heart and examine your legs for swelling, and check your vital signs (temperature, pulse, and blood pressure).
- You will be asked to take a urine pregnancy test.
- You will be asked about your menstrual status, and your medication and medical history.*
- Your body composition will be measured by completing a DEXA exam. This is a non-invasive x-ray procedure with a small amount of radiation and involves lying still on a table for about 15 minutes.
- 3-day diet record or "food journal" will be provided to you. You will be asked to return the 3-day diet record, or "food journal", where you recorded a detailed description of all food and beverages you consume for 3 days. We will review this diary and discuss your diet and food preferences.
- You will be given instructions and supplies to collect your daily morning urine, when instructed, for the next four cycles (beginning with your next period). You will be given special tubes for the urine collection that have a small amount of a nontoxic preservative in them, along with labels to put onto the tubes. You will write the date on the label. You will also be given a box to store the tubes in the freezer.
- You will also be provided home ovulation predictor kits and instructions for use. These kits will help us better

predict the timing of your period and will help us schedule your next visits. Use of these kits will involve dipping a test stick in urine for several days to see if it changes color and notifying the study coordinator.

- You will be provided with an at home fecal collection kit to bring back at visit 1.1 in the Inpatient CTRC. Please bring back the most recent fecal sample you can prior to the 1.1 visit using the at home collection kit. Please follow the kit instructions.

If your screening visit laboratory tests and DEXA appear normal and the investigator determines you are eligible, you will be asked to come in for a study visit at the start of your next cycle.
*This may be completed at a Telehealth or Zoom visit prior to the in-person screening visit.

Cycle 1

Visit 1.1 and 1.2: *There will be two visits approximately 1-2 days apart.*

Frequent Sampling Study (Visit 1.1) This visit will take approximately 6-7 hours.

You are NOT required to fast prior to this visit.
You will report to the CTRC at 7am within 4 days of your first cycle start.

- You will be given a pregnancy test. You cannot continue your participation in this study if you are pregnant.
- We will record your height and weight.
- An IV will be placed in a vein in your arm and about 5 teaspoons of blood will be taken for blood tests routinely ordered to help determine your general health status.
- Frequent blood sampling will occur for 6 hours. We will draw small volumes of blood (a little less than 1 teaspoon) approximately every 10 minutes for 6 hours through the IV. After the first four hours, we will give you the study drug GnRH, through the intravenous line, and will continue to collect blood samples every 10 minutes for another 2 hours.
- At the end of the visit, we will collect approximately 1 teaspoon more of blood for another group of blood tests.
- The total amount of blood collected from you will be approximately 2/3 cup.
- Please bring your fecal sample to this visit and give it to the research coordinator.
- You will be served breakfast and lunch during this visit.
- You will be provided with a Fitbit and instructions for use. A Fitbit is a device that is worn around your wrist continuously. It tracks your activity levels and how long and how well you sleep. You will be asked to use this Fitbit every day until the end of the study.

Insulin Infusion study (Visit 1.2) This visit will take approximately 3-4 hours.

You will be required to fast (no food or drink) for 12 hours prior to this visit.
You will report to the CTRC at 7am the day after your first visit (1.1).

- We will record your height and weight.
- An insulin infusion technique will be used to measure your insulin resistance. This involves placing two IV lines in your arms. Blood will be sampled from one of your arms approximately every 10-15 minutes, which will be covered in a heating sleeve. The other arm will have a continuous infusion of insulin and dextrose. This procedure will take a total of approximately 3 hours.
- Prior to starting and at the end of the visit, we will collect approximately 1 teaspoon of blood for blood tests routinely ordered to help determine your general health status.
- The total amount of blood collected from you will be approximately 2/3 cup.

- You will be served lunch at the end of this visit.
- You will continue daily morning urine collection and use of your Fitbit.
- You will be provided with a three-month supply of iron supplements. You will be asked to take one 325mg tablet once daily for the next three months.

Cycle 2

Visits 2-5: *These visits will take approximately 30-45 minutes.*

You will report to the Clinical Translational Research Center (CTRC) on day 1 of your second menstrual cycle. At this visit you will begin a high fat diet and continue on it for approximately the next 30 days or until visit 6.2. While you are on this diet you will be asked to eat only the meals and snacks provided. This means you will also be asked to refrain from eating out at restaurants.

- Throughout this cycle you should continue collection of daily morning first urine, use of your Fitbit, intake of iron supplements and use of the home ovulation predictor kits.

You will be asked to come to the CTRC twice a week during this cycle.

At your *first visit* each week, you will:

- Pick up your meals for the first half of the week.
- Have your weight recorded.
- Return your urine collection tubes and review your Fitbit activity levels.
- Provide a fasted blood sample to be tested for fatty acids, which reflects how well the diet is working for you.

At your *second visit* each week, you will pick up food for the second half of each week and return your empty food containers. You will also have an opportunity to ask any questions you have about the diet. At you last diet visit you will receive a second fecal collection kit to return at Visit 6.1.

Cycle 3

Visit 6.1 and 6.2: *There will be two visits approximately 1-2 days apart*

Frequent Sampling Study (Visit 6.1)
You are NOT required to fast prior to this visit.
You will report to the CTRC at 7am within 4 days of your third cycle start. This visit will be exactly the same as Visit 1.1 described above, except instead of beginning use of the Fitbit and collection of your daily morning urine, you will be asked to continue these and you will be asked to eat breakfast and lunch from your high fat diet during the visit.

Please bring your second fecal sample to this visit and give it to the research coordinator or nurse.

Insulin Infusion study (Visit 6.2)
You will be required to fast (no food or drink) for 12 hours prior to this visit.
You will report to the CTRC at 7am the day after visit 6.1. This visit will be exactly the same as visit 1.2 above

Cycle 4

Visit 7: *This visit will take approximately 30 minutes.*

You will report to the Clinical Translational Research Center (CTRC) within 6 days of the start of your fourth menstrual cycle. At this visit:

- You will return your urine collection tubes and your Fitbit activity levels will be reviewed.
- We will record your height and weight.
- You will be asked to take a urine pregnancy test.
- Your body composition will be measured by completing a DEXA exam. This is a non-invasive x-ray procedure with a small amount of radiation and involves lying still on a table for about 15 minutes.
- You will continue daily morning urine collection, use of your Fitbit, and will stop taking the iron supplements. We will ask you to return your empty bottles of the iron supplements.

Cycle 5

Visit 8: *This visit will take approximately 1 hour.*

You will be required to fast (no food or drink) for 12 hours prior to this visit. You will report to the CTRC within 5 days of the start of your fifth menstrual cycle. At this visit:

- You will have an examination of your skin, head, mouth, and neck as well as your heart and stomach.
- We will record your height and weight. You will have someone listen to your heart and examine your legs for swelling, and check your vital signs (temperature, pulse, and blood pressure).
- You will be asked about your medication use.
- You will return your urine collection tubes and review your Fitbit activity levels.
- We will record your height and weight to calculate your BMI.
- About 5 teaspoons of blood will be taken from a vein in your arm for blood tests routinely ordered to help determine your general health status

At the end of visit 8, your participation in this study will end and you will be asked to complete an anonymous exit survey. If you do not complete the study in its entirety, you will still be asked to complete the survey.

Optional Future Experiments on Collected Samples:

The researchers would like to save any part of the blood, urine and fecal samples not used up by this study for future research. The choice to let Dr. Santoro keep the blood, urine and fecal samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your blood, urine and fecal samples can be kept for research, you can change your mind at any time and contact Dr. Santoro at 303-724-2041 to let her know that you do not want her to use your blood, urine and fecal samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. Santoro decides to destroy them.

In the future, people who do research with your blood, urine and fecal samples may need to know more about your health. While Dr. Santoro may give them reports about your health, Dr. Santoro will not give them your name, address, phone number or any other information that will let the researchers know who you are.

The possible benefits of research from your blood and urine include learning more about what causes infertility and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of information from your health records. Dr. Santoro will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any blood, urine or fecal collected and stored by Dr. Santoro.

Please read each sentence below and think about your choice. After reading each sentence, check "yes" or "no." If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your blood samples, you may still take part in the study.

I give my permissions for my blood and urine samples to be kept by Dr. Santoro for use in future research to learn more about problems related to obesity and pregnancy.

☐ Yes, blood only ☐ Yes, urine only ☐ Yes, fecal only ☐ Yes, blood, urine & fecal ☐ No

I give my permissions for my blood samples to be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

☐ Yes, blood only ☐ Yes, urine only ☐ Yes, fecal only ☐ Yes, blood, urine & fecal ☐ No

What are the possible discomforts or risks?

Risk of screening/safety blood draws: In this study we will need to get about 6 tablespoons for screening labs and safety labs throughout the study. This amount of blood will be withdrawn in small amounts each time, but there will be several times when blood samples are taken. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. It is common to feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

Risks of frequent blood sampling: This procedure is commonly associated with bruising and bleeding at the site of the IV line. Rarely, anemia can result if amounts of blood withdrawn are excessive. You will participate in two 6-hour frequent blood sampling sessions. During these sessions an IV will be placed in a vein in your arm and small amounts of blood (a little less than 1 teaspoon) will be drawn approximately every ten minutes (less than 1 cup total over 6 hours, or approximately 1.2 full cups of blood to be drawn in the total of two, 6-hour sessions). Rarely, anemia can result when large amounts of blood are collected. We will ask you to take iron supplements for three months while you are in this study to help prevent anemia.

During the time you are participating in this study and for 8 weeks following the completion of your participation, you will also be asked not to donate blood or have blood drawn for any other studies unless medically necessary.

Risk of study drugs:

Insulin: A common risk of use is hypoglycemia, or low blood sugar. We will monitor your glucose level every 5 minutes during the insulin infusion procedure to make sure your levels stay within a normal range.
GnRH (gonadotropin releasing hormone): This drug has minimal side effects. We only use this drug by injecting it into your vein in this study. If it is injected under the skin, sometimes it can cause itching or burning (rare). When GnRH is used with an infusion pump for several days or weeks, the following side effects have occurred, but are uncommon and not anticipated in this study: rash, itchiness, local skin or vein infection, or a black-and-blue mark at the injection site.

Dextrose: There are no foreseeable risks associated with the use of dextrose.

Iron supplements: Common side effects include an upset stomach, pain, constipation or diarrhea, nausea, or vomiting.

Risk of DEXA: As part of this study we will perform 2 DEXA scans of your body. DEXA is a way of looking inside the body by using X-rays. X-rays are a type of radiation. Your natural environment has some radiation in it. A DEXA will give you about the same amount of radiation that you would get from the environment in 4 days.

Risks of a high fat diet: While long term consumption of diets that are high in fat has been associated with heart disease, we have no reason to believe that a diet with this short of a duration will have any kind of negative impact.

Patient confidentiality*:* There is a risk that people outside of the research team will see your research information. Through operating in accordance with university standards and in compliance with HIPAA, we will do all that we can to protect your information, but it cannot be guaranteed.

Pregnancy*:* If you become pregnant, the particular treatment or procedures involved in the study may involve risks to the embryo or fetus, which are currently unclear. Before we conduct any study procedures, we will ask you to take a pregnancy test. If you are pregnant, you will not continue in the study. Please consult with your doctor regarding available contraception options.

The study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about more about the impact of the food we eat on our reproductive hormones.

This study is not designed to treat any illness or to improve your health. In addition, there may be risks, as discussed in the section describing the discomforts or risks.

Who is paying for this study?

This research is being sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Will I be paid for being in the study?

You will be paid for completion of the following procedures:

- $75/cycle for collection of urine. This is a total of $300 for collection of urine in your four cycles.
- $75/visit for completion of visits 1.1, 1.2, 6.1, and 6.2. This is a total of $300 for completing all four visits.
- $25 for completion of visits 2-5. This is a total of $100 for completing the four visits.
- $10 for each fecal sample returned.

This will add up to a total of $720.00 if you complete all of the visits. If you leave the study early, or if we must take you out of the study, you will be paid only for the visits you have completed. You will also be provided with a Fitbit as part of this study (approximately $100 value) to keep at the completion of the study.

It is important to know that payments for participation in a study is taxable income.

Will I have to pay for anything?

It will not cost you anything to be in the study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. Also, the sponsor may stop the study at any time.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Santoro immediately. Her phone number is 303-724-2041.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Whom do I call if I have questions?

The researcher carrying out this study is Dr. Santoro. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Santoro at 303-724-2041. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Santoro with questions. You can also call the responsible Institutional Review Board (COMIRB) at 303-724-1055.

You can also talk to a Subject Advocate at the Clinical Translation Research Center (CTRC). Their phone number is 720-848-6662.

A description of this clinical trial will be available on http://www.Clinical Trials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who will see my research information?

The University of Colorado Anschutz Medical Campus and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include the University of Colorado Anschutz Medical Campus and the University of Colorado Hospital.

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the University of Colorado Anschutz Medical Campus and its affiliate hospitals may not be

covered by this obligation. We will do everything we can to maintain the confidentiality of your personal information, but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Dr. Nanette Santoro
University of Colorado Anschutz Medical Campus, Obstetrics & Gynecology
12631 E. 17th Ave., Campus Box B198-1
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research participants like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- The Eunice Kennedy Shriver National Institute of Child Health and Human Development, who is paying for this research study.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. However, we will always keep the names of the research participants, like you, private. You have the right to request access to your personal health information from the Investigator.

Information about you that will be seen collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.)
- Research Visit and Research Test records

Certificate of Confidentiality

This study has been issued a Certificate of Confidentiality from the federal government to help protect your privacy. The Certificate prohibits the researchers from disclosing your name, or any identifiable information, document or biospecimen from the research, with the exceptions listed below. A certificate provides protections against disclosing research information in federal, state, or local civil, criminal, administrative, legislative or other proceedings.
These protections apply only to your research records. The protections do not apply to your medical records.
The researchers may disclose your name or identifiable information, document or biospecimen, under the following circumstances:

- To those connected with the research,
- If required by Federal, State or local laws,
- If necessary, for your medical treatment, with your consent,
- For other scientific research conducted in compliance with Federal regulations,
- To comply with mandated reporting, such as a possible threat to harm yourself or others, reports of child abuse, and required communicable disease reporting, or
- Under other circumstances with your consent.

- A Certificate of Confidentiality does not protect information you or a member of your family voluntarily release.

What happens to Data, Blood, Fecal Material and Urine that are collected in this study?

Scientists at the University of Colorado Anschutz Medical Campus and the hospitals involved in this study work to find the causes and cures of disease. The data, blood, and urine collected from you during this study are important to this study and to future research. If you join this study:

- The data, blood, and urine given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, blood, or urine collected from you.
- If data, blood, or urine are in a form that identifies you, University of Colorado Anschutz Medical Campus or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Future Experiments

In this form, you were given the option to agree to additional, optional research experiments (storage of samples for future research). You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these future experiments, as described above.

If you decline to give us permission to use and disclose your information, the samples you provide cannot be used in future experiments, but you can still participate in the main study. Please initial next to your choice:

_____ I **give** permission for my information for my information associated with optional future experiments, I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information associated with the optional future experiments to be used and disclosed.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature:_____ Date:_____

Print Name:_____

Consent form explained by:_____ Date:_____

Print Name: _____

Signature Line for witness (non-reading participants)

Witness signature: _____ Date:_____

Print Name:_____

Check: Witness of Signature ☐ Witness of consent process ☐