Evaluation of Ovarian Morphology and Function in Overweight Women During Weight Loss (NCT01785719)

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Research Participant Information Sheet and Consent Form

Project Title: *Ultrasound Characterization of Ovarian Follicle Dynamics during Weight Loss*

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Before you give your consent to participate in the study, please read the following *Participant Information Sheet and Consent Form* and ask as many questions as necessary to be sure that you understand what your participation will involve.

Key Information:
A short summary of this study to help you decide whether you want to participate is below. More detailed information is listed later in this form. If you have any questions, be sure to ask the study team.

Why am I being invited to take part in a research study?
You are being asked to take part in this study because you expressed an interest in losing weight, your BMI is $\geq$ 27 kg/m^2, and you are not planning on taking any hormonal contraception, fertility drugs, insulin-sensitizing medications and/or becoming pregnant within the next 7 to 8 months.

What is the purpose of this research study?
This study will examine ovarian follicle growth patterns, reproductive hormones, and markers of metabolism during weight loss in women with regular versus irregular/absent menstrual cycles. The purpose of this study is to identify the factors that might explain why fertility potential is compromised in some women with overweight/obesity, but not in others.

How long will this research study last?
This study will last 7 months, including 1 month of baseline data collection plus 6 months of data collection during a weight loss program.

What will you need to do?
You will be asked to come to the Human Metabolic Research Unit at Cornell University every other day during Months 1 and 7, and twice per week during Months 2 through 6. Each study visit will last approximately 15 minutes and will include a blood draw and a transvaginal ultrasound scan. Additionally, you will undergo up to 4 longer study visits (approximately 3 hours each), which will include evaluations of your body composition and metabolic status. Last, you will be asked to follow the provided Nutrisystem® D weight loss program for six months (Months 2 through 7) and to wear a provided Fitbit fitness tracker for the duration of the study.

What are the main risks of taking part in this study?
The main risks of participating in this study are pain or bruising from blood draws or the optional fat biopsy. There is a minimal exposure to radiation during the body composition scan. Any weight loss program can pose physical and mental health risks, including loss of lean body mass, dizziness, and heightened awareness of body image.

What are the possible benefits to you that may reasonably be expected from being in the research?
You will receive six months of the Nutrisystem® D program and a Fitbit device free of charge. By losing weight, you may begin to experience regular ovulations and menstrual cycles. You will also receive information at the end of the study about your health that you may choose to share with your primary care provider. Finally, you will help researchers and doctors learn more about the metabolic and reproductive changes that occur during a weight loss program.

What happens if you do not want to be in this research?
Participation in a research study is voluntary and you are free to end the study at any time. You can also decide not to participate in this study.

I. What the study is about: The researchers plan to investigate how follicles develop in the ovaries of overweight women during weight loss. Namely, the researchers plan to explore how changes in body composition, metabolic status, and reproductive hormones can influence patterns of ovarian follicle development. The researchers plan to recruit up to 50 overweight (i.e. body mass index, BMI, $\geq$ 27 kg/m^2) women with regular menstrual cycles and up to 50 overweight women with irregular/absent menstrual cycles. This study entails one month of data collection during a baseline period (Month 1), plus six months of data collection during a weight loss program (Month 2 through Month 7). This study will represent the first time that patterns of ovarian follicle development are described during weight loss. The researchers believe this study will show that an improvement in metabolic status is necessary for women to resume regular ovulations and menstrual cycles.

II. Why the research is important: In the ovaries, eggs rest in fluid-filled sacs called *follicles*. When follicles grow, they form small fluid-filled cysts that can be easily seen when we use ultrasound to view the ovaries. Recent studies have found that, in women with regular menstrual cycles, numerous follicles grow and regress together at two or three different times during the cycle (usually over a 28-day period). Several of these follicles grow to a stage wherein they develop the potential to ovulate – but, in general, only one is chosen to ovulate. This newly-discovered pattern of ovarian follicle development in women is called *follicle wave dynamics*, and it may help us understand why fertility potential is so variable in women of the same age and why some are more susceptible to infertility than others. Follicle wave dynamics may be especially relevant for understanding the impact of weight on reproductive function. We know that being overweight can impair reproductive hormone production, even in the presence of regular menstrual cycles. We also know that being overweight can increase your chances of not ovulating and having infrequent menstrual cycles. Yet, very little is known about the growth patterns of follicles in overweight women (regardless of menstrual cyclicity) and how factors (like body composition or metabolism) might play a role in the alteration of ovulation and menses. Although improvements in reproductive function can occur with weight loss, no research study has evaluated changes in ovarian follicle development during this transition. By comparing follicle wave dynamics, reproductive hormones, and markers of metabolism during weight loss in overweight women with regular versus irregular/absent menstrual cycles, the researchers plan to identify the factors that might explain why fertility potential is compromised in some women, but not in others. The goal of this research is to understand how diet, body composition, and metabolism regulate ovarian follicle development in women, so that we can better develop lifestyle and drug therapies to help women preserve their fertility potential and long-term health. These studies are especially important, because obesity has recently become the leading cause of infertility in North America.

III. What we will ask you to do: Study participation lasts 7 months and includes a combination of remote and in-person study visits as well as at-home engagement with the provided weight loss program. Remote visits will be conducted using Cornell Zoom video conferencing technology. In-person study visits will take place at Cornell University (Ithaca, NY) in the Human Metabolic Research Unit (HMRU). All participants will be expected to follow the health and safety precautions set forth by the HMRU. The researchers will inform you about these precautions, and any changes to them, over the course of the study. The study-specific expectations are listed below, in the order of occurrence.

1.) Initial Interview (90 minutes, *remote*)
2.) Screening Ultrasound Scan (30 minutes, *in-person*)
3.) Regular Visits (15-20 minutes, *in-person*)
    a. Every other day during Month 1,
    b. Twice per week during Month 2 through Month 6, *and*
    c. Every other day during Month 7.
4.) Early Morning Visits (2-3 hours, *in-person*)
    a. Once during Month 1,
    b. Once during Month 2 through Month 6 after losing 5% of your initial body weight, if attained,
    c. Once during Month 2 through Month 6 after losing 10% of your initial body weight, if attained, *and*
    d. Once during Month 7.
5.) Weight Loss Program (*at-home*)
    a. Daily engagement during Month 2 through Month 7.
6.) Exit Interview (30 minutes, *in-person*).

Initial Interview: If you are interested in participating in the study, you will undergo an Initial Interview with members of the research team via Cornell Zoom. The goals of the interview will be to collect information about your health and eligibility as well as to allow you time to ask questions about any aspect of the study. To achieve this goal, you will be asked to complete the following tasks.

1.) Review a list of Exclusion Criteria to determine whether you have any existing health conditions that might interfere with your participation in the study.
2.) Describe your current health status including:
    a. menstrual cycle history
    b. prior pregnancies and deliveries
    c. relevant medical and surgical history
    d. family history of chronic disease, *and*
    e. current use of medications, vitamins, or supplements.
3.) Complete a Weight Loss Readiness questionnaire.

Screening Ultrasound Scan: If you are eligible for the study based on the Initial Interview, you will be invited to the Human Metabolic Research Unit (HMRU) to undergo a screening ultrasound scan. The goal of the screening ultrasound is to confirm study eligibility by physical assessment. To achieve this goal, you will be asked to complete the following assessments.

1.) Transvaginal ultrasound scan to ensure optimal visualization of your ovaries and uterus.
2.) Assessment of height and weight to confirm that your BMI is $\geq$ 27 kg/m^2.

Regular Visits: If you are eligible for the study based on the Screening Ultrasound Scan, you will be invited to participate in regular visits to the HMRU. The goal of regular visits is to track development of ovarian follicles, patterns of the uterine lining, fluctuations in reproductive hormones, and changes in body mass. To achieve this goal, you will be asked to complete the following assessments.

1.) Transvaginal ultrasound scan to capture images of your ovaries and uterus.
2.) Blood draw to assess concentrations of reproductive hormones.
    Note: Ease of access to your veins is necessary for inclusion and will be evaluated throughout Month 1.
3.) Assessment of weight as well as waist and hips circumference to evaluate body mass.
4.) Menstrual pictogram survey to estimate menstrual blood loss on reported bleeding days. *
5.) Short interview to determine changes in health status and medication use.

Assessments denoted with an asterisk (*) may be completed remotely as needed.

First Regular Visit: At your first regular visit, you will complete all regular visit assessments. Additionally, you will be provided with a Fitbit fitness tracker to help us track your dietary intake and physical activity levels. You will be asked to wear the device for as many days as possible throughout the study. You will be allowed to keep the device at the end of the study.

Scheduling the First Regular Visit: If you report a history of *regular menstrual cycles*, you will be asked to contact the researchers on the first day of your next period (i.e. Day 1 of the menstrual cycle) to schedule your first regular visit on Day 10 of your menstrual cycle. If you report a history of *irregular/absent menstrual cycles*, you will be given the option to schedule your first regular visit on a day that is most convenient for you.

Scheduling Regular Visits in Month 1: Following your first regular visit, you will be asked to return to the HMRU for regular visits **every other day** for the entire month (4 weeks). The goal of regular visits in Month 1 is to capture an inter-ovulatory interval (i.e. IOI, the interval of time from one ovulation to the next ovulation). To achieve this goal, you will be asked to return for <u>daily</u> regular visits to capture the ovulation event if you are about to ovulate. If you report a history of *regular menstrual cycles*, we expect each ovulation event will occur sometime between Day 12 and Day 16 of your menstrual cycle. If there is reasonable evidence for us to anticipate an impending ovulation at the end of Month 1, you will be asked to continue attending every other day visits for up to 2 weeks until the ovulatory event is captured. If you report a history of *irregular/absent menstrual cycles*, we expect each ovulation event, if any, will occur on a random day of your menstrual cycle.

Scheduling Regular Visits in Month 2 through Month 6: During Month 2 to Month 6, you will be asked to return to the HMRU for regular study visits **twice per week** (Mondays/Thursdays *or* Tuesdays/Fridays). The goal of regular visits during Month 2 through Month 6 is to capture all ovulatory events, if any, while reducing participant burden. To achieve this goal, you will be asked to return for every other day or daily regular visits to capture the ovulation event if you are about to ovulate. Frequency of regular visits will be informed by standard physiologic markers regardless of reported menstrual cycle history.

Scheduling Regular Visits in Month 7: During Month 7, you will be asked to return to the HMRU for regular visits **every other day**. The goal of regular visits in Month 7 is to capture an IOI in a manner that mirrors Month 1. To achieve this goal, you will be asked to return for daily regular visits to capture the ovulation even if you are about to ovulate. If there is reasonable evidence for us to anticipate an impending ovulation or menses at the end of Month 7, you will be asked to continue attending every other day visits for up to 2 weeks until the ovulatory or menstrual event is captured. This could add up to two weeks of study participation beyond the 7-month mark. Nutritional support would be provided free of charge during this time.

Early Morning Visits: In addition to regular visits, you will be asked to attend an early morning visit the HMRU following an overnight fast at 2–4-time points:

1.) During Month 1,
2.) After losing 5% of your baseline body weight on the weight loss program,
Note: We anticipate this visit will be during Month 3 through Month 6, if attained.
3.) After losing 10% of your baseline body weight on the weight loss program, *and*
Note: We anticipate this visit will be during Month 5 or Month 6, if attained.
4.) During Month 7.

The goal of early morning visits is to assess metabolic status, body composition, vitals, body hair distribution, quality of life, and usual diet and physical activity. To achieve this goal, you will be asked to complete all assessments included in a regular visit as well as the following additional assessments.

1.) 2-hour oral glucose tolerance test (OGTT) to assess metabolic status.
2.) Multiple measurements to assess body composition, including:
    a. Measurements of height, weight, and waist and hips circumference,
    b. Dual x-ray absorptiometry (DXA) scan (only during Month 1 and Month 7), *and*
    c. Subcutaneous fat biopsy (optional, only during Month 1 and Month 7).
3.) Physical examination of blood pressure and pulse to assess vitals.
4.) Guided verbal interview to assess body hair distribution. *
5.) Health-related quality of life questionnaire to assess quality of life. *
6.) Multiple questionnaires to assess usual diet, physical activity and eating behaviors including:
    a. Food frequency questionnaire (only during Month 1 and Month 7) *,
    b. Physical activity questionnaire (only during Month 1 and Month 7) *, and
    c. Eating disorder examination questionnaire (only during Month 1 and Month 7). *
    Note: These three questionnaires will also be completed at a regular visit during Month 4.

All assessments denoted with an asterisk (*) may be completed remotely via Cornell Zoom as needed. For additional information about the early morning assessments, see section IV below.

Scheduling Early Morning Visits: If you have *regular menstrual cycles* or *evidence of a recent ovulation* near the planned visit time points, then your early morning visit will be scheduled at the beginning of your next menstrual cycle (i.e. between Day 2 and Day 5). Generally, you will have two weeks advance notice to schedule this visit and pick a morning that works best for you. If you have *irregular/absent menstrual cycles*, then you may schedule your early morning visits for any day near these time points. If you do not lose 5% or 10% of your baseline body weight on the weight loss program, then you will only be asked to complete early morning visits during Month 1 and Month 7.

Weight Loss Program: You will be asked to follow the Nutrisystem® D weight loss program for six (6) months during Month 2 through Month 7 of the study. Generally, Nutrisystem® D is a portion-controlled, low calorie, and low glycemic index meal delivery system. In addition, Nutrisystem® D offers a balanced meal plan consistent with nutritional recommendations of the USDA Dietary Guidelines for Americans and American Diabetes Association. Nutrisystem® D helps individuals to follow a diet of about 1250–1500 calories per day, which promotes the targeted weight loss of 1–2 lb per week. This calorie restriction method employed by Nutrisystem® D has been proven to help overweight individuals achieve real and sustainable weight loss results. To maximize the benefits of the weight loss program, you will also be encouraged to work towards: (1) Taking 10,000 steps daily or (2) Engaging in 30 minutes of moderate-to-vigorous physical activity daily. These types of activities are consistent with the physical activity recommendations of Nutrisystem® D and the USDA Dietary Guidelines for Americans. When all meals and snacks are consumed as instructed and physical activity recommendations are followed, typical weight loss exceeds 2 lb per week for the first six weeks and tapers off to 1–2 lb per week thereafter. These changes can result in an average loss of 15-20% baseline weight by the end of the six-month program.

During Month 1, you will meet with a member of the research team in-person or remotely for instructions on how to implement Nutrisystem® D into your lifestyle. They will work with you to customize your meals based on personal dietary preferences from the options available. The established Nutrisystem® D program will not be modified during the study. You will also be advised on how to purchase grocery items that will complete your calorie and nutrient requirements on the Nutrisystem® D program. Lastly, you will be informed that the program may not provide sufficient micronutrients at its lower calorie level. You will be encouraged to take a daily multivitamin to help meet your micronutrient needs.

At the start of Month 2, you will begin to receive the Nutrisystem® D meals as part of the six-month weight loss program. You will be provided with 28-days of ready-to-eat meals per month *free of charge* (i.e. 28 breakfasts, lunches, dinners, and desserts). Meals will be delivered to your home at the beginning of each month. You will meet with a member of the research team in-person or remotely once every two weeks to manage any roadblocks to weight loss as they emerge and discuss behavioral strategies for weight loss. At the start of Month 5, you will be given the option to either: (1) continue with a 28-day plan *or* (2) transition to a 24-day plan. The 24-day plan may be preferable if you would like to have greater variety in your food choices and/or begin preparing to transition off the program before the end of the study. If you choose the 24-day plan, then you will be asked to prepare your own meals on four days of each month. The research team will provide you with sample recipes, comparable to meals on Nutrisystem D®, to use on these days.

To monitor program adherence, you will be asked to keep track of your dietary intake and physical activity during Month 2 through Month 7 You will be asked to record your daily dietary intake with the Fitbit application if you have access to a compatible device (e.g. smartphone or tablet). A paper food diary will be provided to if you do not have access to a compatible device. You will be able to automatically track any physical activity by wearing the provided device daily. Dietary intake and physical activity logged on the Fitbit application will be regularly monitored by the research staff Non-adherence to the program (i.e. not consuming the packaged and/or home-prepared meals as well as recommended additions) may result in early termination of study participation *(see section X below)*.

Exit Interview: At your final regular visit you will receive a summary of the real-time data collected during your participation. You will also be given the option to enroll in a follow-up study that occurs in the six months after the weight loss program.

IV. What are the details and risks of the study procedures:

Transvaginal Ultrasonography: A transvaginal ultrasound scan involves the insertion of an ultrasound probe into the vagina. It is necessary to move the probe during the procedure to obtain pictures of both your ovaries and your uterus. This procedure normally does not cause any discomfort; however, you may request that the ultrasound scan be stopped at any point in time. You will be given the option of inserting the ultrasound probe yourself or having the researcher insert the probe for you. The ultrasound probe will be covered with non-latex sheath. You will be given be a sheet to drape yourself with and you will be covered from the waist down during the ultrasound scan. A member of the research team will perform the ultrasound scan and each exam will take approximately 5–10 minutes. A chaperone will be present in the ultrasound suite during the exam. If you prefer a chaperone not to be present, you may ask the researcher to have the chaperone leave the ultrasound suite. It is important to know that a second person will always be available in the

HMRU when an ultrasound scan is being performed. Ultrasound exams may be associated with minor discomfort upon insertion of the transvaginal probe and a feeling of pressure in the vagina or belly. To minimize discomfort, you will be asked to empty your bladder and an experienced sonographer will conduct the ultrasound scans. There is no evidence of harm to the ovaries, uterus, or embryo (should you become pregnant during the study) resulting from the use of ultrasound at the levels used in this study. To minimize risk, only low frequency ultrasound (9–12 MHz) will be used to visualize the ovaries and uterus. It is important to know that the researcher performing the ultrasound scans is not a physician and is not qualified to make clinical recommendations. These ultrasound scans are performed strictly for research purposes and no physician will review your ultrasonographic images. This procedure is limited to research applications only and does not provide/allow for diagnosis of ovarian or pelvic abnormalities.

Phlebotomy: Having your blood drawn involves exposing the inner surface of your arm and having a tourniquet tied around your arm above the intended site of venipuncture. A small area of skin around the vein will be swabbed with alcohol and a person experienced in drawing blood will pierce your vein with a small needle attached to a blood collection tube. Approximately 6 mL will be drawn into the tube before the tourniquet is released and the needle withdrawn from the vein. Pressure is then applied to the site of puncture for several seconds before being covered with a band-aid. Drawing blood from a vein may cause bruising, prolonged bleeding, and infection at the site of puncture. Drawing blood from a vein may also cause lightheadedness or fainting. To minimize risk, the site of puncture will be swabbed with alcohol to disinfect the area, disposable sterile needles and tubes will be used to collect blood and pressure will be applied to the puncture site following the blood draw to minimize bruising. You will also be provided with information on how to monitor for signs of infection and care for the wound. It is important to know that the researcher drawing and analyzing your blood is not a physician and is not qualified to make clinical recommendations. These blood tests are performed at the HMRU strictly for research purposes. No physician will review the results of these blood tests since the researchers are not using these tests to make a diagnosis, but rather to understand how differences in reproductive potential and metabolism might be different in women with different body compositions.

Menstrual Pictogram (MP): The MP allows the investigator to estimate total menstrual blood loss by asking questions about sanitary napkin and/or tampon usage. The MP will be given using a regenerating survey link for each reported day of bleeding. The MP will take approximately 5 minutes to complete. To minimize confidentiality risks, you will have the opportunity to complete the online questionnaire on a computer in a secure area or on a personal electronic device. Research staff will be available in-person or remotely to answer any questions you may have.

Oral Glucose Tolerance Test (OGTT): An OGTT involves coming to the HMRU after an overnight fast to have your blood drawn 5 times after drinking a concentrated sugar solution. The researchers are curious about how your blood sugar levels change after you ingest sugar. When you arrive, you will have an initial blood sample drawn and a drop of your blood will be used to immediately measure your fasting sugar levels. If your fasting sugar is within the normal range, you will be given a sugar solution to drink over a 10-minute period. Once you have finished drinking the solution, the researcher will start a timer to ensure that blood samples are taken 30, 60, 90, and 120 minutes later. Each of these blood samples will be immediately tested for their sugar levels.

If your fasting sugar level is abnormally high or you know that you are diabetic, you will not be asked to complete the test. If your value ranges between 120–200 mg/dL, then the researcher will advise you to contact your primary care provider as soon as possible. If your value is higher than 200 mg/dL, then you will be advised to call your primary care provider urgently or will be directed to the emergency room if you do not have a primary care provider. If the sample taken at the 2-hour mark shows sugar levels higher than 200 mg/dL, then similar to above, you will be advised to call your primary care provider urgently or will be directed to the emergency room if you do not have a primary care provider. If your 2-hour value is slightly higher than expected (i.e., ranges from 140–200 mg/dL), then you will be advised to contact your primary care provider as soon as possible.

Dual X-ray Absorptiometry (DXA) Scan: DXA uses low-dose x-ray to capture images of the body. The DXA scan will provide researchers with a highly accurate measurement of how much fat your body has and how it is distributed throughout your body. The DXA scan is being performed strictly for research purposes and no physician will view the results of your scan. This procedure is limited to the assessment of body composition and therefore, does not provide diagnosis of any medical conditions. Having a DXA scan involves lying still on the bed of a DXA scanner and having a whole-body scan taken over the course of about 6 minutes. You must be able to lie still and breathe normally over these 6 minutes. You will be asked to wear a gown for the procedure only if your own clothes have metal components

such as zippers, clasped or underwire. Because the DXA involves some radiation exposure, you will be provided with a urine pregnancy test kit when you arrive at the HMRU and will be asked to perform this pregnancy test before undergoing the scan. Although the low level of exposure is not harmful to the ovaries and uterus, the risks to a developing fetus are uncertain. To minimize risk, a NYS Licensed Technologist will administer scans and scans will only be performed in women that demonstrate a negative pregnancy test result. There are several other reasons why someone may not be eligible to have a DXA, as well as factors that can influence the accuracy of the test. The researchers will provide you with an additional information sheet on DXA, so you will be made aware of these issues before the scan. You will be asked to fill out this additional consent form the day of the DXA scan. It is important to know that the researcher ordering your DXA scan is not a physician and is not qualified to make clinical recommendations. These scans are performed strictly for research purposes and no physician will review your scan.

Subcutaneous Fat Biopsy: The fat biopsy involves removing a 2–3mm piece of skin with underlying fat to obtain fat cells that lie just beneath the skin's surface. The skin will first be swabbed with alcohol and then a 2–3mm puncture will be made with a sterile, disposal punch biopsy tool that is approximately 10mm deep. Only a few fat cells are needed so the procedure will be performed within minutes. Prior to the day of the skin biopsy, you will be provided with a vial of anaesthetic cream and Tegaderm® patch to take home with you. You will be instructed on how to apply the numbing cream onto the patch and how to stick the patch onto your body (i.e. the hip/gluteal region). You will be advised to place the patch on your body at least 45 minutes prior to your visit to the HMRU. The researchers are interested in analysing fat cells since newly discovered hormones produced by fat have been shown to influence ovulation, reproductive hormone secretion, and risk of developing diabetes. A subcutaneous fat biopsy may cause tenderness, inflammation, bruising, prolonged bleeding at the site of puncture, infection, or scarring. To minimize risk a local anesthetic cream will be used to numb the skin and a sterile tool with only a 2–3mm diameter will be used to puncture the skin and take the fat sample. A sterile band-aid (Steri-Strip®) will be used to close the biopsy site and reduce the risk of scarring and infection. You will also be provided with information on how to monitor for signs of infection and care for the site of puncture.

Diet, Physical Activity, and Eating Behavior Assessments: The VioScreen™ Food Frequency Questionnaire (FFQ) allows the investigator to efficiently collect information on your usual dietary intake. It asks about the types of food you have consumed, portion sizes, and frequency of intake within the last three months. The VioScreen™ FFQ takes approximately 30 minutes to complete. The Physical Activity Questionnaire (PAQ) is a self-administered questionnaire that asks about physical activity and other habits within the previous month. It provides the investigator with comprehensive information on your usual physical activity levels. The PAQ will take approximately 30 minutes to complete. The Eating Disorder Examination Questionnaire (EDEQ) is a self-administered questionnaire that asks about disordered eating behaviors and thoughts over the past week. The EDEQ takes approximately 10 minutes to complete. Please note that the researchers are not mental health professionals and will not follow up on individual survey responses. At the time of the EDEQ administration, participants will receive a Cornell Health resource about eating disorders and contact information for relevant health care providers. To minimize confidentiality risks, a member of the research team will provide you with a username and password and you will have the opportunity to complete the online questionnaires on a computer in a secure area. You will not be interrupted during this time and we will be available to answer any questions you may have. Please note that the researchers are not mental health professionals and will not be following up on any survey responses.

Weight Loss Program: The Nutrisystem® D program is as portion-controlled, low calorie, and low glycemic index (GI) meal delivery system. It has been proven to help overweight individuals achieve real and sustainable weight loss results. It offers a balanced meal plan consistent with the nutritional recommendations of the USDA Dietary Guidelines for Americans and American Diabetes Association. It is safe for independent consumer consumption. However, the researchers will monitor your weight throughout the study to ensure that you do not experience unsafe weight loss (i.e. to a BMI <18.5 kg/m^2). If you lose substantial weight and shift into the normal-weight category (i.e. BMI 18.5–24.9 kg/m^2) before the end of the six-month program, then you will be asked to transition to a weight maintenance diet for the remainder of the study. A member of the research team will work with you to add foods to the provided Nutrisystem® D program to ensure that you can maintain your weight. This approach is consistent with Nutrisystem, Inc.'s recommendations for appropriate weight maintenance. If your BMI drops below 18.5 kg/m^2, then your participation in the study will be discontinued and you will be provided with the full compensation (*see below*). You will also be encouraged to follow-up with your primary healthcare provider. In addition, any weight loss program can cause constipation, muscle cramps, dehydration, diarrhea, dizziness, dry or cold skin, fatigue, gallbladder inflammation or

gallstones, gout, hair loss, headaches, heart palpitations, loss of lean body mass, reduced tolerance to cold, and other possible side effects. Any weight loss program can also lead to increased thoughts about food and eating, as well as heightened awareness of body image. To minimize risks, you will be instructed on proper use of the Nutrisystem® D program by a member of the research team. You will also have constant contact with the researchers during your regular visits, and they will use some of that time to follow up with you about your progress and concerns. If any concerns associated with dieting arise, then the researchers will recommend that you contact your primary healthcare provider, or if you are a student, that you contact Cornell Health at (607) 255-5155 or log onto myCornellHealth, to evaluate your continued participation in the study.

Use of Video Conferencing Technology for Remote Study Participation: Your confidentiality will be kept to the degree permitted by the technology being used. While no technology can guarantee to be free of security vulnerabilities, we have taken steps to minimize the likelihood of third-party communications interception. Remote visits will take place via the secure Cornell Zoom platform. Access to these Zoom calls will require a special invitation link and password, and the calls will not be recorded.

V. Eligibility: You are eligible to participate in this study if you are between the ages of 18–35, are considered overweight by the World Health Organization criteria (i.e. BMI $\geq$ 27 kg/m^2) and are interested in losing weight, and have not taken hormonal contraception, fertility medications, or insulin sensitizers in the last two months. During the Initial Interview, you will also be asked to review a list of Exclusion Criteria to determine if you have any existing health conditions that might interfere with your participation in the study. If you wish to participate in the study, you must be willing to refrain from using hormonal contraception, fertility medications, or insulin sensitizers during the study, because follicle growth may be affected by these drugs. If you are sexually active, you will be encouraged to use other methods of contraception to avoid becoming pregnant during the study. You must be willing to report the use of any medications or drugs during this study because some medications, including herbal formulations, may affect follicle growth and egg release. If you wish to participate in the study, then you must also be willing to follow the Nutrisystem® D program. You must be willing to report any failure to adhere to this diet to members of the research team.

VI. Benefits of the Study: By participating in this research study, you will receive six months of the Nutrisystem® D program *free of charge*. By losing weight, you may begin to experience regular ovulations and menstrual cycles. However, these events might not yield changes in your fertility status. At the end of the study, results from your ultrasound scans, weight and waist/hips circumference measurements, oral glucose tolerance tests, DXA scans, and dietary assessments will be made available to you. We recommend that you share your results with your primary healthcare provider so that you may be counseled on any issue that you or the researchers feel is important. Should the researchers consider a finding unexpected, they will provide a written description of these findings to you.

VII. Compensation: A total payment of $2,000 will be provided after having completed participation in this study. The financial compensation will be provided in addition to the six-month subscription to the Nutrisystem® D program and the Fitbit – a roughly $2,000 value. You will be paid the dollar amounts indicated below in four allotments ($250 at Week 4; $500 at Week 12; $500 at Week 20; and $750 at Week 28). If you are unable to complete the study, a prorated payment will be assessed, based on the number of weeks completed (e.g. $62.50 per week for Week 1 to Week 20 or $93.75 per week for Week 21 to Week 28). If you are unable to complete the study and wish to keep the Fitbit device, then its value will be deducted from your prorated payment.

VIII. Use of Tissue Samples and Images for Future Studies: The ultrasound images and biological specimen that we collect during the study will be stored for potential use in future studies. At present, we have no other specific plans for these images and specimen outside of the research objectives of this study. However, we imagine that these excess images and specimen might be very useful in helping to address future research questions that may arise following the completion of this study. At the time of storage, the images and specimen will be identified only by catalogue numbers and any link to your personal information will be removed. The Principal Investigator will oversee the storage of these images and specimens for up to 15 years and will regulate access to these data by other researchers. Because your personal information will no longer be linked to the stored images and specimen, it will not be possible for a participant to have future access to the images and specimen.

IX. Confidentiality: In the research records for this study, you will be identified by your initials and an assigned study subject number only. Access to identifying information in the research records will be limited to members of the

Research Team. We may also need to collect some identifying information for administrative purposes (i.e. for Nutrisystem, Inc. orders and delivery; study compensation; Cornell parking services; and/or an unexpected finding report); but, this will not be linked to the research records. In the unlikely event of an emergency, we will also need to provide your information to medical and/or emergency assistance personnel. The results of this study may also be used for scientific publications, but your identity will not be disclosed. Research records will be kept in a locked file cabinet and a password-protected computer database; only the researchers will have access to the study records. Please note that electronic communication (e.g. email, text-messaging, Cornell Zoom video conferencing) may not be private or secure. Though precautions are taken to protect your privacy, you should be aware that information sent through electronic communication could be intercepted by a third party.

In addition, please note that, if you choose to use the Fitbit device and application as self-monitoring tools, then you will be asked to provide Fitbit's website with identifiable information (e.g. name, contact information, and date of birth). You will also be asked to bring your device to every regular visit and provide the researchers with access to any dietary or physical activity data that you record throughout the study. Any information that you choose to share with the researchers will be kept in a password-protected computer database. However, it is important for you to be aware that the Fitbit Privacy Policy indicates that your personal information could also be shared with third-party websites. Please review the link below before you decide to use these tools. The research team and Cornell University are not affiliated with Fitbit and are not responsible for any distribution of your personal information made by the website: https://www.fitbit.com/legal/privacy-policy.

De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

To help us protect your privacy, this study is covered by a Certificate of Confidentiality from the National Institutes of Health (NIH). With this Certificate, we cannot be forced (for example by court order or subpoena) to disclose information that may identify you in any federal, state, local, civil, criminal, legislative, administrative, or other proceedings. In general, we cannot disclose information that may identify you to any other person who is not connected with this research, unless you give consent for that information to be disclosed. The researchers will use the Certificate to resist any demands for information that would identify you, except to prevent serious harm to you or others. You should understand that a Certificate of Confidentiality does not prevent you, or a member of your family, from voluntarily releasing information about yourself or your involvement in this study.

X. Taking part is voluntary: Your participation in this study is purely voluntary. You may decide not to participate or may withdraw at any time. If you are a student, staff, or faculty member at Cornell University and you decide not to participate or to later withdraw from the study, then your decision will not affect your academic standing, employment, promotion, or the services you would otherwise expect to receive at Cornell.

Additionally, your participation in this study may be ended at any time without your consent. Reasons may include but are not limited to: your failure to follow study instructions, unsuccessful weight loss, certain unexpected events (e.g. an unexpected finding detected on ultrasound or intolerance for any of the study procedures), or study cancellation due to administrative reasons. If you fail to follow study instructions, experience certain unexpected events, or if the study is cancelled due to administrative reasons, then you will be immediately provided with an exit summary of the data collected to date and a prorated payment. Your degree of weight loss will be evaluated with respect to Nutrisystem® D standards during Month 3 of the study. If it seems the program has been unsuccessful in helping you to lose weight, then you will be encouraged to discuss its efficacy with the researchers, and to decide whether your continued participation in the study is warranted. If, after one additional month of the intervention (during Month 4 of the study), the program is still unable to help you lose weight, you will no longer be eligible to remain in the study. You will be provided with an exit summary of the data collected to date and a prorated payment.

XI. Funding: This research study is/has been funded by grants provided to Cornell University by Nutrisystem® D, the Academy of Nutrition and Dietetics Foundation, National Institutes of Health, United States Department of Agriculture, President's Council of Cornell Women, Canadian Institute for Health Research, and the PCOS Awareness Association.

XII. Incidental Findings: It is possible that the researchers may detect an anomaly related to the items being investigated by a study procedure. This is called an "incidental finding." Incidental findings may or may not be medically significant. If an incidental finding is detected, then you will be notified and provided with relevant documentation (i.e. ultrasound exam picture and/or summary of results) to share with your primary health care provider, if you wish to do so. Because the procedures conducted for this study are not medical, the researchers cannot provide any medical diagnoses or communicate incidental findings to your primary care provider on your behalf. The research team and Cornell University are not responsible for follow-up examination or treatment of any incidental finding. The decision to proceed with further examination or treatment of an incidental finding resides with you. You or your insurance company will be responsible for payment of follow-up examinations or treatment. Insurance may not cover these expenses, and life, medical, or long-term disability insurance may be affected if an incidental finding proves to be of clinical significance. **To participate in the study, you must agree to potentially receive incidental findings.**

Please mark here to indicate that you agree to receive any incidental findings. ☐

XIII. Questions Regarding Participation: If you have any questions regarding your participation in this study, please call the Principal Investigator, Marla Lujan PhD, Assistant Professor of Human Nutrition, at (607) 255-3153 or marla.lujan@cornell.edu. If you have any questions or concerns regarding your rights as a study subject, you may contact the Cornell University's Institutional Review Board (IRB) at (607) 255-5138 or access their website at www.irb.cornell.edu. Participants may also report their concerns or complaints anonymously through Ethicspoint www.hotline.cornell.edu or by calling toll free at 1-866-293-3077. Ethicspoint is an independent organization that serves as a liaison between the University and the person bringing the complaint so that anonymity can be ensured.

Sample Schedule for a Participant

Participating in the study involves a commitment of seven months. Below is a hypothetical schedule of your visits to the HMRU. Please note that, during Month 2 through Month 6, Regular Visits can occur on Mondays/Thursdays (shown below) *or* Tuesdays/Fridays, depending on your preference and unit availability. In addition, if you are about to ovulate at any time during the study, then we will invite you to return for daily ultrasound scans to catch the ovulation. Early Morning Visits will occur at 2–4-time points, depending on your degree of weight loss.

MONTH 1	**Sunday**	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week 1 *Baseline*		TVUS Blood Weight		TVUS Blood Weight		TVUS Blood Weight	
Week 2 *Baseline*	TVUS Blood Weight		TVUS Blood Weight		TVUS Blood Weight		TVUS Blood Weight
Week 3 *Baseline*		TVUS Blood Weight		TVUS Blood Weight		TVUS Blood Weight	
Week 4 *Baseline*	TVUS Blood Weight		TVUS Blood Weight		TVUS Blood Weight		TVUS Morning Visit DXA Fat
MONTH 2	**Sunday**	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week 5 *Nutrisystem® D*	*Food delivery*	TVUS Blood Weight			TVUS Blood Weight		
Week 6 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
Week 7 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
Week 8 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
MONTH 3	**Sunday**	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week 9 *Nutrisystem® D*	*Food delivery*	TVUS Blood Weight			TVUS Blood Weight		
Week 10 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
Week 11 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
Week 12 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		TVUS Morning Visit
MONTH 4	**Sunday**	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week 13 *Nutrisystem® D*	*Food delivery*	TVUS Blood Weight			TVUS Blood Weight		
Week 14 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
Week 15 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
Week 16 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		

MONTH 5	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Week 17 *Nutrisystem® D*	*Food delivery*	TVUS Blood Weight			TVUS Blood Weight		
Week 18 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
Week 19 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
Week 20 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		TVUS Morning Visit
MONTH 6	**Sunday**	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week 21 *Nutrisystem® D*	*Food delivery*	TVUS Blood Weight			TVUS Blood Weight		
Week 22 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
Week 23 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
Week 24 *Nutrisystem® D*		TVUS Blood Weight			TVUS Blood Weight		
MONTH 7	**Sunday**	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week 25 *Nutrisystem® D*	*Food delivery*	TVUS Blood Weight		TVUS Blood Weight		TVUS Blood Weight	
Week 26 *Nutrisystem® D*	TVUS Blood Weight		TVUS Blood Weight		TVUS Blood Weight		TVUS Blood Weight
Week 27 *Nutrisystem® D*		TVUS Blood Weight		TVUS Blood Weight		TVUS Blood Weight	
Week 28 *Nutrisystem® D*	TVUS Blood Weight		TVUS Blood Weight		TVUS Blood Weight		TVUS Morning Visit DXA Fat

Abbreviations: TVUS, transvaginal ultrasound scan; **Blood**, blood draw; **Weight**, weight, and waist/hips circumference measured; **Morning Visit**, includes an oral glucose tolerance test, physical examination (i.e. weight, waist/hips circumference, body hair distribution), vitals assessment (i.e. blood pressure, pulse), and health-related quality of life questionnaire; **DXA**, dual x-ray absorptiometry scan; **Fat,** subcutaneous fat biopsy; and  diet, physical activity, and eating behavior assessments.

Statement of Consent

I have read and understood the attached Research Participant Information Sheet, and I freely and voluntarily agree to take part in the study entitled *Ultrasound Characterization of Follicle Dynamics during Weight Loss*. I understand that the researcher is not a physician and that I am not taking part in the study for the purpose of diagnosis or treatment of any medical condition. I understand that by losing weight I may begin to experience regular ovulations and menstrual cycles, but that these events might not necessarily yield changes in my fertility status. I understand that I will be encouraged to share expected or unexpected findings made by the researchers with my primary care provider and that my participation in the study may be terminated if these findings are thought to interfere with the study. I understand that any medical costs related to the treatment of unexpected findings become the responsibility of me and my insurance provider.

I have been given a copy of the Research Participant Information Sheet and will be given a copy of this signed and dated Consent Form. I have received an explanation of the purpose and duration of the study and am aware of the potential benefits and risks associated with participating in this study. I was given sufficient time and opportunities to ask questions and to reflect on my understanding of what my participation in this study will entail. I have received satisfactory answers to my questions and feel well-informed about my decision to participate in this study. I agree to cooperate fully with the study personnel and will keep them informed of any medicines, drugs, or alternative therapies (e.g. herbal remedies) I am taking or have taken in the recent past, as well as any other changes in my adherence to study instructions. I have also disclosed my knowledge of any conditions (e.g. allergies, vaginal abnormalities, blood disorders) that might affect my eligibility to participate. Study personnel or other regulatory authorities may wish to review my study records to verify the information collected. If I choose to use the Fitbit device and application as self-monitoring tools, then I agree to accept Fitbit's Terms of Use and understand that the researchers are not responsible for distribution of my personal data to third parties by the website. I have been assured that my name, address, and telephone number will be kept confidential to the extent permitted by applicable laws or regulations. By signing this document, I give permission for such review and data collection.

Signature of Participant: _____ Date: _____

Printed Name of Above: _____

This consent form will be kept by the researcher for at least three years beyond the end of the study.

Do you give the researchers permission to use your blood, tissue, or images for future research?
Please indicate if you agree to let us use your samples for future research. You do not have to give permission to use your samples for future research to participate in other parts of this study. Please ask questions if you do not understand why we are asking for your permission to use your blood samples and ultrasound images for future research.

I agree to allow use of my blood samples or ultrasound images for future research. *Please check Yes or No.*

- ☐ Yes – Please sign: _____
- ☐ No

Do you give the researchers permission to re-contact you for participation in future studies?
Please indicate if you agree to let us re-contact you for participation in future studies. You do not have to give permission to re-contact you for participation in future studies to participate in this study. Please ask questions if you do not understand why we are asking for your permission to re-contact you for participation in future studies.

I agree to allow the researchers to re-contact me for participation in future studies. *Please check Yes or No.*

- ☐ Yes – Please sign: _____
- ☐ No

For Researchers: I confirm that I have explained the purpose and procedures of this study, as well as any potential risks and benefits to the subject whose name and signature appears above.
Signature of Researcher: _____ Date: _____

Printed Name of Above: _____ Study Role: _____