Research Participant Information Sheet and Consent Form

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

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You are being asked to volunteer in a research study in the Women's Imaging Research Laboratory because you have a history of either regular or irregular/absent menstrual cycles, are overweight and interested in losing weight, are not planning to take hormonal contraception, fertility drugs, or insulin sensitizing medications for the next seven months, and are not intending to become pregnant in the next seven months. 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.

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, $\geq$ 25 kg/m^2) 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.

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.

What we will ask you to do: The study is divided into 4 types of visits. Length of participation is 7 months.

(1) An initial interview and ultrasound scan with members of the research team (90 minutes).
(2) Regular visits:
    a. Every other day during Month 1 and Month 7 (15–20 minutes) *and*
    b. Twice per week during Month 2 through Month 6 (15–20 minutes).
(3) Up to four early morning visits following overnight fasts (~3 hours).
(4) An exit interview with members of the research team (~30 minutes).

Initial Interview and Ultrasound Scan: If you are interested in participating in the study, you will be invited to an initial interview with members of the research team at the Human Metabolic Research Unit (HMRU) on the second floor of Martha Van Rensselaer Hall (MVR). The goals of the interview will be to collect information about your health and eligibility and to allow you time to ask questions about any aspect of the study. You will be asked to review a List of Exclusion Criteria to determine whether you have any existing health conditions that might interfere with your participation in the study. You will be prompted to describe your current health status including: menstrual cycle history; prior pregnancies and deliveries; relevant medical and surgical history; family history of chronic disease; and current use of medications, vitamins, or supplements. You will also have your height and weight taken (to calculate your BMI), undergo a screening ultrasound scan (to confirm optimal visualization of your ovaries and uterus), and complete a Weight Loss Readiness Test (to determine whether you are motivated to lose weight). If you are eligible to participate and report a history of *regular menstrual cycles*, you will be asked to call the researchers on the first day of your next period (i.e. Day 1 of the menstrual cycle) to arrange a start date on Day 10 of your menstrual cycle. If you are eligible to participate and report a history of *irregular/absent menstrual cycles*, then you will be given the option to start the study on a day that is most convenient for you. At the initial interview, 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 on your arm for as many days as possible throughout the study. You will be allowed to keep the device at the end of the study.

Regular Visits: Regular visits to HMRU will involve undergoing a transvaginal ultrasound scan to capture images of your ovaries and uterus. The ultrasound scans will allow the researchers to track how follicles are developing in your ovaries and see how your uterus is responding to hormones produced by the growing follicles. Regular visits will occur at two different frequencies during the study:

- *During Month 1 (baseline) and Month 7 (weight loss program)*:
  - Ultrasound scans will be performed every other day for the entire month.

- *During Month 2 through Month 6 (weight loss program):*
  - Ultrasound scans will be performed twice per week (Mondays/Thursdays *or* Tuesdays/Fridays).

If you have *regular menstrual cycles*, then ultrasound scans will be performed every other day for one inter-ovulatory interval (i.e. IOI; from one ovulation to the next ovulation) during Month 1. We will begin every-other-day visits on Day 10 of your menstrual cycle to ensure we do not miss your first ovulation, which we expect to occur sometime between Day 12 and 16. At the beginning of Month 2 (and after your second ovulation), we will transition to twice-weekly visits and scans will be performed twice per week for the next five months. At the beginning of Month 7, we will transition back to every-other-day visits to ensure we capture another IOI and can perform direct comparisons with data collected in Month 1. If you have *irregular/absent menstrual cycles*, then scans will be performed every other day for four weeks during Month 1. We will begin every-other-day visits on a day that is most convenient for you. At the beginning of Month 2, we will transition to twice-weekly visits and scans will be performed twice per week for the next five months. At the beginning of Month 7, we will transition back to every-other-day visits to enable direct comparisons with data collected in Month 1. Please note that, regardless of menstrual cyclicity, 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 event.

Following each ultrasound scan, you will also have your blood drawn to allow the researchers to track changes in hormones that occur with ovarian follicle development and ovulation. Therefore, ease of access of your veins is necessary for inclusion and will be evaluated throughout the baseline month. Your weight and waist and hips circumference will also be measured to monitor any fluctuations that occur during the study.

Early Morning Visits: You will be asked to visit the HMRU following an overnight fast at 2–4-time points:

(1) During Month 1 (baseline)
(2) After you lose 5% of your baseline body weight on the weight loss program (likely during Month 3)
(3) After you lose 10% of your baseline body weight on the weight loss program (likely during Month 5)
(4) During Month 7

The following additional tests will be performed:

(1) 2-hour oral glucose tolerance test (OGTT)
(2) Assessment of height, weight, waist and hips circumference, and body hair distribution
(3) Assessment of vitals (i.e. blood pressure and pulse)
(4) A health-related quality of life questionnaire

A dual x-ray absorptiometry (DXA) scan and subcutaneous fat biopsy will also be performed during the early morning visits in Months 1 and 7. If you have *regular menstrual cycles* or evidence of a recent ovulation near these time points, then your early morning visit will be scheduled at the beginning of your next menstrual cycle (i.e. between Day 2 and 5). Menses generally occurs two weeks after ovulation, so you will have several days to pick a morning that works best for you. If you have *irregular/absent menstrual cycles*, then you may schedule your early morning visit 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 an early morning visit in Months 1 and 7.

Usual Diet and Physical Activity Assessments: At the end of Month 1 (before the weight loss program), Month 4 (after three months of the weight loss program), and Month 7 (after six months of the weight loss program), a member of the research team will meet with you to assess your *usual* dietary intake and physical activity. You will be asked to complete a food frequency questionnaire (FFQ; online using Vioscreen™) and physical activity questionnaire (PAQ; online using Qualtrics). Each questionnaire will take 30 minutes to complete. We will do our best to perform these assessments during your early morning visits in Months 1 and 7. However, this may be challenging during Month 4, because the timing of the mid-intervention early morning visit(s) will depend on your degree of weight loss. Thus, please note that, completing the diet and physical activity assessments may extend the duration of one of your regular visits in Month 4.

Weight Loss Program: By participating in this study, you will receive six months of the Nutrisystem® D weight loss program (i.e. 3 meals and 1 dessert per day) *free of charge*. During the first two weeks of the study, you will meet with a member of the research team for instructions on how to implement Nutrisystem® D into your lifestyle. Generally, Nutrisystem® D is a portion-controlled, low calorie, and low glycemic index (GI) meal delivery system, which helps individuals to follow a diet of about 1250–1500 calories per day. Because this caloric intake promotes the targeted weight loss of 1–2 lb per week, Nutrisystem® D has been proven to help overweight individuals achieve real and sustainable weight loss results. When *all* meals and snacks are consumed *as instructed*, typical weight loss exceeds 2 lb per week for the first six weeks, and then 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 six months. In addition, Nutrisystem® D offers a balanced meal plan consistent with nutritional recommendations of the USDA Dietary Guidelines for Americans and American Diabetes Association. However, it is important for you to know 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. After baseline data collection is complete (i.e. after Month 1), you will begin to receive the Nutrisystem® D meals as part of the six-month weight loss program. Meals will be delivered to your home address at the beginning of each month. Adherence to the program includes the consumption of packaged meals plus recommended additions. A member of the research team will work with you to customize your meals from the various options available. You will also be advised on how to purchase grocery items that will complete your calorie and nutrient requirements on the Nutrisystem® D program. Although you will have the opportunity to customize your meals based on personal dietary preferences, the established Nutrisystem® D program will not be modified in any other way during the study. 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. *Adherence:* You will be asked to keep track of the following information throughout the weight loss program: (1) your dietary intake; (2) your physical activity; (3) your menstrual cycles; and (4) any changes in health status and/or medication use. You will be asked to record your 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 Fitbit device. You will be asked about your menstrual cycles, health status, and/or medication use at the regular visits.

Exit Interview: You will be asked to visit the HMRU one final time at the end of the study. 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.

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 during the study. 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 event. 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

Sample schedule (continued)

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		

Sample Schedule (continued)

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 dietary and physical activity assessments.

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.

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.

Usual Diet and Physical Activity Assessments: The VioScreen™ 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 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. 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 both 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.

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 honorarium (*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.

Eligibility: You are eligible to participate in this study if you are between the ages of 18–38, are considered overweight by the World Health Organization criteria (i.e. BMI $\geq$ 25 kg/m^2) and are interested in losing weight, have not taken hormonal contraception, fertility medications, or insulin sensitizers in the last two months, and have had a physical exam, which included a pelvic exam, performed by your primary care provider in the last three years. 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 eat all Nutrisystem® D entrees and snacks and nothing else. You must be willing to report any failure to adhere to this diet to members of the research team.

Benefits of the Study: By participating in this research study, you will receive six months of the Nutrisystem® D program (i.e. 3 meals and 1 dessert per day) *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.

Compensation: A total honorarium 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 $2,000.00 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 honorarium 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 honorarium.

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.

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) 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 read 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.

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. ☐

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. 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 pro-rated honorarium. Your degree of weight loss will be evaluated with respect to Nutrisystem® D standards after two months of the intervention (or three months of your participation in 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 (or four months of your participation in 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 pro-rated honorarium.

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, and Canadian Institute for Health Research.

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.

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: _____