Print your name here: _____

Are you participating in any other research studies? _____ Yes _____No

## PURPOSE OF RESEARCH

You are invited to participate in a research study to assess the uterine environment in unexplained recurrent pregnancy loss and unexplained infertility.

Recurrent pregnancy loss and unexplained infertility are emotional and difficult diagnoses. Despite a thorough medical investigation, many cases of recurrent pregnancy loss and infertility remain unexplained. Understanding endometrial factors that may contribute to these diseases may lead to improved treatment options in the future. The purpose of this study is to determine if patients with recurrent pregnancy loss or unexplained infertility have an altered uterine gene expression or uterine microbiome (micro-organism composition) during the window of embryo implantation. Furthermore we would like to assess for women with an abnormal uterine gene expression whether vaginal progesterone medication improves or alters gene expression.

A standard evaluation for infertility includes a uterine cavity evaluation, evaluation for ovarian reserve testing, and for patients with recurrent pregnancy loss parental testing for uterine infection, chromosome analysis, autoimmune and thyroid screening. This standard workup, however, does not include a molecular or microbial assessment of the endometrium. Studies suggest that endometrial factors may contribute to unexplained infertility or recurrent pregnancy loss however the extent of this is unknown.

If you are enrolled in this study, you will undergo the standard evaluation of infertility and/or recurrent pregnancy loss that every patient seen in our office receives. As part of this study, you will also have 1-2 endometrial biopsies to test for the molecular and genetic environment of your uterus. Each patient enrolled will be treated according to medical standard of care practice and no standard treatment will be withheld from you if you choose to participate in this study.

If you decide to terminate your participation in this study, you should notify Dr. Sara Churchill at (650) 498-7911

## VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

## DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 5 years from the date of your enrollment. This length of time is anticipated to complete a thorough fertility and medical evaluation in addition to following the outcome of your subsequent pregnancies.

## PROCEDURES

If you choose to participate, Dr. Sara Churchill and her research study staff will consent you for the following:

You will undergo a standard infertility OR recurrent pregnancy loss evaluation that includes ovarian reserve testing, hormonal analyses (blood tests), ultrasound(s), a uterine cavity evaluation, genetic testing (blood work), autoimmune testing (blood work) and thyroid screening (blood work).

As a study participant, you will be offered an endometrial biopsy that will specifically test the receptivity of your endometrium as well as identify the bacterial composition of the uterine environment (microbiome). The endometrial receptivity array (ERA) and microbiome testing will be performed by Ivigen at no extra costs. The ERA provides information on the receptivity of a patient's endometrium to the implantation of an embryo. This may yield additional information regarding the etiology of a patient's infertility and/or recurrent pregnancy loss. If your ERA is abnormal we will repeat the biopsy after vaginal progesterone supplementation to see if this normalizes the ERA results.

Your follow up visits and treatment regimens will be determined by the treating physician according to the standard of care treatment of infertility or other medical comorbidity. Repeat laboratory testing may be recommended if any lab abnormalities are identified and treated while you are receiving care in our clinic.

We will track your clinical outcomes without intervening with your treatments until you have a successful pregnancy and for a minimum of one year after enrollment. If your outcomes are not in your medical record you may be contacted by phone for additional follow up information.

Your clinical data and pregnancy outcomes will be entered into a secure database. No publications as a result of this study will have any patient identifiers.

Tissue Sampling for Research

Research using tissues is an important way to try to understand human disease. You have been given this information because the investigators want to include your tissues in a research project and because they want to save the samples for future research. There are several things you should know before allowing your tissues to be studied.

Your tissues will be stored in a locked freezer under your medical record number in order to protect your identity.

You have the right to refuse to allow your tissues to be studied now or saved for future study. You may withdraw from this study at any time. The investigators might retain the identified samples, e.g., as part of your routine clinical care, but not for additional research.

Because your samples will not be linked to your name after they are stored, you cannot withdraw your consent to the use of the samples after they are taken.

You will be told the results of tests that are part of your clinical care, but you will not be told the results of the research tests, including any future research tests.

_____ I consent to my samples being saved for future research

_____ I do not consent to my samples being saved for future research

Any of your samples which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of samples do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

## PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

## WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Sara Churchill at (650) 498-7911.

If you withdraw from the study, there will be no health consequences to you.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

## POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

A uterine cavity evaluation consists of either a saline sonohysterogram or hysteroscopy. These procedures involve placing saline within the endometrial cavity to allow complete visualization of the shape and contour of the cavity. This procedure is performed under sterile conditions and involves a rare risk of infection and vaginal bleeding after the procedure. Some patients experience cramping during the procedure that resolves shortly upon completion of the procedure.

The endometrial biopsy is performed under sterile conditions with minimal risk however some patients do experience cramping during the procedure. Although this is a sterile procedure, there is a rare risk of infection and vaginal bleeding after the procedure.

Blood draws are routinely performed for our patients and pose minimal risks to participants. Drawing blood may cause some discomfort, bleeding or bruising where the needle enters the skin and there is a small risk of infection.

Patient who have been on vaginal progesterone have reported side effects such as abdominal pain, nausea, abdominal bloating, constipation, vomiting, fatigue, urinary tract infections, headache and vaginal bleeding. Vaginal progesterone may also have similar side effects compared to other drugs containing progesterone including breast tenderness, mood swings, irritability, and drowsiness. If you were to experience bothersome side effects that are not easily treated we would stop vaginal progesterone treatment and these side effects would not be expected to persist.

Please let your physician know if you experience any of these complications.

## POTENTIAL BENEFITS

Information about the endometrial receptivity and uterine microbiome obtained during the study will be shared with you. However, we cannot and do not guarantee or promise that you will receive any benefits from this study.

## ALTERNATIVES

The alternative to participating in this study is to not participate and to undergo testing and treatment based on your doctor's clinical reccomendations.

## PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

## ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

## CONFIDENTIALITY

Your identity will be kept as confidential as possible as required by law. Your personal health information related to this study: name, medical record number, date of birth that is required for processing laboratory specimens may be disclosed as authorized by you. Your research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed**.**

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

# Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

## What is the purpose of this research study and how will my health information be utilized in the study?

The investigators of this study hope to identify which prognostic factors are most clearly correlated with poorer outcomes in the obese infertile population. As a participant, in addition to receiving standard of care treatment of infertility, you will receive additional information regarding the receptivity of your endometrium as a possible explanation for your infertility. The results of the screening examinations in the overweight/obese population will allow for comparison of different prognostic factors that may be contributing to the cause of infertility, response to assisted reproductive technologies, and pregnancy outcomes.

## Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

## If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health

information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Dr. Ruth Lathi at Stanford University Medical Center, Reproductive Endocrinology, 900 Welch Road, Suite 350, Palo Alto, CA 94304.

**What Personal Information Will Be Obtained, Used or Disclosed?**

Your health information related to this study may be used or disclosed in connection with this research study, including, but not limited to patient name, your age, date of birth, medical record number, previous infertility
treatment, obstetrical history, results of laboratory testing, and outcome of pregnancy.

**Who May Use or Disclose the Information?**

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director: Dr. Sara Churchill
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary

**Who May Receive or Use the Information?**

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The Stanford Research Staff

- The Federal Drug Administration
- Ivigen

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

**When will my authorization expire?**
Your authorization for the use and/or disclosure of your health information will end on February 28, 2050 or when the research project ends, whichever is earlier.

_____ _____
Signature of Participant Date

_____
Print Name of Participant

## FINANCIAL CONSIDERATIONS

Payment
You will not be paid to participate in this research study.

Costs

If you participate in this study, there may be additional costs to you. These include the personal time it will take to come to all of the study visits.
The study will pay for those services, supplies, procedures, and care associated with this study that are not a part of your routine medical care.

Your insurance will be billed for the cost of the standard infertility evaluation.
The study will pay for the endometrial receptivity array (ERA) that is associated with this study and is not a part of your routine medical care.

Participation in this study is not a substitute for health insurance. You and/or your health insurance must pay for those services, supplies, procedures, and

care that you require during this study for routine medical care. **You will be responsible for any co-payments and/or deductibles as required by your insurance.**

Sponsor
Ivigen is providing the endometrial receptivity array (ERA) and microbiome testing for this study.

## COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

## CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. Sara Churchill. You may contact her now or later at (650) 498-7911.

Injury Notification: If you feel you have been hurt by being a part of this study, please contact the Protocol Director.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about

the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

## EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?
____ Yes ____ No

Signing your name means you agree to be in this study and that you were given a copy of this signed and dated consent form.

_____
Printed Name of Participant

_____ _____
Signature of Adult Participant Date

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date



Participant ID:

STUDY