Principal Investigator: Lyndsey DuBose, PhD
COMIRB No: 21-2903
Main Study Title: Premature Vascular Aging in Women Following an In Vitro Fertilization Pregnancy
Short Title: Vascular HEAlth afteR In Vitro Fertilization (HEART-IVF)
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You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done? Women who utilize in vitro fertilization (IVF) to become pregnant may be at increased risk for high blood pressure 1-5 years after delivery. High blood pressure is a leading risk factor for the development of cardiovascular disease, the leading cause of death in women. Recent research shows that women who conceive using a frozen-thawed embryo may demonstrate adverse changes in vascular function during early pregnancy compared with women who used a fresh embryo transfer or had an unassisted pregnancy. Detrimental changes in vascular function are associated with high blood pressure and the development of cardiovascular disease and cognitive impairment. However, if the risk of high blood pressure differs by type of IVF and is associated with vascular function after pregnancy is unknown.

Therefore, this study will investigate if women who have a history of IVF exhibit greater vascular dysfunction compared with women with an unassisted pregnancy and if differences in vascular function is related to the development of high blood pressure. We also want to understand if differences in vascular function or high blood pressure differ between women who used frozen-thawed compared with a fresh embryo to become pregnant. Results of this study will help to understand if women with a history of IVF use are at increased risk for the development of cardiovascular disease later in life and to help provide insight into potential future mechanisms underlying the development of vascular dysfunction and high blood pressure with IVF.

Other people in this study. Up to 100 healthy women from the Denver metropolitan area will participate in this study.

What happens if I join this study? If you join the study, we will ask you to come in to the CTRC (Clinical Translational Research Center) for **1 screening visit to determine if you are eligible for the study,** and **1 visit** within a **3-month period (for a total of 2 visits plus equipment drop-off)**. The table below is a general outline of all the procedures, and when these procedures may occur at a study visit. There can be some flexibility in some visits to move procedures to a different visit to accommodate your schedule. The paragraphs under the table describe these visits and procedures in more detail.

Outline of Study Visits:

	Study Procedure	Location	Estimated Time
Screening Visit 1	Consent, medical history and obstetric history questionnaire	CTRC	45 minutes

First, we must find out if you are eligible for the study. We will ask you to complete surveys on the computer to collect information on your health history (which will take about 25 minutes):

- Obstetric history questionnaire. You will be asked questions about your health history, reproductive and obstetric history including information about your pregnancies and complications you may have experienced during each pregnancy. We may review your medical records to confirm key information (e.g., IVF history, IVF treatment, past medical history) if you consent to this study.

If you are eligible to continue in the study and you agree to participate, you will come to the CTRC to complete additional testing. These research tests are necessary to meet the goals of the study. Women with a regular menstrual cycle or on oral contraceptives will complete vascular testing during the early follicular phase of the menstrual cycle or placebo phase of oral contraceptives. Testing may occur at anytime in women not experiencing a menstrual cycle or on certain types of contraceptives (e.g., long-acting contraceptives).

Visit #	Study Procedure	Location	Estimated Time
Visit 1	Instructions: 12-hour fast (no food or caffeine, water is encouraged) before visit. Please refrain from caffeine or alcohol for >8 hours. No exercise 20+ hours before the visit, bring a t-shirt and shorts; no anti-inflammatory medications for 48 hours prior to study. You will be provided with a snack after the blood draw. Procedures: Urine pregnancy test, IV placement, blood draw, endothelial cell biopsy, history and physical exam, clinic blood pressure, vascular testing, ambulatory blood pressure monitoring, physical activity monitoring, body composition and bone mineral density testing	CTRC	5 hours
Equipment return	The study PI or research staff member will coordinate study equipment return with you on an individual basis.	-	-

- Pregnancy test. A urine pregnancy test will be given to rule out pregnancy.
- Blood tests. A blood sample (approximately 6 tablespoons) will be taken for standard blood tests (such as cholesterol, glucose, thyroid, complete blood count, and liver function) as well as sex hormones and other factors that influence vascular function. This will take about 15 minutes
- Endothelial cell collection. To help us understand how IVF impacts the health of arteries, we will collect cells that line the inside of your vein called endothelial cells. A study doctor or nurse will place a needle with a plastic sleeve into a vein in your arm. The needle will be removed, but the plastic sleeve will remain in place (IV) so that multiple blood samples can be obtained and solutions given without using a needle each time. The endothelial cells will be collected from the IV by placing 2 very small (0.021-inch diameter) J-shaped wires inside the catheter and immediately pulling the wire out to collect the endothelial cells.
- Blood pressure. A cuff will be placed around your arm and will be inflated and deflated to measure your blood pressure. Your blood pressure will be measured in both arms and will be repeated 3 times or until it becomes stable. This will take about 15 minutes.
- Arterial endothelial function test. We will also perform non-invasive measures of endothelial cell function. We will place a blood pressure cuff around your upper forearm and inflate it for 5 minutes and then release it quickly. We will measure changes in your blood flow and the size of the artery before, during and after release of the blood pressure cuff using an ultrasound probe.

- Arterial stiffness test**.** A research staff member will place a blood pressure cuff around your upper arm and record your blood pressure approximately 2-3 times. You will also have ECG stickers taped to your chest so we can monitor your heart rate and rhythm. A researcher will then place a non-invasive tonometer probe on your wrist (radial artery), arm (brachial artery), neck (carotid artery) and your upper/inner thigh (femoral artery) and record your pulse at these sites. We will then use a tape measure to measure the distance from your neck to your wrist, your neck to your arm, and your neck to your upper/inner thigh sites. The researcher will also take short video clips using an ultrasound of the carotid artery in your neck and the major vessel around your heart called the aorta to measure the blood flow flowing through the artery as well as the diameter and thickness of the artery.
- Beat-to-beat blood pressure. A research member will place a blood pressure cuff on your upper arm and a smaller cuff around the middle knuckle of one of your fingers. You will also have ECG stickers taped to your chest so we can monitor your heart rate and rhythm. The finger cuff will inflate and deflate continuously at a low pressure to measure small changes in your blood pressure each time your heart beats for 5-10 minutes. If time allows, we will measure small changes in your blood pressure while you hold your breath.
- 24-hour ambulatory blood pressure monitoring. You will be fitted with a small portable blood pressure monitor to wear home and while you sleep for 24 hours. We will ask you to record your activities during the time you are wearing the monitor. If we don't get enough recordings during the 24-hour period or if the results are unexpected or out of line with your other blood pressure readings, we may ask you to repeat wearing blood pressure for another 24 hours.
- Body composition and bone mineral density. Your body fat and bone mineral density will be measured by dual energy x-ray absorptiometry (DXA). This test involves lying still on a padded table for about 15 minutes and uses a special type of x-ray involving very low radiation exposure. Because this test involves a small dose of radiation, we will ask you to complete a urine pregnancy test prior to DXA testing.
- Physical activity monitoring. You will be asked to wear an activity monitor (like a pedometer) on your upper thigh for 7 days. The monitor will tell us how active you were.
- Surveys. We will ask you to complete several surveys on the computer through Redcap about your sleep quality, feelings of mood and stress.

What are the possible discomforts or risks? Every effort has been made by the investigators to keep the risks and discomforts involved to a minimum. The risks associated with these procedures include:

Fasting. You may feel hungry, lightheaded, dizzy, and/or weak.

Venipuncture. In this study we will need to get about 6 tablespoons total of blood from you. We will get blood by putting a needle in your vein. This is the standard method used to obtain blood for tests. You will feel pain when the needle goes into the vein, common. A bruise may form at the site, common. There is also a rare risk that it could make you feel dizzy or faint.

IV and endothelial cell collection. An IV will be placed into a vein in your arm for taking blood samples and 2 thin J-shaped wires will be inserted and removed immediately to collect cells lining your blood vessel. We will remove the IV after cell collection. When the needle goes into a vein, it hurts for a short time, common. Also, there will be the minor discomfort of having the catheters taped to your arm, common. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise, less common. Rare risks include a blood clot forming in the vein is about 1 in 100; the risk of infection or significant blood loss is about 1 in 1,000. There is a rare risk that you may feel lightheaded or faint from the needle going into your arm. There is also a rare risk that the J-shaped wire could get stuck in the

vein and/or that the vein could be damaged.

24-Hour ambulatory blood pressure monitoring. There is a risk that you could become tangled in the tubing or strap of the blood pressure monitor and you could be strangled. A member of the research will fit the monitor properly before you leave the clinic and give you instructions about the monitor. It is recommended that you wear the cuff under your clothing, even when you are sleeping, to reduce the risk of becoming tangled in the tube or strap. You may have some discomfort or be awakened at night when the cuff is inflating. You may get a bruise or a scratch or reddening of the skin from the cuff when it inflates. You may take the cuff and monitor off if it becomes too uncomfortable or interferes with your activities or sleep or notice bruising.

Ultrasound imaging. If you are sensitive to ultrasound gel, you may experience skin irritation.

Activity monitors – you will be asked to wear an activity monitor on your thigh using a hypoallergenic adhesive pad. There is a small chance of skin irritation if you are sensitive to the adhesive.

Risk of pregnancy. You will be given pregnancy tests before the DXA scan to make sure you are not pregnant. The radiation from the DXA could harm a fetus. If you think you may be pregnant at any time during the study, contact the investigators.

Body composition and bone mineral density testing. You will be exposed to some radiation in this study. The total radiation dose you will receive if you participate in this study is estimated to be less than 1% of the annual limit recommended by the FDA. Radiation exposure is not risk-free. We know for sure that high levels of radiation cause cancer. This, however, does not mean that everyone exposed to these levels will get cancer. It only means that cancer incidence is higher in these populations as compared with the incidence among the less exposed. Everyone receives some background radiation, even from rocks and plants. This radiation is about 2.5% of the annual limit recommended by the FDA. The exact increase, if any, in your cancer risk is not known. If you are or might be pregnant, you should not take part in this study to prevent your unborn child from receiving unnecessary radiation. The amount of radiation that you will receive during the DXA test is about the same as the amount of radiation you would receive being outdoors in Denver for one day.

Confidentiality and privacy. The interviews, questionnaires, and collection of medical information may cause you to feel embarrassment or a loss of privacy, rare. There is a possibility that some or all of the research information collected could become part of your permanent medical record. There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

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

Certificate of Confidentiality. This study has been issued a Certificate of Confidentiality from the federal government to help protect your privacy. The Certificate prohibits the researchers from disclosing your name, or any identifiable information, document or biospecimen from the research, with the exceptions listed below. A certificate provides protections against disclosing research information in federal, state, or local civil, criminal, administrative, legislative or other proceedings.

These protections apply only to your research records. The protections do not apply to your medical records.

The researchers may disclose your name or identifiable information, document or biospecimen, under the following circumstances:

- To those connected with the research,
- If required by Federal, State or local laws,
- If necessary for your medical treatment, with your consent,
- For other scientific research conducted in compliance with Federal regulations,

- To comply with mandated reporting, such as a possible threat to harm yourself or others, reports of child abuse, and required communicable disease reporting, or
- Under other circumstances with your consent.

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

What are the possible benefits of the study? You will not receive any direct benefits from participating in this study. We will provide you with some of your health information (e.g., blood work, blood pressure). However, this study is designed for the researcher to learn more about how vascular function may differ in women who go through IVF to become pregnant and may contribute to an increased risk for the development of high blood pressure. This study is not designed to treat any illness or to improve your health.

Who is paying for this study? This research is supported by a pilot grant through the University of Colorado Anschutz Medical Campus Colorado Clinical Translational Science Institute (CCTSI) Child-Maternal Health program.

Will I be paid for being in the study? For your participation, you will be paid $100 for completing the vascular testing,$25 for the endothelial cell collection and $25 for ambulatory blood pressure monitoring. If you withdraw prior to completing the vascular testing, you will not be compensated.

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

Will I have to pay for anything? There is no cost to you for taking part in this study other than the costs of transportation to and from the testing facilities. There will be no charge for any tests required by the study.

Is my participation voluntary? Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled. If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

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

What happens if I am injured or hurt during the study? If you have an injury while you are in this study, you should call Lyndsey DuBose, PhD at 303-724-1188 immediately. Additionally, you can call the study doctor, Dr. Cassandra Roeca, at (720)704-8221.

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

Who do I call if I have questions? The researcher carrying out this study is Lyndsey DuBose, PhD. You may ask any questions you have now. If you have questions later, you may call Dr. DuBose at 303-724-1188, or the study doctor, Dr. Roeca, at (720)704-8221. You will be given a copy of this form to keep.

While your main source of information about taking part in this study are the principal investigator, Dr. DuBose, a Research Subject Advocate is also available at the Clinical Translational Research Center at (720) 848-6662 to answer questions about taking part in this study.

If you have questions about your rights as a research subject, please call the Colorado Multiple Institutional Review Board (COMIRB) office at (303) 724-1055.

What happens to data collected in this study? The data we collect will be used for this study but may also be important for future research. Your data may be used for future research or distributed to other researchers for future study without additional consent if information that identifies you is removed from the data.

Optional Consent and Authorization for Data and Specimen Banking for Future Research. Dr. DuBose would like to keep some of the data, blood and cells that are taken during the study but is not used for other tests. If you agree, the data and samples will be kept and may be used in future research to learn more about the physiology of female hormones and how they affect women's health. The research that is done with your data and samples is not designed to specifically help you. It might help women who have health risks such as cardiovascular disease in the future. Reports about research done with your data and samples will not be given to you or your doctor nor will not be put in your health records. The research using your data and samples will not affect your care.

The choice to let Dr. DuBose keep the data and samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your data and samples can be kept for research, you can change your mind at any time and contact Dr. DuBose to let her know that you do not want her to use your data and samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. DuBose decides to destroy them.

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The possible benefits of research from your data and samples include learning more about what causes increases in disease risk in women after pregnancy and how to prevent and treat diseases. The greatest risk to you is the release of your private information. Dr. DuBose will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or sample collection and storage.

I give my permission for my data, blood and tissue to be stored in a central tissue bank at the University of Colorado Anschutz Medical Campus for future use by the study investigators:

1. I give my permissions for my data, blood and cell samples to be kept by Dr. DuBose for use in future research to learn more about pregnancy, sex hormones and how they affect women's health.

☐ Yes ☐ No _____Initials

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

☐ Yes ☐ No _____Initials

3. I give my permission for Dr. DuBose (or someone she chooses) to contact me in the future to ask me to take part in more research.

☐ Yes ☐ No _____Initials

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

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

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

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

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

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

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

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator. To ensure proper evaluation of test results, your access to these study results may not be allowed until after the study is completed.

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

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.)
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records

- Psychological and mental health tests
- Tissue samples and the data with the samples.

What happens to Data, Tissue and Blood that are collected in this study? Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue and blood collected from you during this study are important to this study and to future research. If you join this study:

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

HIPAA Authorization for Optional Additional Study Procedures. In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

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

Signature:_____ Date:_____

Print Name:_____

Consent form explained by:_____ Date:_____

Print Name: _____

Witness Signature: _____ Date:_____

Print Name:_____

Witness of Signature ☐

Consent Form Approval

Witness of consent process ☐