Consent Form

Title of Research Study: Autonomic regulation of blood pressure in premature and early menopausal women

Investigator Team Contact Information:

For questions about research appointments, the research study, research results, or other concerns, call the study team at:

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Key Information About This Research Study

The following is a short summary to help you decide whether or not to be a part of this research study. More detailed information is listed later on in this form.

What is research?

Doctors and investigators are committed to your care and safety. There are important differences between research and treatment plans:

- The goal of research is to learn new things in order to help groups of people in the future. Investigators learn things by following the same plan with a number of participants, so they do not usually make changes to the plan for individual research participants. You, as an individual, may or may not be helped by volunteering for a research study.

Why am I being asked to take part in this research study?

I am asking you to take part in this research study because you have identified yourself as being either pre-menopausal or postmenopausal.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

This study is being done to learn more about the impact that hormone levels have before and after menopause has on women's blood pressure.

How long will the research last?

We expect that you will be in this research study for two visits. If you are currently taking hormone replacement therapy or hormonal contraceptives, you may be asked to come in for up to three additional study visits. If after three additional visits, estrogen is not at desired levels, then you will be excluded from the study. You will be compensated for each visit you attend.

What will I need to do to participate?

You will be asked to come in for two study visits; the first visit will take about 45-90 minutes and the second visit will take about 2.5-3 hours. If you are currently taking hormone replacement therapy there maybe additional study visits with blood draws that could take up to 30 minutes. If you are premenopausal, you will be asked to come in during your menstrual cycle phase where estrogen and progesterone are considered low. This is days 1-6 of your menstrual cycle, which is when menses begins. There is an optional third visit for women who come off of hormone therapy only; the visit will take about 2.5 to 3 hours.

During the study visits, we will take your blood pressure and measure your height and weight. You will complete questionnaires and have blood drawn. If you are pre-menopausal, a urine pregnancy test will be taken. You will have your heart rate measured with a three-lead electrocardiogram and your blood pressure monitored with a finger cuff. Your forearm blood flow will be measured using two cuffs that go around your wrist and upper arm. You will complete nerve activity testing (two small needles are inserted behind or on the side of the knee; one needle is an acupuncture needle and one needle is a small recording microelectrode), cold pressor testing (your hand is placed in ice-cold water) and an intense muscle-fatiguing exercise.

At the time of your consenting visit, you will be asked to provide proof of one of the following COVID-19 vaccinations:

- Two doses of the Moderna COVID-19 vaccine
- Two doses of the Pfizer COVID-19 vaccine
- A single dose of the Johnson & Johnson COVID-19 vaccine

If you are planning to, but have not yet received full COVID-19 vaccination, or you do not have proof of completing the COVID-19 vaccination at the time of your consenting visit, you will be asked to bring your vaccination card to your first in-person study visit. A laboratory member will meet you at the door before your appointment and verify proof of vaccination before allowing you in the building for this study visit.

If you have not received full COVID-19 vaccination, or you cannot provide proof of receiving full COVID-19 vaccination, you will be asked to provide a negative COVID-19 test result taken within 48 hours of each in-person study visit. If you cannot locate a copy of your COVID-19 vaccination card or are unable to provide a negative test result 48 hours before your scheduled study visit, please contact the study team.

Hormone replacement therapy: If you are currently taking hormone replacement therapy you will be

asked to come off the medication for a minimum of two weeks, the length of time is based on your estradiol (estrogen) level. Stopping hormone replacement therapy may cause symptoms similar to those experienced during menopause. These symptoms may include hot flashes, night sweats, difficulty sleeping, vaginal dryness, changes in libido, spotting or irregular vaginal discharge, dryness of skin or hair and mild changes to mood or memory. ***This part of the study is not optional; you will not be able to take part in this study without agreeing to this.*** You may be off therapy as long as six weeks. Postmenopausal women who agree to discontinue hormone replacement therapy or hormonal contraceptive use must also agree to blood draws for appropriate documentation of hormone levels. If you do not agree to these additional blood draws, you may not participate in the study.

Fasting: Prior to the second study visit, ***you are required to fast***. This means refraining from food and over-the-counter medications for 8 hours prior to the study visit. We will also ask you to refrain from caffeine and exercise for 12 hours before the study and alcohol for 24 hours before the study. After you have completed all procedures that require you to fast, we will provide a small snack. There are some risks associated with fasting. If you experience any of the following symptoms, please contact researchers and discontinue your fast: shakiness, nervousness, sweating, dizziness or light-headedness, sleepiness, confusion, difficulty speaking, anxiety, or weakness. Should you experience any of these symptoms and you feel they are intolerable, eat something and call the research team to reschedule your study visit. You should not delay taking your prescription medications longer than indicated by your doctor. We may need to alter your study visit schedule to ensure that you don't delay taking your medications outside of the clinically prescribed window. Additionally, we will need to discuss your prescriptions, including how frequently you are expected to take your medications, so that we may schedule your visit appropriately. You must also bring your prescribed medications with you to your study visit, so you may take them after your study visit.

You will not be able to take part in this study if:

- You have used nicotine and/or tobacco within the past 6 months
- You have diabetes
- You are asthmatic
- You are pregnant or breastfeeding,
- You had caffeine or alcohol or exercised 12 hours before the study testing at visit 2
- You have eaten within eight hours of testing at visit 2

During the COVID-19 pandemic, some research appointments may be held remotely using a video teleconferencing software called Zoom or through a phone call.

More detailed information about the study procedures can be found under ***"What happens if I say yes, I want to be in this research?"***

Is there any way that being in this study could be bad for me?

Blood draw: The risks of drawing blood include pain, bruising at the site of the blood draw, or in rare cases, infection at the site of the needle stick. There is also the risk of fainting during the blood draw.

Nerve activity measurement: There is a small risk of infection with insertion of the microelectrodes and acupuncture needle. Sterile techniques will reduce the chance of infection. It is possible that you could

experience a “pins and needles” sensation for several days after the procedure. This sensation disappears spontaneously without treatment in less than a week. There may be soreness around the area where the needles were inserted into the nerve.

Blood flow measurement: Inflation of the wrist cuff may cause your hand to feel uncomfortable because it will temporarily cut off the circulation to your hand. This sensation will last approximately five minutes and poses no long-term risks.

Valsalva maneuver (modified): This test, in which you will blow through a tube against pressure, may induce light-headedness or dizziness. In rare cases fainting can occur with vigorous Valsalva maneuvers; there are no documented cases of fainting with the modified Valsalva used in this protocol.

Cold pressor testing: This test will cause pain. You can voluntarily withdraw from the study at any time during the testing should the pain become too much for you to tolerate. There are no long-term risks associated with this test.

Upper extremity fatiguing contraction with post exercise circulatory occlusion (PECO): This test may cause discomfort or pain. You can withdraw from the study at any time during the testing should the pain become too much to tolerate.

Electrocardiogram (ECG) electrodes: Occasionally the adhesives can cause redness of the skin or irritation where the pads are placed. This usually goes away within 48 hours.

Stopping hormone replacement therapy: If you are currently taking hormone replacement therapy or hormonal contraceptives we will ask you to stop taking this therapy in order to complete the study. Stopping this medications may cause an increase in menopausal symptoms. You may withdraw from the study at any time if you would like to go back to taking hormone therapy. Women who have completed menopause premature or early, agree to discontinue hormonal contraceptive use, and have not had previous documentation of menopause or surgery that induces menopause may become pregnant subsequent to the discontinuation of hormonal contraceptives. To prevent unwanted pregnancy in this case, you are advised to use alternative methods of contraception such as condoms or diaphragms.

Stopping hormonal contraceptives: Premenopausal women who discontinue the use of hormonal contraceptives may become pregnant subsequent to this discontinuation. To prevent unwanted pregnancy in this case, you are advised to use alternative methods of contraception such as condoms or diaphragms.

Will being in this study help me in any way?

There are no benefits to you from your taking part in this research. We cannot promise any benefits to others from your taking part in this research. However, possible benefits to others include learning more about menopause and how it affects blood pressure.

What happens if I do not want to be in this research?

There are no known alternatives, other than deciding not to participate in this research study.

Detailed Information About This Research Study

The following is more detailed information about this study in addition to the information listed above.

How many people will be studied?

We expect about 160 women will be in this research study. The study is enrolling participants for the following categories:

- 100 participants (younger group): Postmenopausal females who are 35-49 yrs. old who completed menopause at or before age 45 yrs.
- 100 participants (younger group): Pre-menopausal females who are 35-49 yrs. old and are not taking hormonal contraceptives
- 100 participants (older group): Postmenopausal females who are 50-70 yrs. old who completed menopause at or before age 45 yrs.
  100 participants (older group): Postmenopausal females who are 50-70 yrs. old who completed menopause at a typical age (greater than 45 yrs.)

What happens if I say "*Yes, I want to be in this research*"?

In-person study procedures will occur in Children's Rehabilitation Center, which is located at 426 Church St. SE, Minneapolis, MN 55455. In the rare case the trained study staff member is unable to draw blood, you will be taken to the Clinical Research Unit, which is located at 516 Delaware St. SE, Minneapolis, MN 55455, to have your blood drawn by Fairview Research Services.

Study Procedures

Screening/Consent Visit 1

This visit will last between 45-90 minutes:

- You will be asked to consent to the study.
- You will be asked to provide proof of full COVID-19 vaccination.
- You will have your blood pressure taken (if conducted in person).
- You will have your height and weight taken (if conducted in person).
- You will be asked to complete questionnaires, you do not have to answer any questions that make you feel uncomfortable.
- You will have your blood drawn, about 3-3.5 teaspoons of blood, to confirm menopause/premenopause and to test for levels of estrogen, progesterone, testosterone, hemoglobin-A1c, and vitamin D. (If this visit takes place remotely due to COVID-19, this blood draw will take place during Visit 2.)
- You will have a urine pregnancy test, if you are premenopausal. (If this visit takes place remotely due to COVID-19, this test will take place during Visit 2.)
- If you are currently taking hormone replacement therapy or hormonal contraceptives we will ask you to discontinue therapy in order to complete the study.
- You will be asked to practice the handgrip exercise test by performing three maximal voluntary contractions and then practicing the 30% target force contraction.

Visit 2

Visit two may be scheduled at any time following the completion of visit one. For most postmenopausal participants, approximately 2-6 weeks elapse between visit 1 and visit 2, but there is a possibility that up to a year or more may elapse between these visits.

This visit will last approximately three hours:

- You will be asked to fast for eight hours prior to coming to this visit.
- You will be asked to refrain from caffeine for 12 hours before the study, alcohol 24 hours before

the visit and exercise 12 hours before the visit.

- You will be asked to complete questionnaires.
- You will be asked to show either 1) proof of full COVIVD-19 vaccination if you did not provide this proof at visit one OR 2) a negative COVID-19 test result from a test taken within 48 hours of your first in-person study visit.
- Your blood pressure will be continuously taken during the testing procedure.
- Your heart rate will be measured with a three-lead electrocardiogram (ECG).
- Respiratory rate will be measured with a belt placed around your stomach.
- To find the nerve in your lower leg, electrical stimulation or ultrasound will be used. Electrical stimulation may cause some tingling and make the muscles in your lower leg contract. If ultrasound is used, you may feel a slight sensation of warmth where the device is placed on your leg. The ultrasound probe will be covered with a single-use, sterile, latex-free cover, and a sterile gel will be used where the ultrasound head contacts your skin. You will sit in a slightly reclined seated position with your knee showing for this test.
- Muscle sympathetic nerve activity (MSNA) will be measured (two small needles are inserted behind or on the side of the knee; one needle is an acupuncture needle and one needle is a small recording microelectrode). A sticky pad will be placed on your skin next to one of the needles that was inserted.
- After the test avoid strenuous exercise with that leg for 24 hours.
- You will complete three Valsalva maneuvers (blowing through a tube against pressure).
- Upper extremity fatiguing contraction with post exercise circulatory occlusion (PECO) and cold pressor test (CPT) will last about 33 minutes:
    - CPT requires your hand to be completely placed into a bucket of ice-cold water for two minutes.
    - PECO requires you undergo a muscle strengthening exercise with one arm until fatigue. At the conclusion of the exercise a blood pressure cuff will be inflated around the arm to a pressure of 50 mmHg higher than the last measured systolic blood pressure. This cuff will remain inflated for two minutes.
- Your blood will be drawn (about two teaspoons) if you are stopping menopausal hormone therapy or if you completed visit 1 remotely.

COVID-19 Infection Risk: Just like any in-person interaction, attending in-person research appointments comes with a risk of becoming infected with COVID-19. Some procedures will require close contact between you and our study staff. To lower the risk of spreading COVID-19, we will follow these steps:

- Our staff will wear equipment designed to protect you and them from spreading germs.
- We will also require you wear a mask while inside our buildings.
- Staff will constantly be monitoring themselves for symptoms, including taking their temperature. If staff start having symptoms of COVID-19 or test positive, the will follow quarantine guidelines.
- All participants will be screened for symptoms and other risk factors before each appointment.
- Participants and staff will wash their hands before and after each appointment.
- Social distancing will be enforced (when possible).
- And surfaces and equipment will be disinfected before and after each appointment.

We imagine the risk of becoming infected with COVID-19 during study procedures is no more than the risk presented during an average trip to the grocery store. If you test positive for or experience symptoms of COVID-19 during the course of the study, please notify study staff immediately so proper precautions can be taken to reduce spread. If we learn that you may have been exposed to COVID-19 during a study visit, we will contact you as soon as possible.

Please INITIAL HERE to confirm you have reviewed the above information: _____

Additional Blood Draw Visits (if you are currently taking hormone replacement therapy or hormonal contraceptives)
This visit will last between 15-30 minutes

- You will have your blood drawn, up to a half of a teaspoon to test for estradiol level.
- If a blood draw is your first in-person study visit and you have not yet shown proof of full COVID-19 vaccination, you will be required to bring to this visit either 1) your vaccine card OR 2) a negative COVID-19 test result from a test taken within 48 hours of your visit.
- These visits are required for women who are discontinuing hormone replacement therapy or hormonal contraceptives. If you do not agree to these additional blood draws, you will not be able to participate in the study.

Optional Visit 3
This optional visit is for participants who have come off hormone therapy only.

- You will be asked to fast prior to coming to this visit
- You will be asked to refrain from caffeine for 12 hours before the study, alcohol 24 hours before the visit and exercise 12 hours before the visit
- We will perform the same procedures as visit 2.

What happens if I say "Yes", but I change my mind later?

You can leave the research study at any time and no one will be upset by your decision.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. This means that your choice not to be in this study will not negatively affect your right to any present or future medical care.

Will it cost me anything to participate in this research study?

There is some travel reimbursement available to you but if your travel costs are higher than the max reimbursement, you will have to pay for that yourself.

If you have children and need to pay for childcare to participate in the in-person study visits, there is some childcare reimbursement available to you. If the cost of childcare is more than the max reimbursement per visit, you will have to pay for the remaining cost yourself.

For more detailed information about your reimbursement options, see ***"Will I Be Compensated for My Participation?"***

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research

study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information include the Institutional Review Board (IRB), the committee that provides ethical and regulatory oversight of research, and other representatives of this institution, including those that have responsibilities for monitoring or ensuring compliance.

Certificate of Confidentiality

To help protect your privacy, the National Institutes of Health has granted a Certificate of Confidentiality. The researchers can use this Certificate legally to refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate does not prevent a researcher from reporting information learned in research when required by other state or federal laws, such as mandatory reports to local health authorities for abuse or neglect of children/vulnerable adults, or information to the Food and Drug Administration (FDA) when required in an FDA audit. However, the Certificate limits the researcher from disclosing such information in follow up civil, criminal, legislative or administrative legal proceedings if the information was created or compiled for purposes of the research.

You also 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 research. If an insurer, medical care provider, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

Will I receive research test results?

Most tests done on samples in research studies are only for research and have no clear meaning for health care. If the research with your identifiable information or samples gives results that do have meaning for your health, the investigators will contact you to let you know what they have found.

Will anyone besides the study team be at my consent meeting?

You may be asked by the study team for your permission for an auditor to observe your consent meeting. Observing the consent meeting is one way that the University of Minnesota makes sure that your rights as a research participant are protected. The auditor is there to observe the consent meeting, which will be carried out by the people on the study team. The auditor will not document any personal (e.g. name, date of birth) or confidential information about you. The auditor will not observe your consent meeting without your permission ahead of time.

A description of this clinical trial will be available at 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.

Whom do I contact if I have questions, concerns or feedback about my experience?

This research has been reviewed and approved by an IRB within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 (Toll Free: 1-888-224-8636) or go to z.umn.edu/participants. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

Will I have a chance to provide feedback after the study is over?

The HRPP may ask you to complete a survey that asks about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous.

If you are not asked to complete a survey, but you would like to share feedback, please contact the study team or the HRPP. See the "Investigator Contact Information" of this form for study team contact information and "Whom do I contact if I have questions, concerns or feedback about my experience?" of this form for HRPP contact information.

What happens if I am injured while participating in this research?

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury let the study physicians know right away.

Will I be compensated for my participation?

If you agree to take part in this research study, we will pay you $25 for visit one, $100 for visit two, and $100 for optional visit three, for your time and effort. If you do not complete the study, you will be paid for the visits you complete. If you are asked to come in for additional blood draws, you will receive an additional $15 for each visit.

If you begin, but are unable to complete visit 2, we will use the following guidelines to determine compensation:

- If you come to the lab but do not complete instrumentation (e.g., found to be ineligible because BMI is > 35kg/m2) will receive $15.
- If you come to the lab and complete instrumentation but no other study procedures (i.e., VOP, Valsalva maneuvers, IHG, or CPT) will receive $50.
- Participants who come to the lab and complete instrumentation as well as at least one other study procedure will receive $75.

Potential Reimbursement(s):

- If you need to travel more than 60 miles to get to Visit 2 (or Visit 3), we will reimburse your travel expenses up to $150 for your hotel costs and up to $300 for gas or airfare.
- If you need to use a rideshare app (Uber or Lyft) to travel to and from Visit 2 (or Visit 3), we will reimburse you for the cost up to $75 roundtrip. You will need to forward the receipt to us before we can reimburse the cost. Alternatively, we can arrange the rideshare for you on our account so that you will not have to pay the travel cost up front and then wait to be reimbursed.
- If have children and need to pay for childcare in order to attend Visit 2 (or Visit 3), we will

reimburse your childcare costs at $15/hour with a max reimbursement of $100.

Payment will be made using a pre-paid debit card called Greenphire ClinCard. It works like a bank debit card. We will give you a debit card and each time you receive a payment for participation in this study, the money will be added to the card after each completed visit.

You may use this card at any store that accepts MasterCard or you can use a bank machine to remove cash. However, there may be fees drawn against the balance of the card for cash withdrawals (ATM use) and inactivity (no use for 3 months). We will give you the ClinCard Frequently Asked Questions information sheet that answers common questions about the debit card. You will also receive letters with additional information on how you can use this card and who to call if you have any questions. Be sure to read these letters, including the cardholder agreement, for details about fees.

The debit card system is administered by an outside company. The company, Greenphire, will be given your name. They will use this information only as part of the payment system. Your information will not be used for any other purposes and will not be given or sold to any other company. Greenphire will not receive any information about your health status or the study in which you are participating. Any demographic information collected and provided to Greenphire is stored in a secure fashion and will be kept confidential, except as required by law.

Payment you receive as compensation for participation in research is considered taxable income. If payment to an individual equals or exceeds $600 in any one calendar year, the University of Minnesota is required to report this information to the Internal Revenue Service (IRS). Research payments to study participants that equal or exceed $600 during any calendar year will result in a FORM 1099 (Miscellaneous Income) being issued to you and a copy sent to the IRS.

Use of Identifiable Health Information

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Those persons who get your health information may not be required by Federal privacy laws (such as the 1099 Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission. Please read the HIPAA Authorization form that we have provided and discussed.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings. The results of this study will not contain any identifiable information.

Optional Elements:

The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

I agree	I disagree	
_____	_____	I consent to undergo microneurography, or nerve activity measurement.
_____	_____	I consent to have my blood drawn.
_____	_____	The researcher may audio or video record me to aid with data analysis. The researcher will not share these recordings with anyone outside of the immediate study team.
_____	_____	The researcher may audio or video record me for use in scholarly presentations or publications. My identity may be shared as part of this activity, although the researcher will attempt to limit such identification. I understand the risks associated with such identification.
_____	_____	The researcher may contact me in the future to see whether I am interested in participating in other research studies by the Principal Investigator of this study.

Signatures:

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____

Signature of Participant Date

_____

Printed Name of Participant

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

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