Date: 4/14/2021

Title: Mechanisms of Hypertension in Women With Polycystic Ovary Syndrome

ID: NCT04327934

Document(s): ICF

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
JOHN B. PIERCE LABORATORY
YALE SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Mechanisms of hypertension in women with polycystic ovary syndrome
Principal Investigator: Nina Stachenfeld, Ph.D. The John B. Pierce Laboratory 290 Congress Ave. New Haven, CT 06519
Funding Source: Yale School of Medicine: Department Obstetrics, Gynecology and Reproductive Sciences
Aim 3 Title: Mechanisms of hypertension in women with polycystic ovary syndrome

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to look at the effect of testosterone and blood pressure. You have been selected because you are a young (18-40 years old) woman who meets the screening criteria for this study. As you enter the study, you will be placed in one of two groups: women with the diagnosis of Polycystic Ovary Syndrome (PCOS) or women without any of the symptoms of PCOS ("controls"). We are interested in studying how hormones effect the cardiovascular differences in women with and without PCOS.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed judgment. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form. You will also be randomized to either the Antagon only group or the Antagon plus methyl-testosterone group.

Exclusion criteria. If you are pregnant, or have a history of blood clots, diabetes, stroke, breast cancer, liver disease, undiagnosed abnormal vaginal bleeding not related to your period, have abused drugs or alcohol in the last six months, been diagnosed with sleep apnea or smoke cigarettes, you may not participate in this study. In addition, if you have a history of severe migraine headaches, high blood pressure, fibroids in your uterus, epilepsy, or gallbladder disease, administration of sex hormones may be harmful and therefore, you may not participate in this study. In addition, if you cannot tolerate taking "Antagon," or testosterone (see below for an explanation of these drugs), you will be excluded from the study.

APPROVED BY THE YALE UNIVERSITY IRB 4/14/2021

Description of Procedures

All tests and procedures will be done at The John B. Pierce Laboratory and Yale School of Medicine. The research will involve 6 visits to the lab over approximately 30 days. All procedures are experimental. None of the following procedures are part of your standard care.

Research Design:
Visit 1: **Screening, informed consent, orientation.**
Visit 2: **Vaginal Ultrasound (Yale Medical Group)**
Visit 3: **Oral glucose tolerance test (OGTT).**
Visit 4: (BL): **Physiological studies**
Visit 5: (while taking Antagon): **Physiological studies**
Visit 6: (while taking Antagon + testosterone): **Physiological studies**

Visit 1: We will describe the study to you in detail. You will fill out a medical history form so we can make sure it is safe for you to be in this study. You will have a pregnancy test at no cost to you. If you are eligible for the study and decide to participate, we will teach you how to give yourself an injection of Antagon, a drug that will be used in this study. We will also show you the room where the research studies will be done, and demonstrate the equipment and procedures that will be used for the study.

Visit 2: Dr. Lubna Pal will determine whether or not you have PCOS using transvaginal ultrasound. She will perform an ultrasound examination of your ovaries using a vaginal ultrasound probe. This procedure takes about 20 minutes. The probe is a plastic device approximately two inches in diameter that is covered in a sterile sheath, coated with a water-based lubricant and placed into your vagina. You will experience mild pressure but no pain. There are no known risks of the procedure. Any abnormal findings during this exam will be reported to your physician. The transvaginal ultrasound will be performed in the Reproductive Endocrinology clinic at Yale New Haven Hospital.

Visit 3 (at John B. Pierce Laboratory): Within 2 weeks of the start of the study you will come back to the lab for an **oral glucose tolerance test** to determine how your body breaks down sugar. This test will take about 4 hours.

1) You will come to the lab at 8 am having eaten nothing after 10:00 pm the night before.

2) You will have an **oral glucose tolerance test**. It will last about 4 hours. Here is what will happen:

a) You will go into a room that will be 82 degrees. You will be seated in a comfortable chair.

b) We will then put an IV in one of your arms. We will use the IV to draw your blood. We will attach one blood pressure cuff to your arm to monitor your blood pressure during the study. We will draw a blood sample (about 1 tablespoon (15ml).

APPROVED BY THE YALE UNIVERSITY IRB 4/14/2021

c) You will then drink 12 ounces of an orange or fruit punch flavored sugar drink.

d) Thirty minutes after you finish drinking the drink, we will draw a blood sample. We will draw your blood every 30 minutes over a three-hour period. You will have your blood drawn 7 times today, for a total of about 3 tablespoons. We will be testing your blood for levels of glucose (blood sugar) and hormones related to metabolism.

3) After we provide you with a healthy snack and a drink you can then go home.

We need to make sure that every participant has similar levels of water in their body before the testing takes place therefore, we will ask you to eat a low-fat breakfast and refrain from alcohol and caffeine for 12 hr prior to the experiment. We also ask you to maintain your normal diet and activity level for three days prior to the test day. On the morning of the test day, we will ask you to drink 5ml/kg body weight of water at home before arriving to the lab. We will tell you exactly how much this amount of water is based on your weight.

When you are finished with this test, we will give you a urine collection container. You will use this to collect your urine overnight before visits 4, 5 and 6.

Before visits 4, 5 and 6, you will collect you all of the urine you excrete overnight into the urine collection container. You will bring this container with you when you come to the lab for each of those visits.

Visit 4: Physiological studies (at John B. Pierce Laboratory): You will come to the lab again. You will be at the lab for approximately 5 hours.

1) You will eat a light, low-fat breakfast and drink 8 ounces of water at home. Avoid caffeine and alcohol.

2) You will come to the lab at 8 a.m. and change into a sports bra and exercise shorts. You will be asked to provide a urine sample and you will be weighed.

3) You will have a blood pressure regulation test. It will last about 5 hours. Here is what will happen:

a) You will go into a room that will be 82 degrees. You will lie on your back on a comfortable table. We will attach EKG electrodes to your chest.

b) We will put an I.V. in one of your arms to draw your blood. You will have your blood drawn 7 times today, for a total of about 8 tablespoons (160 ml). We will be testing your blood for levels of hormones related to blood pressure. We will attach one blood pressure cuff to your arm and another to your middle finger. We will put 2 small sensors on your skin on your forearm to measure skin blood flow.

APPROVED BY THE YALE UNIVERSITY IRB 4/14/2021

c) Next you will do a **flow mediated vasodilation test.** A narrow blood pressure cuff will be placed on your lower arm. We will take ultrasound pictures of the artery in your upper arm without the cuff inflated. The cuff will then be inflated for 2, 3, or 5 minutes. The ultrasound pictures will be taken again for 2 minutes immediately following the deflation of the cuff. We will also ask you to perform handgrip exercise at 20 % of your maximal handgrip strength for 2 or 3 minutes while the arterial cuff inflated. We will take ultrasound picture before and after the cuff inflated as described above.

d) Next you will do a **Lower Body Negative Pressure test**. You will lie on your back with the lower half of your body in a box. For this test, we will apply suction 4 times, for up to 4 minutes each time. While this is happening, we will be checking your heart rate, blood pressure and skin blood flow. We will draw a blood sample before and after the test, and at each level of suction.

4) At the end of the test we will collect a urine sample.

Taking medication at home: You will be taking 2 medications:

1) **Antagon**: On the 25th to 27th day after you began your last period, you will start giving yourself injections of Antagon once a day, at the same time each day. (We will give you a pregnancy test to take at home that first day. If you are pregnant, you should not start the Antagon.) You will take Antagon for 10 days. If there is a scheduling issue with Visit 6, you may continue to take Antagon for up to 18 days. Antagon is an approved drug that stops your brain from releasing the hormones that make your ovaries release an egg. You will inject Antagon below the skin in your abdomen or outer thigh. Injecting Antagon is not very painful, and we will teach you how. If you have an allergic reaction to Antagon, we will switch you to a similar drug called Cetrotide, which you will inject in the same way. Cetrotide is similar to Antagon, but you must fill the syringe yourself.

2) **Testosterone**: On the 4th day of taking Antagon, you will begin taking testosterone pills by mouth for 7 days. You will take 1 pill/day (5 mg/day). In the event that a scheduling conflict arises for Visit 6, you may be asked to take testosterone up to 11 days. More than likely we will delay the testosterone start date to match up with the new date for Visit 6.

Visit 5: Physiological studies (at John B. Pierce Laboratory): After you have taken the Antagon for 3 days, you will come to the lab again. This is exactly the same as Visit 4. It will happen on the 3rd day that you are on Antagon.

Visit 6: Physiological studies (at John B. Pierce Laboratory): This is exactly the same as Visit 4. It will happen on the 10th day that you are on Antagon. If there is a scheduling conflict that prohibits Visit 6 from being conducted on Day 10 of the protocol you will remain on the Antagon for up to an additional 8 days.

APPROVED BY THE YALE UNIVERSITY IRB 4/14/2021

Taking other medications while in this study:

1) While you are in this study, if you are sexually active, you must use a barrier method of birth control such as condoms or a diaphragm. You cannot use hormone methods like the pill or patch.

2) You can take Tylenol but should not take Advil (ibuprofen).

3) Please call Dr. Stachenfeld (203-562-9901 x219) or Dr. Pal (203-785-4247 or 203-785-4708) if you need to take any other medications while you are participating in this study.

Risks and Inconveniences

Research may involve unforeseen risks. We will tell you if we learn any new information that could change your mind about taking part in this study.

1) **Antagon** will stop your normal menstrual cycle. You may begin to have "hot flashes" after using the drug for about a week. You may also feel some mood changes during the first 24 hours you are on it. You may have headaches or bloating. The month you are on Antagon, your period may come earlier or later than you expect and the flow may be heavier or lighter than usual. As far as we know, there are no long-term side effects of Antagon.

   Short-term methyl-testosterone treatment is not associated with any major health risks. **Long-term** use of methyl testosterone (greater than one month) can cause abnormal hair growth, abnormal skin sensations, anxiety, hair loss on the scalp, breast growth, changes in sexual desire, general body discomfort, headache, mood changes and acne. Methyl testosterone has been approved to treat low sexual desire disorder in premenopausal women. The risk of testosterone treatment in women for longer than 6 months has not been studied.

2) **Intravenous line placement**: In order to assess medical eligibility, blood tests will be performed using two intravenous lines to be placed during the test day. A bruise or, quite rarely, infection may develop at the puncture site. Having intravenous line placement performed by experienced personnel using good clinical technique will minimize the risks. The intravenous catheters will be kept in place for only 3 hours, further minimizing risks of infection or thrombosis.

3) **Transvaginal ultrasound.** There is a small risk of infection with transvaginal ultrasound if proper disinfection procedures are not followed. The procedure is painless and will require approximately twenty minutes to perform. There is some slight pressure during this procedure, which some women may find uncomfortable. This is performed in the Obstetrics/Gynecology Yale Medical Group clinic.

4) **The Lower Body Negative Pressures** tests might make you feel dizzy, nauseous or disoriented. If so, we will stop the test. You may feel fatigued after the test due to the lowering of your blood pressure. Your blood pressure can potentially fall by 20-30mm Hg during the procedure.

APPROVED BY THE YALE UNIVERSITY IRB 4/14/2021

5) **Flow mediated vasodilation** is associated with some discomfort at the end of the five minute occlusion period. If this feels too uncomfortable, you can stop the test.

6) **Blood drawing**: Over the course of the study you will have about 8 Tablespoons of blood drawn. This is 20% of the amount taken when you donate blood, and is not dangerous for a healthy person.

Benefits

You will receive no direct benefit from your participation in this study. The results could benefit medical science, as we hope to gain an improved understanding of the effects of on blood pressure regulation in women with and without PCOS.

Economic Considerations

You will not be charged for any of the tests. You will be paid $40.00 for the orientation procedure (including ultrasound), $60 for the oral glucose tolerance test, $100.00 for each blood pressure research study, $15.00 for each day you are taking Antagon, and a $100.00 finishing bonus. If you complete all aspects of the study, you will be paid up to $770.00 for your participation. If you do not complete all parts of the study, you will be paid for the parts you completed. You will be paid by check at the end of the study. You may either pick the check up by hand at the Pierce Laboratory, or we will mail the check to you at an address of your designation. If you need transportation the laboratory will reimburse you up to $20. According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. You will be identified within the laboratory with code names and numbers. The Pierce Laboratory will keep files for 25 years after the study is completed. The individual subjects' files are stored in the John B. Pierce Laboratory, either in the office of the Principal Investigator or in locked storage areas in the laboratory. Access to these files is limited to the Principal Investigator. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained. The Yale Human Investigation Committee (the committee that reviews, approves and monitors research on humans) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This

may include information that might directly identify you, such as your name and social security number. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. We store your personal information in locked cabinets, and do not use your name on our computers relating to the study. You are identified with code numbers or initials on password-protected computers. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for no more than 25 years after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form for 25 years until it is destroyed. The information about your health that will be collected in this study includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.
- The entire research record and any medical records relevant to this research held by The John B. Pierce Laboratory/Yale School of medicine.
  - Including:
  - Records about phone calls made as part of this research
  - Records about your study visits
    Information obtained during this
    research regarding: Physical exams
  - Records about any study drug you received

  No other information will be collected from any other of your medical records.

Information about you and your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those individuals at The John B. Pierce Laboratory who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator, Nina Stachenfeld.
- The U.S. Food and Drug Administration (FDA)

- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale-New Haven Hospital, Yale Medical Group are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

If you decide to take part in this research study, you will be required to give us information about your health status. Because this research is sponsored by the Department of Health and Human Services through NIH, a Certificate of Confidentiality (CoC) is automatically granted. The researchers can use this Certificate to legally 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 protection offered by the CoC does not stop us from voluntarily reporting information about suspected or known sexual, physical, or other abuse of a child or older person, or a participant's threats of violence to self or others. If any member of the research team is given such information, he or she will make a report to the appropriate authorities.

Because this research is sponsored by the Department of Health and Human Services through NIH, staff from that and other DHHS agencies may review records that identify you only for audit or program evaluation. They cannot report anything that would harm you or other research subjects. Even when a CoC is in place, you and your family members must still continue to actively protect your own privacy. If you voluntarily give your written consent for anyone to receive information about your participation in the research, then we may not use the CoC to withhold this information.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

In Case of Injury

Medical therapy will be offered for any physical injuries sustained as a consequence of your participation in this research. You or your insurance company will be responsible for the cost of such therapy. No additional financial compensation is available. You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with the study doctors or affiliated with Yale University School of Medicine or The John B. Pierce Laboratory.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. The researchers may withdraw you from participating in the research if necessary. They would have you stop the study if you got pregnant, became ill or if you do not comply with the procedures as described in this consent form.

Withdrawing Your Authorization to Use and Disclose Your Health Information

You may withdraw or take away you permission to use and disclose your health information at any time. You may withdraw you permission by telling the study staff or by writing to Dr. Nina Stachenfeld, The John B. Pierce Laboratory 290 Congress Avenue, New Haven, CT 06519. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Alternatives

Your alternative is not to participate.

Questions

Before you sign this form, please take the time to read it carefully and ask questions about any aspect of this research that is unclear to you. You are welcome to discuss your participation in the study with your physician or anyone else before deciding. We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully--as long as you feel is necessary--before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject:_____

Signature:_____

Date:_____

_____ _____
Signature of Principal Investigator Date

or

_____ _____
Signature of Person Obtaining Consent Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203/432-5919

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator (Nina Stachenfeld, 203-562-9901x 219). If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.