COVERPAGE

Ovarian Morphology and Theca Cell Androgen Production in Women with Polycystic Ovary Syndrome(PCOS)

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
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Version date: 9/30/2013

1. PROJECT TITLE

Ovarian Morphology and Theca Cell Androgen Production in Women with Polycystic Ovary Syndrome (PCOS)

2. PRINCIPAL INVESTIGATOR

R. Jeffrey Chang, M.D.

3. FACILITIES

Clinical and Translational Research Institute and UCSD/Reproductive Partners Medical Group

4. ESTIMATED DURATION OF THE STUDY

2 years

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Women with PCOS suffer from excess male hormone (androgen) production by the ovary. Androgen is made by cells that surround follicles that contain eggs. As the follicles (and eggs) grow and mature, there are more androgen producing cells. Women with PCOS have more follicles than normal women and therefore more androgen producing cells. While androgen production has been associated with the number of follicles, the relationship to the individual size of follicles in PCOS or normal women. This study intends to determine whether the size and number of ovarian follicles are correlated to androgen production in PCOS and normal women.

6. SPECIFIC AIMS

Specific Aim: To determine the relationship between ovarian follicle size and ovarian androgen production in women with PCOS and normal women
Hypothesis: In PCOS excess androgen production is positively correlated to ovarian follicle size

7. BACKGROUND AND SIGNIFICANCE

In women with polycystic ovary syndrome (PCOS), the major abnormality is excessive ovarian androgen production marked by increased serum testosterone (T) and androstenedione (A) levels. Studies to determine the alteration in ovarian steroidogenesis that lead to abnormal production of ovarian androgens have revealed increased CYP17 gene expression with accentuated 17-hydroxylase activity leading to exaggerated 17-hydroxyprogesterone (17P) responses to LH stimulation. In contrast, T and A responses did not distinguish between PCOS and normal women, although these androgens were clearly greater in the former compared to the latter group. As a result, 17P responsiveness has been employed to determine the functional capacity of the ovary to produce androgen. Stimulatory agents have included GnRH agonist, Lupron, at a dose of 10 microgram per kilogram, or hCG at a dose of 10,000 IU.

We recently showed that hCG administered intravenously in a dose-response fashion revealed gradual increases of 17P and a non-dose dependent increase of serum T and A. The pattern of steroid hormone production revealed the predominant pathway by which androgens are generated in women with PCOS. Extending these studies, we selected the mid-maximal dose of hCG to stimulate ovarian androgens and included morphometric measures of the ovary, such as ovarian follicle number (as determined by ultrasound) and related hormones, such as anti-mullerian hormone and inhibin B, both products of the ovarian follicle. The results showed that increased androgen and 17P responses in PCOS women were associated with increased antral follicle number and greater AMH levels compared to normal women. Inhibin B levels were similar between groups.

Based on responses observed in normal women, the PCOS women were divided into two groups. Those with 17P responses that did not exceed the normal mean plus 2 standard deviations (normal responder PCOS; NR-PCOS) and those that did exceed the normal response (high responder PCOS; HR-PCOS). This separation occurred at a rate of 50%. Notably, serum AMH levels were 2-fold higher in NR-PCOS compared to HR-PCOS. This finding was puzzling as serum AMH levels have been shown to correlate to the number of small follicles present in ovaries suggesting that AMH may be a surrogate for small follicle number. However, both PCOS subgroups had equivalent follicle numbers. We hypothesize that the NR-PCOS have greater number of small follicles compared to HR-PCOS. To address this issue we propose to assess the number of small follicles in NR- and HR-PCOS women and normal controls.

In a secondary consideration the HR-PCOS group was heavier than the NR-PCOS. This implies that the HR-PCOS women may have had greater insulin resistance and hyperinsulinemia that may have contributed to the significantly higher 17P responses to hCG. As a result, we will also perform an oral glucose tolerance test in all subjects.

Power Analysis
Results of our pilot study have shown that approximately 50% of PCOS women will exhibit 17OHP responses to hCG stimulation similar to those of normal women. Consequently, a sample size of 20 subjects in each group has an 80% power to detect a difference in the means of 0.820 ng/ml (the difference between the average 17OHP expression level in high responder PCOS women (HR-PCOS), 2.840 ng/ml, and that of normal responder PCOS (NR-PCOS) women, 2.02 ng/ml), which is a 33% increase. In the proposed study, we believe that HR-PCOS (n=20) will show significantly greater (33% more) 17OHP production in response to hCG stimulation than NR-PCOS (n=20) at a power of 0.8 and a type I error rate of 0.05. We will recruit 25 subjects in each group to allow for subject drop out. A secondary analysis will be performed between women with PCOS and normal controls (n=20).

8. PROGRESS REPORT

See item 7

9. RESEARCH DESIGN AND METHODS

Screening
40 women with PCOS and 20 normal women will be studied. Patients will be recruited from reproductive medicine clinics at UCSD or from the community by means of advertisement. Subjects will have a screening visit to establish eligibility and to sign the informed consent. They will have a history and physical examination performed which will include a urine pregnancy test, thyroid studies, a fasting chemistry panel, and a hemoglobin. If the hemoglobin is less than 11 gm/dL, the subject will be given ferrous sulfate pills and will return at another date when her hemoglobin is above 11 gm/dL.

Protocol

1. Subjects will have a urine pregnancy test at UCSD/Reproductive Partners Medical Group. Images of the both ovaries will be obtained using vaginal ultrasound and the number, size, and spatial arrangement of ovarian follicles will be noted for both ovaries in each subject. The ultrasound will be completed for each subject according to schedule availability and each subject shall maintain normal activity before and after the imaging study.
2. Normal subjects will be admitted to the CTRI during the mid follicular phase (Days 5-9) while PCOS women will be anovulatory and will not have a cycle day parameter. A urine pregnancy test will be done on admission.
3. On study day one, recombinant-hCG (r-hCG) will be administered intravenously at a dose of 25

micrograms.
4. Blood samples will be obtained at T = -0.5, 0, and +24 hours.
5. Blood sample will be used for DNA testing to identify genes that may be associated with androgen production.
6. Sera will be assayed at all time points for steroid and peptide hormones including AMH, inhibin B, insulin, 17OHP, androstenedione, testosterone, dehydroepiandrosterone, estradiol, progesterone, LH, and FSH.
7. One to two weeks after hCG stimulation testing each subject will come to the CTRI for an Oral Glucose Tolerance Test (OGTT). Each subject will ingest 75 gm of a glucose solution and blood samples will be obtained at 0, 15, 30, 60, 120 and 180 minutes after the glucose load.
8. Subjects will be advised to follow a 150gram carbohydrate diet for 3 days prior to OGTT

10. HUMAN SUBJECTS

A group of 40 women with PCOS and 20 normal women ages 18-37 will be studied.

Exclusion criteria:

1. Women with hemoglobin less than 11 gm/dl at screening evaluation
2. Women with untreated thyroid abnormalities
3. Pregnant women or women who are nursing
4. Women with BMI > 37
5. Women with known sensitivity to the agents being used
6. Women with diabetes, or renal, liver, or heart disease.

Inclusion criteria:

1. Subjects will be determined to have PCOS based on clinical history of irregular menses and clinical or laboratory evidence of hyperandrogenism and polycystic ovaries on ultrasound.
2. Subjects should not have been on any hormonal therapy or metformin for at least 2 months prior to study start.
3. Subjects will be determined to be normal controls if they have a clinical history of regular periods

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Individuals from UCSD Reproductive Medicine Clinics, Community advertisement, or social media (Craig's list, etc) will be asked whether they would be interested in participating in a research study by a reproductive endocrinology faculty or fellow. A brief description of the study will be made. If the patient is interested, then the study will be thoroughly explained to the patient by one of the investigative team members at a subsequent time. This will be done over the phone or by meeting with the patient in private. The patient will be given a consent form to take home and read. A few days later, the patient will be contacted by one of the investigative team members and asked if there are any questions and whether she wishes to participate. At the start of the study, the patient will bring a signed consent to the CTRI or sign the consent at the CTRI. This process will allow the patient several opportunities to withdraw if they decide not participate in the study and minimize any element of coercion.

12. INFORMED CONSENT

Participation will be completely voluntary. The purpose of the study will be thoroughly explained to all subjects. The information being communicated to the participant during the consent process will include any exculpatory language through which the participant is made to waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher or the University or its agents from liability for negligence. A Human Subject Protection Program approved written consent and HIPAA form will be obtained prior to study commencement. See attached.

13. ALTERNATIVES TO STUDY PARTICIPATION

N/A

14. POTENTIAL RISKS

Hematological:
Blood drawing may cause minor discomfort and potentially a slight bruise. There is a minimal chance of infection. Serum hemoglobin will be checked on all subjects prior to sampling and individuals with hemoglobin < 11 gm/dl will not be studied. We estimate approximately 38 cc blood loss per patient study.

Pharmacologic:
hCG: Ovarian theca cells are primarily stimulated by endogenous pituitary LH secretion. The bioactive beta-subunit of recombinant hCG is identical to LH and is used as a surrogate. Pharmodynamic studies have shown that following iv administration, beta hCG rises acutely and follows a biphasic exponential disappearance curve similar to other gonadotropins. Subcutaneous hCG may be associated with ovarian hyperstimulation syndrome, headache, confusion, dizziness, irritability, restlessness, depression, fatigue, fluid retention, breast tenderness, and swelling or irritation at the injection site. IV administration has only been associated with headache and no immunogenicity. We have employed this drug for several years in numerous individuals and not observed any side effects from the drug.

Transvaginal ultrasound may be associated with mild cramping or discomfort during positioning of the vaginal probe.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Qualified GCRC nurses using sterile technique will perform placement of indwelling catheters. To assess the hematologic status of the subjects, we will measure hemoglobin at the beginning of the study. A hemoglobin of 11 gm/dL will be the minimum allowed. If the hemoglobin is less than 11 gm/dL, subjects will be given ferrous gluconate pills and return at another date when their hemoglobin is above 11 gm/dL.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Each patient will be assigned a study number. None of the study documents will contain the patient's name or other identifying information. In order to protect the patient's identity and protected information, the investigators will keep the list of subjects and study numbers in a locked and protected area in our research office. Access will be restricted to the PI.

17. POTENTIAL BENEFITS

There will be no direct benefit to the subject by participation in this study. In addition, you will not be provided with any results or information regarding your DNA test. However, this study may further clarify the mechanisms of excess androgen production in PCOS and may help us better understand the disorder. In the future this study may lead to improved strategies to suppress androgen production.

18. RISK/BENEFIT RATIO

While the control group has no direct benefit from this protocol, the information gained from their participation will provide important knowledge about PCOS. Also, the dose of medication to be is minimal and we expect minimal if any risk to the control group. Furthermore, there is minimal risk with transvaginal ultrasound and we do not expect any complications with this imaging modality. Therefore, in view of the potential reproductive benefits and lack of significant identified risks associated with this study, the risk/benefit ratio favors performing the study.

19. EXPENSE TO PARTICIPANT

There will be no out-of-pocket expense to the subjects other than donation of time and possibly loss of wages from work on the day of study. Study drug provision and laboratory testing will be done free of charge to the subjects.

20. COMPENSATION FOR PARTICIPATION

Subjects undergoing ultrasound will be paid a total of $50 for their participation. Subjects undergoing hCG stimulation and blood sampling will be paid a total of $100 for their participation. Subjects undergoing OGTT and blood sampling will be paid a total of $100 for their participation.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

R. Jeffrey Chang, MD, Licensed in California, practicing privileges at UCSD*
Michael Homer, M.D., Licensed in California, practicing privileges at UCSD**
Jingwen Hou, M.D., Ph.D., Licensed in California, practicing privileges at UCSD**
Kevin Maas, M.D., Ph. D.. Licensed in California, practicing privileges at UCSD**
Heidi Cook-Andersen, M.D., Ph.D., Licensed in California, practicing privileges at UCSD***
Antoni Duleba, M.D. Licensed in California, practicing privileges at UCSD*
Irene Su, M.D., MSEC, Licensed in California, practicing privileges at UCSD*

All members of our research team are privileged/certified and/or licensed to perform all of the medical procedures discussed in this protocol. All individuals will recruit and consent for this study. Drs. Homer, Hou, and Maas will be responsible for scheduling subjects, performing blood draws, and maintaining study records.

* Board-certified in reproductive endocrinology and infertility (REI); ** Postdoctoral REI Clinical Fellow; *** Board-eligible in REI

22. BIBLIOGRAPHY

Rosencrantz MA, Coffler MS, Haggan A, Duke KB, Donohue MC, Shayya RF, Su HI, Chang RJ. Clinical Evidence for Predominance of Delta-5 Steroid Production in Women with Polycystic Ovary Syndrome. 2011 J Clin Endocrinol Metab 96:1106-13.

Pigny P, Jonard S, Robert Y, Dewailly D. Serum anti-Mullerian hormone as a surrogate for antral follicle count for definition of the polycystic ovary syndrome. J Clin Endocrinol Metab. 2006 91:941-5.

Dewailly D, Gronier H, Poncelet E, Robin G, Leroy M, Pigny P, Duhamel A, Catteau-Jonard S. Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the definition of polycystic ovaries. Hum Reprod. 2011 26:3123-9.

Laven JS, Mulders AG, Visser JA, Themmen AP, De Jong FH, Fauser BC. Anti-Müllerian hormone serum concentrations in normoovulatory and anovulatory women of reproductive age.
J Clin Endocrinol Metab. 2004 89:318-23.

23. FUNDING SUPPORT FOR THIS STUDY

Funding for this study is through an NIH grant to the Principal Investigator R. Jeffrey Chang.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

N/A

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

See attachment.

26. IMPACT ON STAFF

Blood drawing will be done by GCRC nurses. No additional nursing staff training will be required.

27. CONFLICT OF INTEREST

N/A

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

N/A

29. OTHER APPROVALS/REGULATED MATERIALS

N/A

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

N/A

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