

Hot off the Press

ANDROGEN EXCESS

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McCartney CR, Bellows AB, Gingrich MB, Hu Y, Evans WS, Marshall JC, Veldhuis JD. *Exaggerated 17-hydroxyprogesterone response to intravenous infusions of recombinant human LH in women with polycystic ovary syndrome.* Am J Physiol Endocrinol Metab. 2004 Jun;286(6):E902-8. Epub 2004 Jan 21.

Unluhizarci K, Karababa Y, Bayram F, Kelestimur F. *The investigation of insulin resistance in patients with idiopathic hirsutism.* J Clin Endocrinol Metab 2004 Jun; 89(6):2741-4

Vanky E, Salvesen KA, Heimstad R, Fougner KJ, Romundstad P, Carlsen SM. *Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study.* Hum Reprod. 2004 Jun

Weiner CL, Primeau M, Ehrmann DA. *Androgens and mood dysfunction in women: comparison of women with polycystic ovarian syndrome to healthy controls.* Psychosom Med. 2004 May-Jun;66(3):356-62.

MEETINGS OF INTEREST

60th Annual Meeting of the American Society for Reproductive Medicine
October 16-20, 2004
Pennsylvania Convention Center - Philadelphia, Pennsylvania
www.asrm.org

International Committee for Insulin Resistance
November 18-20, 2004
Universal City, CA
www.insulinresistance.us

Androgen Excess Society Annual Meeting
June 3, 2005
San Diego, CA
www.androgenexcesssociety.org

The Endocrine Society
June 4-7, 2005
San Diego, CA
www.endo-society.org

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Welcome

October 2004 Vol. 1, Issue 2

Sheila Y. Bolour, MD, Assistant Director - CARD

The Center for Androgen-Related Disorders (CARD) is going full steam ahead! In less than one year after its inception we have been extremely active in not only increasing services to our patients but also in expanding the research and education of physicians and scientists.

- We have established the CARD Quarterly Lecture Series which now provides CME credits and has brought numerous internationally renowned physicians to Cedars-Sinai to lecture on groundbreaking research in the field of androgen disorders. Be sure to mark your calendar and attend our next lecture on **October 26** to hear **Dr. John Nestler** discuss *Insulin Resistance and PCOS: Musings on Endometrial Events and Inositolphosphoglycan Mediators*.

- We've also added two new faculty members: **Dr. Lee Kao** and **Dr. Margareta Pisarska** who have helped to solidify the research and patient care we provide in CARD. Both bring a wealth of information from their work at Stanford.

- In January, CARD will host the first annual PCOS Conference **January 14-15, 2005**. The first day (Friday, January 14) has been reserved for a CME conference that will focus on the practical application of new research to clinical practices. All physicians and allied health professionals are encouraged to attend. The second day (Saturday, January 15) will provide patients with an opportunity to learn more about this syndrome and how it may affect their risk of disease and will also provide educational information on new treatment options that are available. If you would like more information on the conference or if you would like to recommend this conference to your patients, please contact April Moore at april.moore@cshs.org or (310) 423-4887 to request a brochure.

The activity of our members has remained a hallmark for this Center and I look forward to your continued participation.

Sincerely,

CARD Calendar of Events

October 26, 2004

LECTURE SERIES

John Nestler, MD - Professor & Chairman, OB-GYN - Medical College of Virginia/Virginia Commonwealth University; Topic: *Insulin Resistance and PCOS: Musings on Endometrial Events and Inositolphosphoglycan Mediators*

November 3, 2004

LECTURE SERIES

Andrea Dunaif, MD - Division Chief
Division of Endocrinology, Metabolism and Molecular Medicine
Northwestern University

January 5, 2005

LECTURE SERIES

Richard S. Legro, MD - Associate Professor
Department of Obstetrics & Gynecology
Hershey Medical Center @ Penn State University Medical School

January 14-15, 2005

PCOS Conference

Friday, Jan. 14 - CME Physician/Clinician Conference
Saturday, Jan. 15 - Patient Conference
Harvey Morse Auditorium - Registration required (*additional information inside*)

All CARD Lecture locations will be announced on Exchange and to the CARD Email Group. If you would like to be added to the CARD Contact List, please contact April Moore at april.moore@cshs.org.

From the Bench

Yi-Der Ida Chen, PhD

CARD (Center for Androgen Related Disorders) investigators are actively engaged in research that is related to androgen abnormalities. In addition to the steroid assay core facilities managed by Dr. Ida Chen, she is also the director of a central biochemistry lab that serves the Center. This laboratory is capable of measuring blood lipids such as cholesterol, triglyceride (esterified fatty acids) and free fatty acid (non-esterified form), is able to differentiate the good cholesterol from the bad and is able to measure sugar and the hormone insulin thereby assessing the risk for diabetes. This lab also quantifies many other hormones and inflammatory factors. These tools help us define whether an individual is at risk for diabetes or heart disease.

CARD has also acquired new instruments that allow research studies using state of the art technologies. For example, some CARD investigators study the presence or absence of genes found in tissues or organs that contribute to the androgen disorders in individuals. The new technologies use gene chips and other nanotechnology, and laser scanner detection to identify the abnormal level of gene products. Because gene-chips allow us to investigate thousands of genes at once, using these new technologies, we are able to detect biological problems very efficiently. Other technologies allow us to detect gene changes at a very sensitive level.

One of the projects conducted by Dr. Chen involves examining the cause of diabetes and cardiovascular risks. This is important because women suffer from infertilities, excess hair growth, and who are obese, are at high risk for diabetes (high blood sugar) and heart disease. Diabetes leads to many health complications such as blindness, extremity injuries, infection and sometimes amputation; kidney disease; and blood vessel changes and other cardiovascular conditions that compromise the quality of life and sometimes are direct threats to life. By identifying these risks early in an individual, one may manage the risks by adopting a different lifestyle, such as eating better diet, exercise more, and live with less stress. It is important to note that a better diet formula for one individual is not necessary the solution for a different person. Therefore, individualized risk identification and specific health management are the keys to the new paradigm of personalized medicine.

New development of diagnostic tools using blood factors or gene products previously unknown to us will eventually permit earlier detection of disease follow by early management and even prevention, instead of waiting to treat the outcome at a later stage. With their goal of understanding the genesis of androgen abnormalities, CARD investigators are dedicated to this effort in improving diagnoses and therapy for these disorders.

Dr. Chen may be contacted at (310)423-8828 or by email at cheny@cshs.org.

TRANSDERMAL TESTOSTERONE FOR MENOPAUSAL WOMEN WITH LOW LIBIDO

Dr. Glenn Braunstein is conducting a new IRB-approved study of transdermal testosterone for menopausal women with low libido who are not currently using estrogen or estrogen-progestin.

Participants must be in a stable relationship and report a decrease in desire for sex. Inclusion criteria includes naturally menopausal women aged 40-70 whose last menstrual period was at least two years ago and women aged 20-70 who are surgically menopausal at least 12 months. Exclusion criteria includes diabetes, breast cancer, recent (last 12 weeks) use of SSRI's, any form of estrogen (except Vagifem or Estring), progesterone or testosterone. Participants will receive medical evaluations, including a mammogram and transvaginal ultrasound, without charge. Eligible participants in this double-blind trial will be randomized to one of three treatment assignments: 300 mcg, 150 mcg or placebo. Participants will have eight visits over one year.

Potential participants are invited to contact the clinical research coordinator, **Keta Hodgson, RN**, at (310) 423-3850 or hodgson@cshs.org.

IR in Adolescent Girls at High Risk for PCOS

The goal of this international collaborative study is to characterize the insulin sensitivities (OGTT, FSGT) of healthy 8-14 year-old daughters or younger siblings of women with established PCOS. Insulin resistance with subsequent hyperinsulinemia is thought to promote the androgen excess characteristic of PCOS, both at the cellular and whole body level. Treatment with insulin sensitizing agents improves both reproductive function and insulin resistance, buttressing the argument that insulin excess facilitates androgen over-production. The reproductive abnormalities of PCOS appear soon after the development concludes, while mid-pubertal insulin resistance is characteristic of normal pubertal maturation. Our hypothesis is that insulin insensitivity unresolved by later adolescence heralds the emergence of androgen excess in the genetically at-risk female. If true, changes in insulin sensitivity, perhaps in combination with determined peptide/steroid surrogate markers, might then be used to predict progression to frank disease. We have begun recruitment for this longitudinal study at Cedars-Sinai, and are seeking additional testing sites worldwide. Uniquely, this study will generate a longitudinal databank of serum for adolescents at highest risk for PCOS, spanning puberty, from which to evaluate the (changing) role of numerous hormonal influences and adipocytokines. We anticipate submission of a multi-center R01 in winter 2005; currently, we have approximately 20 collaborating partners.

If you would like more information regarding possible addition of your institution to this global consortium, please contact **Dr. David Geller** of Pediatric Endocrinology at David.Geller@cshs.org, or by phone at (310) 423-1508.

Androgen Excess and Infertility: an alternative link?

Lee C. Kao, MD, PhD



Polycystic ovarian syndrome (PCOS) is currently defined by a constellation of symptoms, namely elevated androgen, irregular ovarian ovulation and/or polycystic appearing ovary by ultrasound. One of the most notable and commonly

related complaints in these reproductive age women is infertility. The obvious and major cause of this infertility is due to irregular ovulation or the lack of ovulation.

However, several intriguing observational clinical studies have suggested an alternative link between poor reproductive performance and women with PCOS. A case-control study detected ultrasonic evidence of PCOS in 82% of women with a history of recurrent miscarriages, and in a subsequent prospective study, ultrasound-confirmed PCOS was more frequent in women with recurrent miscarriages than in controls without such history. Another case-control study of women with otherwise unexplained recurrent miscarriages revealed significantly higher levels of androstenedione during the follicular phase among cases, compared with infertile women without a prior spontaneous miscarriage. Also, women undergoing in vitro fertilization (IVF) who have higher levels of luteinizing hormone (LH) right before oocyte retrieval had a reduced clinical pregnancy rate. One report demonstrated that once ovulation was restored in women with PCOS, this group of women exhibited a surprisingly poor reproductive potential as they continued to experience a lower-than-expected rate of conception and a higher-than-anticipated rate of miscarriage. Further more, when treating women with PCOS with gonadotropin-releasing hormone agonists suppression, it partially reversed these ill outcomes. These all suggest that the culprit of poor reproductive outcome in these patients to be a hormonally related defect.

The reason for repetitive pregnancy loss has yet to be determined, but some researchers believe that it is attributable to the poor quality of the endometrium. Our current knowledge about androgen hormonal action indicates that androgen effect is mediated through the androgen receptor. Androgen receptors have been identified in human endometrium, however, their role in endometrial cyclic development and function remains poorly understood. Using immunohistochemistry and reverse transcription-polymerase chain reaction, it has been

shown that women with PCOS exhibited elevated endometrial androgen receptor expression, when compared to normal, fertile controls. This over-expression of endometrial androgen receptor, therefore, provides potential alternative linking the abnormal hormonal milieu, i.e. the hyperandrogenism, to the reported deficiencies in endometrial quality. Furthermore, when a well-characterized biomarker of uterine receptivity is examined, PCOS endometrium showed delay or absence of this particular marker, yet another evidence of abnormalities in endometrial development. All these evidences lend support to a new link between hyperandrogenism and poor reproductive outcome through an endometrial pathology.

With the establishment of CARD, through its seamless working relationships with the Center for Reproductive Medicine and the Division of Reproductive Medicine and Infertility, CSMC is uniquely positioned to be one of the most qualified research centers to research this link, and ultimately we will develop specific treatments for patients with this pathology.

Dr. Kao is the co-director for the Center for Reproductive Medicine at Cedars-Sinai Medical Center. His primary areas of research interests involve the mechanisms of human embryo implantation, infertility, reproductive endocrinological abnormalities, fibroids and endometriosis. He may be contacted at (310)423-6613 or lee.kao@cshs.org.

POLYCYSTIC OVARIAN SYNDROME:

FROM HIRsutISM TO FERTILITY, A MULTIDISCIPLINARY APPROACH TO THE MANAGEMENT OF THE WHOLE PATIENT

Friday, January 14, 2005

7:30 - 8:30	Registration/Breakfast/Expo Opens
8:30 - 9:30	Internal Medicine Grand Rounds <i>New Concepts in the Diagnosis & Management of PCOS</i> Ricardo Azziz, MD, MPH, MBA
9:30-10:30	<i>The link between PCOS, IR, & CAD</i> Sheila Y. Bolour, MD
9:50-10:30	<i>The Genetics of PCOS: Progress & Challenges</i> Mark Goodarzi, MD, PhD
10:30-11:10	<i>Evaluation of Oligomenorrhea in Adolescents</i> David Geller, MD, PhD
11:45 - 1:15	<i>Neuroendocrine Abnormalities</i> Buffet Lunch and keynote address Jeffrey Chang, MD
1:30 - 2:10	<i>Evaluation & Treatment of Hirsutism</i> Ricardo Azziz, MD
2:10 - 2:50	<i>Fertility & PCOS Part I</i> Margareta D. Pissarska, MD
2:50 - 3:30	<i>Fertility & PCOS Part II</i> Lee C. Kao, MD, PhD
3:30	Closing Session Ricardo Azziz, MD

Expo remains open until 4:00

The PCOS Conference will be held in Harvey Morse Auditorium. Registration fee includes CME credit, continental breakfast, lunch, parking and course materials.

Postmarked by November 30, 2004 - \$75.00
Postmarked after November 30, 2004 & on-site - \$125.00

For further information, please call the Office of Continuing Medical Education at (310) 423-2936 or visit us at www.cedars-sinai.edu/cme.

CME Credit:

Cedars-Sinai Medical Center designates this educational activity for a maximum of six category 1 credits toward the AMA Physician's Recognition Award.

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