

## Hot off the Press

### ANDROGEN EXCESS

- Apridonidze T, Essah PA, Iuorno MJ, Nestler JE.** Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2005 Apr; 90(4):1929-35.
- Carmina E, Chu MC, Longo RA, Rini GB, Lobo RA.** Phenotypic variation in hyperandrogenic women influences the findings of abnormal metabolic and cardiovascular risk parameters. *J Clin Endocrinol Metab.* 2005 May;90(5):2545-9
- Chang WY, Knochenhauer ES, Bartolucci AA, Azziz R.** Phenotypic spectrum of polycystic ovary syndrome: clinical and biochemical characterization of the three major clinical subgroups. *Fertil Steril.* 2005 Jun; 83(6):1717-23.
- Corbould A, Kim YB, Youngren JF, Pender C, Kahn BB, Lee A, Dunaif A.** Insulin resistance in the skeletal muscle of women with PCOS involves intrinsic and acquired defects in insulin signaling. *Am J Physiol Endocrinol Metab.* 2005 May; 288(5):E1047-54
- Diamanti-Kandarakis E, Alexandraki K, Protogerou A, Piperi C, Papamichael C, Aessopos A, Lekakis J, Mavrikakis M.** Metformin administration improves endothelial function in women with polycystic ovary syndrome. *Eur J Endocrinol.* 2005 May; 152(5):749-56.
- Gennarelli G, Rovei V, Novi RF, Holte J, Bongioanni F, Revelli A, Pacini G, Cavallo-Perin P, Massobrio M.** Preserved insulin sensitivity and  $\beta$ -cell activity, but decreased glucose effectiveness in normal-weight women with the polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2005 Jun; 90(6):3381-6.
- Hahn S, Fingerhut A, Khomtsiv U, Khomtsiv L, Tan S, Quadbeck B, Herrmann BL, Knebel B, Muller-Wieland D, Mann K, Janssen OE.** The peroxisome proliferator activated receptor gamma Pro12Ala polymorphism is associated with a lower hirsutism score and increased insulin sensitivity in women with polycystic ovary syndrome. *Clin Endocrinol (Oxf).* 2005 May; 62(5):573-9.
- Jaaskelainen J, Korhonen S, Voutilainen R, Hippelainen M, Heinonen S.** Androgen receptor gene CAG length polymorphism in women with polycystic ovary syndrome. *Fertil Steril.* 2005 Jun; 83(6):1724-8.
- Kumar A, Woods KS, Bartolucci AA, Azziz R.** Prevalence of adrenal androgen excess in patients with the polycystic ovary syndrome (PCOS). *Clin Endocrinol (Oxf).* 2005 Jun; 62(6):644-9.
- Legro RS, Chiu P, Kunselman AR, Bentley CM, Dodson WC, Dunaif A.** Polycystic ovaries are common in women with hyperandrogenic chronic anovulation but do not predict metabolic or reproductive phenotype. *J Clin Endocrinol Metab.* 2005 May; 90(5):2571-9.
- Legro RS, Gnatuk CL, Kunselman AR, Dunaif A.** Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. *J Clin Endocrinol Metab.* 2005 Jun; 90(6):3236-42.
- Raskauskiene D, Jones PW, Govind A, Obhrai M, Clayton RN.** Do polycystic ovaries on ultrasound scan indicate decreased insulin sensitivity in sisters of women with polycystic ovary syndrome? *J Clin Endocrinol Metab.* 2005 Apr; 90(4):2063-7.
- Vryonidou A, Papatheodorou A, Tavidou A, Terzi T, Loi V, Vatalas IA, Batakis N, Phenekos C, Dionyssiou-Asteriou A.** Association of hyperandrogenemic and metabolic phenotype with carotid intima-media thickness in young women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2005 May; 90(5):2740-6.
- White T, Jain JK, Stanczyk FZ.** Effect of oral versus transdermal steroidal contraceptives on androgenic markers. *Am J Obstet Gynecol.* 2005 Jun; 192(6):2055-9.

### MEETINGS OF INTEREST

**61<sup>st</sup> Annual Meeting of the American Society for Reproductive Medicine**  
October 15-19, 2005  
Palais de Congrès, Montreal, Quebec, Canada  
[www.asrm.org](http://www.asrm.org)

**International Committee for Insulin Resistance**  
November 17-19, 2005  
San Francisco, CA  
[www.insulinresistance.us](http://www.insulinresistance.us)

**Androgen Excess Society Annual Meeting**  
June 23, 2006  
Boston, MA  
[www.ae-society.org](http://www.ae-society.org)

**The Endocrine Society**  
June 24-27, 2006  
Boston, MA  
[www.endo-society.org](http://www.endo-society.org)

Insider Information...



8700 Beverly Boulevard,  
South Tower, Suite 3611  
Los Angeles, CA 90046  
(310) 423-9964  
[www.csmc.edu/card](http://www.csmc.edu/card)

### CARD Staff

**Ricardo Azziz, MD, MPH, MBA - Director,**  
Center for Androgen-Related Disorders

**Sheila Bolour, MD**  
Assistant Director

**Glenn Braunstein, MD**  
Associate Director

**Dennis Magoffin, PhD**  
Associate Director

## Center for Androgen-Related Disorders

### Director's Welcome

August 2005 Vol. 2, Issue 1

As a center of excellence at Cedars-Sinai, the Center for Androgen-Related Disorders (CARD) continues to provide the best in educational opportunities to physicians and young investigators who work tirelessly to research these disorders. We are also committed to providing the best in patient care and to help educate those who live with this disorder.

The CARD Lecture Series is continuing to grow and I hope you have benefited as much as I have from our past lecturers. I am continually amazed by the wealth of information and research that we receive from such renowned physicians in this field. We look forward to an even more exciting 2006 Lecture Series.

We are currently planning for the 2nd Annual PCOS Physician/Clinician and Patient Conference. This annual conference is sponsored by CARD and will be held January 13-14, 2006. I hope you will make plans to attend the conference.

As CARD continues to grow, so does our need for more accessible administrative accommodations. In early August, the CARD Administrative Office moved from 930 East Tower to 275 West Tower. Please make a note of this address change.

Sincerely,

Richardo Azziz, MD, MPH, MBA  
Director, Center for Androgen Related Disorders

## CARD Calendar of Events

### September 7, 2005

#### LECTURE SERIES

Barbara Gower, Ph.D.  
Associate Professor  
Department of Nutrition Sciences  
University of Alabama at Birmingham

### October 26, 2005

#### LECTURE SERIES

Ida Chen, Ph.D.  
Director, Micro Array Core Facility  
Department of Obstetrics & Gynecology  
Cedars-Sinai Medical Center

### November 2, 2005

#### LECTURE SERIES

Antoni J. Duleba, M.D.  
Associate Professor  
Department of Obstetrics & Gynecology  
Yale University School of Medicine

### In this issue...

• Lecture Series --  
Mark your calendar!

• Second Annual CARD  
PCOS Conference for  
Physicians, Clinicians, &  
Patients

• Hot off the Press!

• From the Bench

• Clinical Review

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 Faye Byrd at [faye.hyrd@chs.cshs.org](mailto:faye.hyrd@chs.cshs.org)

## From the Bench

### The Genetics of Polycystic Ovary Syndrome: Progress and Challenges

Mark O. Goodarzi, M.D., Ph.D.

Polycystic ovary syndrome (PCOS) is considered a common, complex genetic disorder, as are conditions such as type 2 diabetes, schizophrenia, and asthma. Such common diseases, including PCOS, appear to have a complex, multifactorial etiology, in which a variety of predisposing genes, not just one gene, interact with environmental factors to produce disease.

Family studies demonstrate that PCOS is significantly more prevalent among family members than in the general population. Among first-degree female relatives (on no hormonal therapy) of 93 patients with PCOS, 35% of premenopausal mothers and 40% of sisters were also affected with the disorder. These affection rates are significantly higher than the 4-6% observed in the general population. In another study, 115 sisters of 80 women with PCOS were evaluated; of these, 22% met criteria for PCOS. Twenty-four percent of these sisters had hyperandrogenemia with normal menses. Brothers of women with PCOS also display abnormal androgens: a study of such brothers found them to have elevated levels of dehydroepiandrosterone sulfate.

Not only is PCOS itself a heritable condition, but within PCOS, insulin resistance and insulin secretion appear to be under significant genetic control. Among first-degree relatives of women with PCOS, including women not diagnosed with PCOS and brothers, several studies have demonstrated hyperinsulinemia and decreased insulin sensitivity. In studies of families of women with PCOS, insulin secretion levels, quantified directly by the frequently sampled intravenous glucose tolerance test, displayed significant heritability, suggesting a genetic component to beta-cell dysfunction in PCOS. The most abnormal insulin secretion was observed in women with PCOS and a history of type 2 diabetes in a first-degree relative.

To date, efforts (over 100 publications) to identify genes that influence PCOS susceptibility have largely utilized the candidate gene approach. Candidate genes studied in PCOS have generally targeted loci regulating five areas: i) steroid biosynthesis and action; ii) gonadotropic action; iii) weight and energy regulation, iv) insulin action, and v) cardiovascular disease risk via inflammation, hypercoagulability, or blood pressure. Several provocative genetic associations with PCOS have been reported that are slowly starting to illuminate the underlying causes of PCOS; however, no gene or genes has clearly emerged as most important in PCOS, and many positive results were not confirmed in subsequent studies. Studies of the genetic etiology of PCOS have been hampered by various limitations, including: i) only one or two variants genotyped in each gene; ii) incomplete characterization of the phenotype in family members, iii) inability

to assign a PCOS phenotype to prepubertal girls, postmenopausal women, and men; iv) possible inclusion of patients with non-classic adrenal hyperplasia (NCAH); v) lack of appropriate controls; vi) unclear ethnic/racial composition; vii) varying criteria used to diagnose PCOS in different studies; viii) small numbers of subjects in most studies. Therefore it is likely that many underpowered studies resulted in false negative reports and that several small studies produced false positive results.

At Cedars-Sinai we are entering the field of PCOS genetics. We will maximize our chances of success by studying a large number of subjects, carefully and completely phenotyped, using uniform criteria to diagnose PCOS, and by using haplotypes (collections of genetic markers inherited together on the same chromosome) to capture variation globally across genes. We have already presented abstracts in national meetings detailing the role of several genes (PPARG, CAPN10, and GSK3B) in PCOS susceptibility.

References available on request. Please contact Dr. Mark Goodarzi at [goodarzim@cshs.org](mailto:goodarzim@cshs.org)

#### SECOND ANNUAL CONFERENCE UPDATE

### POLYCYSTIC OVARY SYNDROME: FROM HIRSUTISM TO FERTILITY, A MULTIDISCIPLINARY APPROACH TO THE MANAGEMENT OF THE WHOLE PATIENT

Friday, January 13, 2006

8:30 AM - 4:00 PM

CME/CEU Education Conference

This conference will provide attendees with a minimum of 6 category 1 credits toward the AMA Physician's Recognition Award.

The 2nd Annual Conference will be held in the Harvey Morse Auditorium. Registration materials will be mailed out in the fall but if you would like to reserve a seat at the conference, please contact April Moore at (310) 423-4887 or [april.moore@cshs.org](mailto:april.moore@cshs.org).

Saturday, January 14, 2006

10:00 AM - 2:00 PM

Community Education Conference

This is a one-day conference that's open to the public. There is a registration fee of \$10.00 to attend and this charge includes lunch, validated parking, and all registration materials. Please share this information with your patients.

## PCOS and Fertility: What are the options?



Margareta D. Pisarska, M.D.

Ovulatory disorders are the primary diagnosis in over a quarter of couples seeking fertility treatment. Of those couples with ovulatory disorders, polycystic ovarian syndrome (PCOS) accounts for approximately 70% of those cases. Ovulatory disorders in PCOS are characterized by disordered folliculogenesis and abnormal steroidogenesis. Both are interlinked, however, it is still difficult to identify the initiating abnormality. In addition to alterations in steroidogenesis in women with PCOS there are also alterations in the expression of the 2 different estrogen receptors (alpha and beta) that may be related to abnormal follicular development. More recently, another hormone, antimüllerian hormone was found to be deficient in ovaries from women with PCOS. Antimüllerian hormone was found to be deficient in early developing follicles, possibly contributing to disordered follicular development. Studies done here at Cedars Sinai Medical Center on ovarian function in women with PCOS may help explain the link between hyperinsulinemia and PCOS. Yen and Magoffin, et al, have been able to demonstrate alterations in insulin receptor substrate (IRS) in theca cells from women with PCOS. These alterations are consistent with exaggerated amplifications of the insulin signal and may be contributing factors to ovarian hyperandrogenism and theca hyperplasia found in women with PCOS.

Although a large body of research is currently being conducted on the mechanisms involved in ovarian function of women with PCOS, targeted treatment for normal folliculogenesis is still many years away. However, there are a number of different options for women with PCOS who are interested in pursuing pregnancy. Weight loss alone helps women with PCOS resume menses, ovulate, and achieve pregnancy. A loss as little as 5% of body weight results a cumulative ovulation rate of 45% and a cumulative pregnancy rate of 30%.

In addition to weight reduction, there are numerous pharmacologic agents available for ovulation induction in women with PCOS. Traditionally, Clomiphene Citrate has been used to induce ovulation. Up to 75% of women will ovulate and 40% of women will achieve pregnancy over a 6 month period. Studies predicting success of ovulation have been preformed, and the best predictor of ovulation is the free androgen index (FAI), which is testosterone divided by sex hormone-binding globulin.

Another pharmacologic agent that has been utilized to induce ovulation is Metformin. Metaanalyses have been conducted for Metformin therapy in women with PCOS either alone or in combination with other ovulatory inducing agents, such as Clomiphene Citrate. Metformin alone is effective in achieving ovulation, however improvements in pregnancy rates are not significant. Comparisons of combination therapy, Metformin with Clomiphene Citrate to Clomiphene Citrate alone demonstrates improvements in ovulation and pregnancy rates.

Women who remain anovulatory despite the use of oral agents can be treated with Gonadotropins (FSH). In women who fail to ovulate with Clomiphene Citrate, treatment with FSH results in ovulation rates greater than 80% and pregnancy rates as high as 40%.

Failure to conceive despite ovulation induction in women with PCOS leaves the option of assisted reproductive technologies, such as in vitro fertilization (IVF). Despite ovulatory dysfunction in women with PCOS, IVF results in pregnancy rates comparable to couples with other causes of infertility.

The Center for Androgen Related Disorders, in conjunction with the Center for Reproductive Medicine, is continually conducting studies to understand the mechanism of ovarian function in women with PCOS in order to tailor therapy for ovulation induction. In the interim, the various treatment options discussed are currently being utilized in order to help couples achieve their goal of pregnancy.

Dr. Pisarska is the co-director for the Center for Reproductive Medicine at Cedars-Sinai Medical Center. Her primary areas of research interest involve the mechanisms of early follicle and egg development, infertility, assisted reproductive technologies, abnormalities in reproductive endocrinology, and premature ovarian failure. She can be contacted at (310) 423-5763 or [pisarskam@cshs.org](mailto:pisarskam@cshs.org).

#### CARD UPDATES...

- Beginning February 2006, the CARD Lecture Series will be held on the first Tuesday of each month in HMCC 4-6. Look for a complete schedule in the next edition of the newsletter.
- The CARD Administrative Office is now located in the West Tower, Suite 275W, phone 310-423-8750, fax 310-423-8760.