NIH Office of Disease Prevention

Evidence-based Methodology Workshop on Polycystic Ovary Syndrome

Program Book

December 3–5, 2012

William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Sponsors

Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH
Office of Disease Prevention, NIH

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Dear Workshop Attendees:

It is with great pleasure that I welcome you to the National Institutes of Health (NIH) Evidence-based Methodology Workshop on Polycystic Ovary Syndrome (PCOS). The Office of Disease Prevention (ODP) is pleased to cosponsor this event with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). I would like to thank Dr. Alan E. Guttmacher, Director of NICHD, for his leadership in this endeavor and extend a special thank you to Dr. Louis V. DePaolo, Chief of the Fertility and Infertility Branch, who led the day-to-day development of the workshop alongside ODP staff. The goal of the workshop is to identify methodological and scientific weaknesses and move the field forward through an unbiased and evidence-based assessment of the research.

ODP provides leadership for the development, coordination, and implementation of activities across the NIH and with other public and private partners to increase the scope, support, public health impact, and dissemination of health promotion and disease prevention research. This workshop is just one example of how ODP promotes methodologically sound research to reduce the incidence of disease and increase healthy years of life. The workshop is designed to be interactive, so we encourage you to share your insights during audience discussion sessions about:

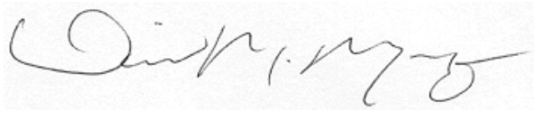
- The benefits and drawbacks of different diagnostic criteria
- The causes, predictors, and long-term consequences of PCOS
- Optimal prevention and treatment strategies.

We will also be accepting public comments on the panel's draft report, which will be posted on the ODP website on December 7, 2012, through January 4, 2013.

It is an exciting time for ODP as we conduct a new strategic planning effort to address the scope, support, and impact of NIH health promotion and disease prevention research. As part of this process, we are working with various stakeholders, including investigators, clinicians, and the general public, to ensure that research is based on good science and that effective intervention programs are carefully designed, disseminated, and evaluated. ODP encourages public feedback on its strategic plan, which will be posted on the ODP website in early 2013.

On behalf of the NIH and ODP, thank you in advance for your contributions. We look forward to an informative and engaging workshop.

Sincerely,



David M. Murray, Ph.D.
Associate Director for Prevention
Director, Office of Disease Prevention
Office of the Director
National Institutes of Health

Dear Colleagues:

I am very pleased to join Dr. Murray and the National Institutes of Health (NIH) Office of Disease Prevention in welcoming you to this important workshop on polycystic ovary syndrome (PCOS). This complex disorder, first described nearly 80 years ago, continues to affect the ability of many women to bear children and severely affects not only fertility status but also quality of life.

While many look to the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) as a focal point at the NIH for pediatric research, our Institute's mission extends much farther. Our science crosses the lifespan, and we highly value our longtime commitment to reproductive health research and to women's health.

This year, the NICHD celebrates its 50th anniversary, which provides us a special opportunity to reflect on past research accomplishments and to anticipate future scientific directions to improve the health and well-being of women, children, and individuals with disabilities. Among the NICHD's past accomplishments, we count our prior PCOS workshop in 1990, which resulted in a set of diagnostic criteria ("the NIH Criteria") that facilitated basic research advances and the design of more effective detection and treatment approaches.

While we have come a long way, there is still much to learn and accomplish. The work you do over the next few days—in discussing optimal diagnostic criteria, causes and consequences of the condition, and effective prevention and treatment strategies—is essential to move the science forward. We hope these scientific advances will someday result in better management of existing disease, as well as optimum strategies to prevent PCOS.

So, on behalf of the NICHD, and the millions of women and families affected by PCOS, I thank you for your dedication and valuable contributions, and I look forward to following your continued progress in the months and years ahead.

Sincerely,

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health

About the Workshop

Polycystic ovary syndrome (PCOS) is a common hormone disorder that affects approximately 5 million reproductive-aged women in the United States. Women with PCOS have difficulty becoming pregnant (i.e., are infertile) due to hormone imbalances that cause or result from altered development of ovarian follicles. One such imbalance is high blood levels of androgens, which can come from both the ovaries and adrenal gland. Other organ systems that are affected by PCOS include the pancreas, liver, muscle, blood vasculature, and fat.

In addition to fertility impairment, other common symptoms of PCOS include:

- Irregular or no menstrual periods (for women of reproductive age)
- Acne
- Weight gain
- Excess hair growth on the face and body
- Thinning scalp hair
- Ovarian cysts.

Women with PCOS are often resistant to the biological effects of insulin and, as a consequence, may have high insulin levels. As such, women with PCOS are at risk for type 2 diabetes, high cholesterol, and high blood pressure. Obesity also appears to worsen the condition. Costs to the U.S. healthcare system to identify and manage PCOS are approximately $4 billion annually; however, this estimate does not include treatment of the serious conditions associated with PCOS.

For most of the 20th century, PCOS was a poorly understood condition. In 1990, the National Institutes of Health (NIH) held a conference on PCOS to create both a working definition of the disorder and diagnostic criteria. The outcome of this conference, the *NIH Criteria*, served as a standard for researchers and clinicians for more than a decade. In 2003, a consensus workshop in Rotterdam developed new diagnostic criteria, the *Rotterdam Criteria*.

The 2012 NIH Evidence-based Methodology Workshop on PCOS will seek to clarify:

- Benefits and drawbacks of using the *Rotterdam Criteria*
- The condition's causes, predictors, and long-term consequences
- Optimal prevention and treatment strategies.

The NIH workshop is sponsored by the Office of Disease Prevention and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. A multidisciplinary steering committee developed the workshop agenda. The NIH Library created an extensive, descriptive bibliography on PCOS to facilitate workshop discussion. During the 2½-day workshop, invited experts will discuss the body of evidence and attendees will have opportunities to provide comments during open discussion periods. After weighing the evidence, an unbiased, independent panel will prepare a report that summarizes the workshop and identifies future research priorities.

Financial Disclosures

The National Institutes of Health, Centers for Disease Control and Prevention, our planners, and our presenters wish to disclose that they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters, with the exception of the following:

Name	Company/Organization	Financial Relationship
David H. Abbott, Ph.D.	Viamet Pharmaceuticals, Inc.	Honorarium, Grant
Silva Arslanian, M.D.	Sanofi-Aventis Novo Nordisk Bristol-Meyers Squibb Gilead Sciences, Inc. Boehringer Ingelheim	Honorarium, Consultant Honorarium, Advisory Board Honorarium, Advisory Board Honorarium, Consultant Honorarium, Data Safety Monitoring Board
Adam Balen, M.B.B.S., M.D., D.Sc., FRCOG	Ferring Pharmaceuticals PregLem Pharmaceuticals Merck Serono Pharmaceuticals	Honorarium, Advisory Board Honorarium, Advisory Board Honorarium, Advisory Board
Shalender Bhasin, M.D.	Abbott Laboratories Ligand Pharmaceuticals	Research Grant Research Grant
Adrian S. Dobs, M.D., M.H.S.	ENDO Pharmaceuticals Clarus Therapeutics Takeda Pharmaceuticals Cadent Medical Communications Abbott Laboratories	Research Grant Research Grant Research Grant Honorarium Honorarium
Andrea Dunaif, M.D.	Amylin Pharmaceuticals Bristol-Meyers Squibb Burroughs Wellcome Fund Translational Research Institute for Metabolism and Diabetes, Florida Hospital, and Sanford-Burnham Institute Pennington Biomedical Research Center	Honorarium, Advisory Board Honorarium, Advisory Board Review Fee, Translational Research Reviewer Honorarium, Scientific Advisory Board Member Honorarium, External Advisory Board Member
David A. Ehrmann, M.D.	Astra-Zeneca	Consultant's Fee, Consultant
Bart C.J.M. Fauser, M.D., Ph.D.	Andromed Ardana Auxogyn Ferring Pharmaceuticals Genovum Gideon-Richter Merck Serono Pharmaceuticals MSD Organon Pantarhei Bioscience PregLem Pharmaceuticals Roche Schering Schering Plough Serono Watson Laboratories Wyeth	Fee, Grant Support Fee, Grant Support Fee, Grant Support Fee, Grant Support Fee, Grant Support Fee, Grant Support Fee, Grant Support Fee, Grant Support Fee, Grant Support Fee, Grant Support Fee, Grant Support Fee, Grant Support

Name	Company/Organization	Financial Relationship
Jose C. Florez, M.D., Ph.D.	Pfizer, Inc. Eli Lilly	Honorarium, Consultant, Invited Scientific Speaker Honorarium, Consultant
Richard S. Legro, M.D. FACOG	American Board of Obstetrics and Gynecology Endocrine Society Practice Guideline Committee American Society for Reproductive Medicine National Institutes of Health (NIH) Study Section Reproductive Health Advisory Panel (Food and Drug Administration) First Affiliated Hospital and Heilongjiang University of Chinese Medicine *Seminars in Reproductive Endocrinology* *Endocrine Reviews* *Journal of Clinical Endocrinology and Metabolism* *Fertility and Sterility* *Human Reproduction* NIH STEP Program Deutsche Bank Securities, Inc. Taiwan Society of Reproductive Medicine British Fertility Society The Association for Clinical Embryologists Society for Reproduction and Fertility The Israel Fertility Society Specialized Cooperative Centers Program in Reproduction and Infertility Research The Endocrine Society European Society of Human Reproduction and Embryology International Congress of Endocrinology and European Congress of Endocrinology	Subspecialty Board Examiner/ Consultant Member Program Chair/Consultant Honorarium, Member Honorarium, Special Government Employee/Consultant Steering Committee Member Editorial Board Editorial Board Editorial Board Associate Editor Associate Editor Honorarium, Consultant Honorarium, Consultant Honorarium, Lecturer Guest Speaker Guest Speaker Guest Speaker Guest Speaker Committee Member Task Force Member Associate Editor, Guest Speaker Guest Speaker
Robert Norman, M.D.	Merck Merck Serono Pharmaceuticals Fertility SA	Speaker Speaker Owner, In Vitro Fertilization Company
All other planners and presenters signed statements that they have no financial or other conflicts of interest.		

There is no commercial support for this activity. Presentations will not include any discussion of the unlabeled use of a product under investigational use.

Policy on Panel Disclosure

Panel members signed a confirmation that they have no financial or other conflicts of interest pertaining to the topic under consideration.

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Agenda

MONDAY, DECEMBER 3, 2012

Bethesda Marriott
5151 Pooks Hill Road
Bethesda, Maryland 20814

5:00 p.m. **Registration Opens**

6:30 p.m. **Workshop Overview**
Louis V. DePaolo, *Ph.D.*
Chief
Fertility and Infertility Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

6:45 p.m. **Welcome**
David M. Murray, *Ph.D.*
Associate Director for Prevention
Director, Office of Disease Prevention
Office of the Director
National Institutes of Health

7:00 p.m. **Overview of the Literature Search Methodology**
Nancy Terry, *M.L.S.*
Biomedical Research Librarian/Informationist
National Institutes of Health Library
Division of Library Services
Office of Research Services
Office of the Director
National Institutes of Health

7:30 p.m. **Facilitated Panel and Audience Discussion**
Moderator: *Paris A. Watson*

8:30 p.m. **Wrap-up, Day 1**

9:00 p.m. **Adjourn, Day 1**

TUESDAY, DECEMBER 4, 2012

Natcher Conference Center
Building 45, Main Auditorium
National Institutes of Health
Bethesda, Maryland 20892

7:00 a.m. **Registration Opens**

8:00 a.m. **Opening Remarks**
Yvonne T. Maddox, Ph.D.
Deputy Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

8:10 a.m. **Session 1: Diagnostic Criteria Used for Polycystic Ovary Syndrome (PCOS)**
Moderator: *Andrea Dunaif, M.D.*

Discussion of the Three Diagnostic Criteria
Andrea Dunaif, M.D.
Charles F. Kettering Professor of Endocrinology and Metabolism
Vice Chair for Research
Department of Medicine
Northwestern University Feinberg School of Medicine

8:30 a.m. **The 2003 Rotterdam Consensus Criteria Put in Perspective**
Bart C.J.M. Fauser, M.D., Ph.D.
Professor of Reproductive Medicine
Utrecht Life Sciences
University Medical Center

8:50 a.m. **The 2006 Androgen Excess and PCOS Society Criteria for PCOS: The Critical Importance of Androgenization**
Ricardo Azziz, M.D., M.P.H., M.B.A.
Professor
Obstetrics, Gynecology, and Medicine
President
Georgia Health Sciences University
Chief Executive Officer
Georgia Health Sciences Health System

9:10 a.m. **The Impact of Assay Quality and Reference Range on Clinical Decision-Making in Patients With Androgen Disorders**
Shalender Bhasin, M.D.
Professor of Medicine
Boston University School of Medicine
Chief
Section of Endocrinology, Diabetes, and Nutrition
Director
Boston Claude D. Pepper Older Americans Independence Center
Boston Medical Center

TUESDAY, DECEMBER 4, 2012 (continued)

9:30 a.m. **Age at Diagnosis**
Sharon E. Oberfield, M.D.
Professor of Pediatrics and Director
Division of Pediatric Endocrinology, Diabetes, and Metabolism
Columbia University Medical Center

9:50 a.m. **Epidemiology of PCOS**
PonJola Coney, M.D.
Senior Associate Dean for Faculty Affairs
Virginia Commonwealth University School of Medicine

10:10 a.m. **Facilitated Panel and Audience Discussion**

12:30 p.m. **Lunch—Panel Meets in Executive Session**

1:30 p.m. **Session 2: Developmental or Genetic Origins of PCOS**
Moderator: *R. Jeffrey Chang, M.D.*

Intrauterine Environment
Daniel Dumesic, M.D.
Division Chief and Professor, Reproductive Endocrinology and Infertility
Department of Obstetrics and Gynecology
University of California, Los Angeles

1:50 p.m. **Role of Postnatal Androgen Exposure**
John C. Marshall, M.B.Ch.B., M.D.
Director
Center for Research in Reproduction
University of Virginia School of Medicine

2:10 p.m. **Early Hormonal Abnormalities in Children Born to Mothers With PCOS**
Teresa Sir-Petermann, M.D.
Professor
Laboratory of Endocrinology and Metabolism, West Division
University of Chile School of Medicine

2:30 p.m. **Ovarian Morphology**
Marcelle I. Cedars, M.D.
Professor and Director
Division of Reproductive Endocrinology
University of California, San Francisco

2:50 p.m. **Role of Obesity Prior to Puberty**
R. Jeffrey Chang, M.D.
Professor and Director
Division of Reproductive Endocrinology
Department of Reproductive Medicine
University of California, San Diego School of Medicine

TUESDAY, DECEMBER 4, 2012 (continued)

3:10 p.m. **Break**

3:30 p.m. **Epigenetic Nonhuman Primate Model Demonstrates Metabolic Antecedents to PCOS-Like Traits**
David H. Abbott, Ph.D.
Professor
Department of Obstetrics and Gynecology
Wisconsin National Primate Research Center
University of Wisconsin

3:50 p.m. **Androgen Effects on the Central Circuits Affecting Fertility**
Sue Moenter, Ph.D., M.S.
Professor
Departments of Molecular and Integrative Physiology, Internal Medicine, and Obstetrics and Gynecology
University of Michigan School of Medicine

4:10 p.m. **Developmental Programming of PCOS Phenotype: Impact of Maternal/Fetal Environment**
Vasantha Padmanabhan, Ph.D.
Professor
Departments of Pediatrics, Obstetrics and Gynecology, Molecular and Integrative Physiology, and Environmental Health Sciences
University of Michigan School of Medicine

4:30 p.m. **Genetics**
Margrit Urbanek, Ph.D.
Associate Professor
Division of Endocrinology
Department of Medicine
Northwestern University Feinberg School of Medicine

4:50 p.m. **Genome-Wide Association Studies: Predisposition to Comorbidities**
Jose C. Florez, M.D., Ph.D.
Assistant Physician in Endocrinology
Center for Human Genetic Research Diabetes Unit
Massachusetts General Hospital
Associate Professor
Harvard Medical School
Associate Member
Broad Institute

5:10 p.m. **Facilitated Panel and Audience Discussion**

6:15 p.m. **Wrap-up, Day 2**

6:30 p.m. **Adjourn, Day 2**

WEDNESDAY, DECEMBER 5, 2012

Natcher Conference Center
Building 45, Main Auditorium
National Institutes of Health
Bethesda, Maryland 20892

8:00 a.m. **Registration Opens**

8:30 a.m. **Session 3: Long-Term Health Consequences of PCOS**

Moderator: *Adrian S. Dobs, M.D., M.H.S.*

Type 2 Diabetes and Prediabetes in Women With PCOS
Adrian S. Dobs, M.D., M.H.S.
Professor of Medicine and Oncology
Division of Endocrinology and Metabolism
The Johns Hopkins University School of Medicine

8:50 a.m. **Cardiovascular Disease**
Evelyn O. Talbott, Dr.P.H., M.P.H.
Professor
Department of Epidemiology
Program Director
Environmental Epidemiology Program
Graduate School of Public Health
University of Pittsburgh

9:10 a.m. **Obstructive Sleep Apnea in PCOS: Causes and Consequences**
David A. Ehrmann, M.D.
Professor of Medicine and Associate Director
University of Chicago Clinical Research Center
Director
Center for Polycystic Ovary Syndrome
University of Chicago Medical Center

9:30 a.m. **Endometrial and Other Cancers**
Kurt T. Barnhart, M.D., M.S.C.E.
William Shippen, Jr. Professor of Obstetrics and Gynecology and Epidemiology
Director
Women's Health Clinical Research Center
Division of Reproductive Endocrinology and Infertility
University of Pennsylvania Medical Center

9:50 a.m. **Break**

WEDNESDAY, DECEMBER 5, 2012 (continued)

10:10 a.m. **Nonalcoholic Fatty Liver Disease**

Silva Arslanian, M.D.
Chief
Weight Management and Wellness Center
Director
Pediatric Clinical and Translational Research Center
University of Pittsburgh Medical Center (UPMC)
Richard L. Day Endowed Chair in Pediatrics
Professor of Pediatrics
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC

10:30 a.m. **Mental Health**

Natalie Rasgon, M.D., Ph.D.
Professor
Department of Psychiatry and Behavioral Sciences
Stanford Center for Neuroscience in Women's Health
Stanford University School of Medicine

10:50 a.m. **Menopause in Women With PCOS**

Rogerio A. Lobo, M.D.
Professor of Obstetrics and Gynecology
Columbia University College of Physicians and Surgeons

11:10 a.m. **Facilitated Panel and Audience Discussion**

12:30 p.m. **Lunch—Panel Meets in Executive Session**

1:30 p.m. **Session 4: Optimal Management Strategies for the Reproductive and Metabolic Consequences of PCOS**

Moderator: *Rogerio A. Lobo, M.D.*

Strategies for Management of Metabolic Phenotypes

Stephen Franks, M.D., FRCP, FMedSci
Professor
Institute of Reproductive and Developmental Biology
Imperial College London
Hammersmith Hospital

1:50 p.m. **Strategies for Management of Reproductive and Metabolic Consequences of PCOS**

Richard S. Legro, M.D., FACOG
Professor of Obstetrics and Gynecology
College of Medicine
Milton S. Hershey Medical Center
Hershey Obstetrics and Gynecology
The Pennsylvania State University

WEDNESDAY, DECEMBER 5, 2012 (continued)

2:10 p.m. **Pregnancy and Its Outcomes**

Adam Balen, M.B.B.S., M.D., D.Sc., FRCOG
Consultant Obstetrician and Gynaecologist and
Subspecialist in Reproductive Medicine
Honorary Professor of Reproductive Medicine and Surgery
Leeds General Infirmary and St. James's University Hospital
The Leeds Teaching Hospitals NHS Trust
University of Leeds

2:30 p.m. **Role of Prevention and Lifestyle Strategies**

Robert Norman, M.D.
Director
Robinson Institute
Faculty of Health Sciences
University of Adelaide

2:50 p.m. **Role of Family Screening**

Okan Bülent Yildiz, M.D.
Professor
Department of Internal Medicine
Endocrinology and Metabolism Unit
Hacettepe University School of Medicine

3:10 p.m. **Facilitated Panel and Audience Discussion**

4:10 p.m. **Final Points by Speakers, Panel, Audience**

5:30 p.m. **Workshop Wrap-up**

6:30 p.m. **Adjourn Workshop**

DIAGNOSTIC CRITERIA USED FOR POLYCYSTIC OVARY SYNDROME (PCOS)

Andrea Dunaif, M.D., currently serves as the Vice Chair for Research and Charles F. Kettering Professor of Endocrinology and Metabolism at Northwestern University's Feinberg School of Medicine. She is a Graduate School Faculty Member at Northwestern University and an Affiliate Scientist at Wisconsin Regional Primate Research Center. She is also a former Chief of the Division of Endocrinology, Metabolism, and Molecular Medicine at Northwestern University's Feinberg School of Medicine. Before joining Northwestern University in 2001, Dr. Dunaif held faculty appointments at the Mount Sinai School of Medicine, Pennsylvania State University College of Medicine, and Harvard Medical School. She served as the first Director of Women's Health at Brigham and Women's Hospital. She also established and served as Chief of the Division of Women's Health in the Department of Medicine at Brigham and Women's Hospital and led the Harvard Medical School National Center of Excellence in Women's Health.

Dr. Dunaif also served as Senior Director, Diabetes, Medical, and Scientific Affairs, at Parke-Davis Pharmaceuticals, where she established the phase IIIB and phase IV research program for the first Food and Drug Administration-approved thiazolidinedione diabetes drug, troglitazone, and oversaw the investigator-initiated diabetes research program.

Dr. Dunaif is an internationally recognized expert in polycystic ovary syndrome (PCOS). Her studies have led the way in redefining PCOS as a major metabolic disorder that is a leading risk factor for type 2 diabetes mellitus. Her research explores the mechanisms linking metabolism and reproduction, the genetics of PCOS, and the developmental origins of disease. She is the Director of the Northwestern University Specialized Center of Research on Sex Differences and leads an international effort to map the genes for PCOS.

Dr. Dunaif has more than 100 original scientific publications and has edited four books. She has received numerous awards and honors. She has been elected to the American Society for Clinical Investigation and the Association of American Physicians. She is a Past President of the Endocrine Society and currently serves as Chair of the National Institutes of Health Integrative and Clinical Endocrinology and Reproduction Study Section and as Associate Editor of the journal *Obesity*. Dr. Dunaif received her B.A. at Sarah Lawrence College and her M.D. at Columbia University College of Physicians and Surgeons.

Presentation Summary

Discussion of the Three Diagnostic Criteria. PCOS was considered to be a poorly understood reproductive disorder characterized by hyperandrogenism, anovulatory infertility, and polycystic ovarian morphology (PCO) until the 1980s when it was discovered that the syndrome was also associated with insulin resistance and an increased risk for type 2 diabetes mellitus. It became apparent that the effective study of PCOS required standardized diagnostic criteria, an issue that was addressed in 1990 at the *Eunice Kennedy Shriver* National Institute of Child Health and Human

Development (NICHD) Conference on PCOS. This conference was a meeting of experts who discussed various features of the syndrome. Participants were asked to vote on potential diagnostic features, including androgen excess, menstrual dysfunction, disordered gonadotropin secretion, and insulin resistance. Those features receiving the most votes, hyperandrogenism and chronic anovulation, with the exclusion of secondary causes, became what are known as the NICHD or NIH criteria and are inaccurately referred to as consensus criteria.

The NICHD criteria did not include PCO because 20%–30% of women with regular menses and no androgenic symptoms had PCO on ovarian ultrasound examination, making this finding nonspecific. Many of these women did have elevated testosterone or luteinizing hormone (LH) levels, although some were endocrinologically normal. Further, recent studies indicate that the prevalence of PCO is age related and decreases in frequency with increasing age, further confounding the diagnostic utility of this finding. In addition, a subset of women with the endocrine features of PCOS has normal ovarian morphology. An increased LH to follicle-stimulating hormone ratio was not included in the NICHD diagnostic criteria, since this finding could escape detection on a random blood sample because of the pulsatile nature of LH release. It also was recognized at this time that women with ovulatory cycles and hyperandrogenemia and/or PCO were metabolically normal.

The 2003 Rotterdam PCOS Conference, where recommendations were again based on expert opinion rather than any formal consensus process, added PCO on ultrasound as a diagnostic criterion to the NICHD criteria. No other diagnostic criteria were added. The result of adding PCO as a criterion was the inclusion of two additional phenotypes in the diagnosis of PCOS: (1) women with hyperandrogenism and PCO but normal ovulation, and (2) women with anovulation and PCO but no hyperandrogenism. The 2006 Androgen Excess Society criteria, also based on expert opinion, deemed hyperandrogenism essential for the diagnosis of PCOS, thereby excluding one of the additional Rotterdam phenotypes.

Family studies have supported hyperandrogenemia as a central feature of the syndrome. Elevated androgen levels are present in male as well as female first-degree relatives, including girls, indicating the early onset of abnormalities in steroidogenesis. Recent genetic analyses have found PCOS risk alleles associated with testosterone levels. These analyses also have found that PCOS diagnosed by the NICHD but not the Rotterdam criteria is associated with risk alleles for the syndrome. Insulin resistance also clusters within a PCOS family but varies in severity according to phenotype. Further, evidence for pancreatic β-cell dysfunction is present in first-degree relative girls in association with elevated testosterone levels, so it is not possible to determine whether metabolic defects precede reproductive ones or vice versa. Cross-sectional studies suggest that only women fulfilling the NICHD criteria for PCOS are at high risk for associated metabolic abnormalities.

Bart C.J.M. Fauser, M.D., Ph.D., is Professor of Reproductive Medicine, University of Utrecht, The Netherlands. Since 2004, he also has been Chair of the Division of Woman and & Baby (Departments of Reproductive Medicine and Gynecology, Obstetrics, and Neonatology), University Medical Center, Utrecht. Dr. Fauser is former Professor of Reproductive Endocrinology and Director of the Center of Reproductive Medicine, Erasmus Medical Center, Rotterdam, The Netherlands (1996–2003); Visiting Professor, University of Southampton, United Kingdom (since 2010); Saal van Zwanenberg Professor, Center of Reproductive Medicine, Free University, Brussels, Belgium (2003–2008); Visiting Professor, Stanford School of Medicine, Palo Alto, California (1993–1995); and Fulbright postdoctoral scholar, University of California, San Diego (1987–1988). He is former Editor-in-Chief of *Human Reproduction Update* (2001–2007).

Presentation Summary

The 2003 Rotterdam Consensus Criteria Put in Perspective. Like any other syndrome, PCOS is a complex of symptoms of unknown etiology. Such conditions are heterogeneous by nature, and the identification of useful diagnostic criteria poses a major challenge. A novel test aiming to identify a disease is usually assessed by its capacity to ascertain the absence or presence of this illness. In any syndrome, a gold standard for the condition to be identified is absent, rendering the usual assessment of sensitivity and specificity of clinical tests elusive. Hence, the debate regarding criteria for PCOS diagnosis seems to come down to which end point of the syndrome is considered most relevant and whether to be inclusive or exclusive.

In the current era of evidence-based medicine, features upon initial screening are being identified that influence the extent and prognosis of the disease or modify the most appropriate treatment strategy. In the context of PCOS, such a strategy may help to identify features (i.e., diagnostic criteria) relevant for health issues during different phases of life.

It was widely recognized at the turn of the millennium that PCOS defined by the 1992 National Institutes of Health (NIH) criteria (with hyperandrogenemia and cycle abnormalities both as mandatory features) was too narrow. Consequently, a consensus meeting was organized in Rotterdam in 2003. At the end of the 2-day closed workshop, it was agreed that diagnosis for PCOS should be widened, with the involvement of three rather than two criteria (the occurrence of polycystic ovaries was added). Thus, the Rotterdam criteria represent an extension rather than a replacement of the NIH PCOS criteria.

The Rotterdam consensus meeting was endorsed by the two largest global reproduction societies, and consequently, two identical papers were published simultaneously in the January 2004 issue of both *Fertility and Sterility* and *Human Reproduction*. The Rotterdam PCOS consensus paper became a citation classic in the field of reproductive medicine, with currently close to 2,000 citations for both papers. This probably reflects that the Rotterdam consensus criteria have been widely accepted in most parts of the world, although controversy remains. In 2009, the Androgen Excess and PCOS Society formulated a position statement in between the Rotterdam and the NIH criteria (but closer to the first), still persisting on hyperandrogenemia being the hallmark of PCOS diagnosis. Since this society mainly focuses on future health risks associated with PCOS, it is no surprise that

hyperandrogenemia was considered the most relevant feature. Certainly, hyperandrogenemia is clearly associated with metabolic dysfunction (and presumably long-term health outcomes) regardless of how PCOS is defined.

As stated repeatedly, the assessment of hyperandrogenemia is notoriously inaccurate, both clinically and biochemically. Precise, accurate, and sensitive androgen assays should be developed and introduced into the clinic, and agreement should be reached on how to best identify the unbound (biologically active) fraction of total testosterone. In addition, evidence is accumulating that the ultrasound diagnosis of polycystic ovaries (added in the Rotterdam consensus criteria) can be replaced by serum concentration of anti-Müllerian hormone, although this assay too is not without problems.

Over the last decade, much relevant information has been generated in well-phenotyped women with PCOS regarding the validity of using various diagnostic criteria and implications for the clinical management of complaints such as hirsutism, cycle abnormalities, infertility, and pregnancy complications, for genetic and ethnic studies, and for the long-term health of the woman herself as well as her offspring. Clinical investigators should continue to focus on the adequate phenotyping of women with PCOS, which may allow prioritizing relevant diagnostic features dependent on the phase of life of the woman and on specific complaints.

Ricardo Azziz, M.D., M.P.H., M.B.A., is Professor of Obstetrics, Gynecology, and Medicine at the Georgia Health Sciences University (GHSU) and Professor of Medical Humanities at Augusta State University. He currently also serves as the President of GHSU and Chief Executive Officer of the Georgia Health Sciences Health System. Formerly, Dr. Azziz served as Deputy Director for the Clinical and Translational Sciences Institute and Assistant Dean for Clinical and Translational Sciences at the University of California, Los Angeles, and Director of the Center for Androgen-Related Disorders and of the General Clinical Research Center at Cedars-Sinai Medical Center in Los Angeles. Dr. Azziz has published over 400 original peer-reviewed articles, book chapters, and reviews, and his research focuses on the study of androgen excess (AE) disorders. He has been funded by the National Institutes of Health (NIH), among other entities, for more than 20 years. He serves as Senior Executive Director of the Androgen Excess and PCOS Society, of which he is also a founding member and received, among other awards, the 2000 President's Achievement Award of the Society for Gynecologic Investigation.

Presentation Summary

***The 2006 Androgen Excess and PCOS Society Criteria for PCOS: The Critical Importance of Androgenization*.** PCOS is a metabolic-endocrine-reproductive syndrome conservatively affecting 6%–10% of all reproductive-aged women worldwide. The modern diagnostic criteria of PCOS were first established through a collation of votes by speakers and attendees at an NIH-sponsored meeting in 1990 (NIH 1990 criteria), which noted that PCOS=clinical or biochemical AE+oligo-ovulation. Subsequent definitions of PCOS have expanded on the NIH 1990 criteria, and all acknowledge the need to exclude similar/mimicking disorders. A meeting of experts convened in Rotterdam in 2003 expanded on this definition, by majority vote of the organizing committee, to also include women who either had (a) only polycystic ovarian morphology (PCOM)+oligo-anovulation, or (b) only PCOM+AE. To address the differing criteria, the Androgen Excess and PCOS Society convened an Expert Task Force. This analysis differed from previous analyses in that (a) a complete systematic review of the published peer-reviewed literature was considered; (b) no unpublished or non-peer-reviewed observations were included; (c) a minority report was allowed; (d) a phenotypic approach was used, whereby the various phenotypes possible were considered individually; and (e) an attempt was made to link the definition to a significant but independent morbidity. The Task Force concluded that PCOS=AE (clinical and/or biochemical)+ovarian dysfunction (oligo-anovulation and/or PCOM). Overall, these phenotypes were those most likely to be associated with metabolic dysfunction. The Task Force also recognized important diagnostic challenges including (a) a clinical phenotype not constant over time; (b) significant referral bias in presentation; (c) significant racial variations in some phenotypes; (d) highly variable circulating androgen assay and PCOM diagnostic specifics; (e) detection of hirsutism, the principal clinical marker for AE, is subjective; (f) use of menstrual dysfunction ignores subjects with subclinical ovulatory dysfunction; and (g) evaluation for similar/mimicking disorders is not standardized.

Shalender Bhasin, M.D., is currently a Professor of Medicine at Boston University School of Medicine and Chief of the Section of Endocrinology, Diabetes, and Nutrition at Boston Medical Center. He serves as the Director of the National Institute on Aging-funded Boston Claude D. Pepper Older Americans Independence Center for Function Promoting Therapies. Dr. Bhasin obtained his medical education at the All India Institute of Medical Sciences in New Delhi, India. He subsequently received his residency training at Northwestern University Medical School and fellowship training in endocrinology and nutrition at Harbor-University of California, Los Angeles, Medical Center. Dr. Bhasin was recently recruited to Brigham and Women's Hospital to head the research program in Men's Health: Aging and Metabolism.

Dr. Bhasin is an internationally recognized expert in men's health, age-related sarcopenia and functional decline, and function promoting anabolic therapies. He chaired the Endocrine Society's Expert Panel for the Development of Guidelines for Testosterone Therapy. He also serves as the Chair of the American Board of Internal Medicine, Endocrinology, and Metabolism Subspecialty Examination Writing Committee. He is a translational researcher, with nearly 200 peer-reviewed manuscripts, two books, and 100 reviews and book chapters. He has been the recipient of numerous teaching and research awards, and supported continuously by several National Institutes of Health-funded grants.

Presentation Summary

The Impact of Assay Quality and Reference Range on Clinical Decision-Making in Patients With Androgen Disorders. The diagnosis of androgen disorders—androgen deficiency syndromes in men and androgen excess syndromes in women—is predicated upon the accurate determination of circulating testosterone concentrations and ascertainment of whether the testosterone level is low, normal, or high. Rigorously established reference ranges constitute the essential basis for identifying whether the circulating levels of an analyte, such as testosterone, are normal or low. Reference ranges for testosterone have been derived mostly from small convenience samples, or from hospital or clinic-based patients; these approaches are limited by their inherent selection bias, as patients seeking medical care are more likely to have a disease than individuals in the general population.

We generated reference limits for total testosterone (TT) and free testosterone (FT) concentrations in a community-based sample of healthy young men, age 19–40, in Framingham Heart Study (FHS) Generation 3; FT was calculated using the law of mass action equation. Values <2.5th percentile of the reference sample were deemed low. We determined the association of low TT and FT with health outcomes in three validation samples: FHS generations 2 and 3, European Male Aging Study (EMAS), and Osteoporotic Fractures in Men Study. We determined whether men in these three cohorts, deemed to have low TT and FT levels by the proposed reference limits, had a higher prevalence of physical dysfunction, sexual symptoms, and diabetes mellitus, the three categories of conditions that have been associated most consistently with low testosterone levels.

In the reference sample of 456 men, mean (standard deviation), median (quartile), and 2.5th percentile values were 723.8 (221.1), 698.7 (296.5), and 348.3 ng/dL for TT and 141.8 (45.0), 134.0 (60.0), and 70.0 pg/mL for FT, respectively. In validation samples, men with low TT and FT were

more likely to have slow walking speed, difficulty climbing stairs or frailty, and diabetes than those with normal levels. In EMAS, men with low TT and FT were more likely to report sexual symptoms than men with normal levels. Men with low TT and FT were more likely to have at least one of the following: sexual symptoms (EMAS only), physical dysfunction, or diabetes.

In conclusion, population-based reference ranges provide a rational basis for categorizing testosterone levels as low or normal. Men with low TT or FT levels by these criteria had higher prevalence of physical dysfunction, sexual dysfunction, and diabetes. These reference limits should be validated prospectively in relation to incident outcomes and in prospective randomized trials.

Sharon E. Oberfield, M.D., is Professor of Pediatrics at Columbia University Medical Center, Director of the Division of Pediatric Endocrinology, Diabetes, and Metabolism, and Director of its Fellowship Training Program. She is board certified in pediatrics and pediatric endocrinology. Dr. Oberfield was a member of the Subboard of Pediatric Endocrinology of the American Board of Pediatrics, served as a Director of the Lawson Wilkins Pediatric Endocrine Society (LWPES) and Chair of the LWPES Drug and Therapeutics Committee, and was Deputy Editor-in-Chief of the *Journal of Clinical Endocrinology and Metabolism.* She has been a member of the Endocrine Society's Annual Planning, Clinical Guidelines, and Core Publication Committees. Dr. Oberfield has chaired international symposia on adrenal disorders and is a co-author on the International Consensus Statement on Congenital Adrenal Hyperplasia and of the Endocrine Society's sponsored committee that updated the guidelines (2010). She has served on a National Institutes of Health Special Emphasis Panel for diabetic research for pediatric endocrinologists, was a member of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Pediatric Subcommittee, and just completed her term as a member of the National Institute of Diabetes and Digestive and Kidney Diseases B Study Section. She is the site principal investigator of the longitudinal NICHD Bone Mineral Density in Childhood Study. She is a member of Columbia University's Advisory Committee of the General Clinical Research Center and is Co-Chair of the Pediatric Clinical Research Governance Committee at Columbia. She has authored or co-authored 177 articles, chapters, and reviews and letters related to dysregulation of the hypothalamic-pituitary-adrenal axis and disorders of steroidogenesis. Her clinical research is focused on assessing the risk of insulin resistance in children with adrenarche and adolescents/young adults with polycystic ovary syndrome (PCOS), and the assessment of metabolic markers and measures of body composition, including muscle and liver fat, in young women with PCOS.

Presentation Summary

Age at Diagnosis. Although the diagnostic criteria for PCOS have become less stringent over the years, determination of the minimum diagnostic features in adolescents is still an area of controversy. Of particular concern is that many of the features considered to be diagnostic for PCOS may evolve over time and change during the first few years after menarche. Nonetheless, attempts to define young women who may be at risk for development of PCOS is pertinent since associated morbidity such as obesity, insulin resistance, and dyslipidemia may benefit from early intervention. The relative utility of diagnostic tools such as persistence of anovulatory cycles, hyperandrogenemia, hyperandrogenism (hirsutism, acne, or alopecia), or ovarian findings on ultrasound is not established in adolescents. Some suggest that even using the strictest criteria, the diagnosis of PCOS may not be valid in adolescents younger than age 18. In addition, evidence does not necessarily support that lack of treatment of PCOS in younger adolescents will result in untoward outcomes, since features consistent with PCOS often resolve with time. The presented data will help determine if it is possible to establish firm criteria that may be used to reliably diagnose PCOS in adolescents.

PonJola Coney, M.D., is Senior Associate Dean for Faculty Affairs and Professor of Obstetrics and Gynecology at Virginia Commonwealth University (VCU) School of Medicine. She is an obstetrician-gynecologist and experienced clinical researcher with strong skills and knowledge in all aspects of general obstetrics and gynecology and reproductive endocrinology. Her research is focused on identifying the determinants and etiologies in reproductive disorders that contribute to health disparities among minority women, specifically polycystic ovary syndrome (PCOS), fibroids, and infant mortality. Presently, she is a co-investigator on the Center of Excellence Award in the Center on Health Disparities at VCU that focuses on determinants of preterm birth, now in its second cycle of funding. This is collaborative work that likely will be of particular relevance to understanding the disparity in these areas between white and black women. In addition to her research, clinically, she has yielded more than 1,000 births through assisted reproductive techniques, while personally directing clinical and laboratory activities, and training residents and fellows in reproductive endocrinology and infertility. She maintains a private practice in gynecology and staff obstetrical clinics for residency training in her teaching role for the VCU Department of Obstetrics and Gynecology. She also works with community agencies, local officials, and particularly the Richmond Health Department as Director of VCU's Center on Health Disparities in a number of collaborative activities to engage the community in prevention and wellness initiatives.

Prior to VCU, Dr. Coney was Professor of Obstetrics and Gynecology at Meharry Medical College, where she also was Senior Vice President for Health Affairs and Dean, and has taught in other universities. Currently, she is a member of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Council; editorial board of *Sexuality, Reproduction and Menopause*; and Chair of the Steering Committee, VCU Center on Health Disparities. She was a member of the Advisory Committee of the National Institutes of Health Office of Research on Women's Health and Board of Directors of the Society for Research in Women's Health. She received the Association of Professors and Gynecology Excellence in Teaching Award in 2002. She has published numerous articles.

Dr. Coney received a B.S. at Xavier University in New Orleans, Louisiana, and her M.D. at the University of Mississippi Medical Center in Jackson, Mississippi. She completed an internship and residency at the University of North Carolina in Chapel Hill and a fellowship in endocrinology and infertility at Pennsylvania Hospital in Philadelphia.

Presentation Summary

Epidemiology of PCOS. PCOS symptoms usually begin at menarche and manifest after puberty. The syndrome may not always be diagnosed, or is misdiagnosed, because it can present with a variety of phenotypes and abnormalities that can be present in other endocrine disorders. Metabolic abnormalities in PCOS can be more or less pronounced, along with increased risk factors in lifestyle diseases in different ethnic populations. Such challenges further contribute to the impact of race and ethnicity on the criteria for diagnosis. The objective of this presentation is to summarize the existing epidemiologic data on the effect of race and ethnicity on the presentation, diagnosis, and prevalence of PCOS.

DEVELOPMENTAL OR GENETIC ORIGINS OF PCOS

Daniel Dumesic, M.D., is Professor and Division Chief of Reproductive Endocrinology and Infertility (REI) in the Department of Obstetrics and Gynecology at the University of California, Los Angeles. Dr. Dumesic completed medical school at the University of Wisconsin, and his obstetrics/gynecology residency and REI Fellowship at the University of California, San Francisco. He has served as Professor, Fellowship Director, and Division Head of REI, Director of *In Vitro* Fertilization, and Chairman of the Department of Obstetrics and Gynecology at the Mayo Clinic. He also has served as Affiliated Scientist at the National Primate Research Center, University of Wisconsin; scientific collaborator in interdisciplinary research; and leader in internationally recognized organizations. Dr. Dumesic has a longstanding interest in the adverse effects of polycystic ovary syndrome (PCOS) on reproduction and has examined how androgen excess and obesity impair ovarian function and oocyte quality. He has been principal investigator of several multidisciplinary grants and has published extensively in the PCOS field. Dr. Dumesic has received innumerable awards, including the Mayo Award for Excellence in Leadership, and he is a three-time recipient of the Star Award for More Than 10 Years of Contributions to Research for the American Society for Reproductive Medicine.

Presentation Summary

Intrauterine Environment. The maternal-fetal environment plays an important role in the developmental programming of adult disease. Fetal androgen excess from congenital adrenal hyperplasia or virilizing tumors precedes development of PCOS-like symptoms after birth; while fetal metabolic, hormonal, and ovarian dysfunction also accompanies gestational diabetes, which is common in PCOS mothers. Clinical studies measuring infant blood at term have yet to confirm that androgen excess during human fetal development promotes PCOS development after birth. None of these studies, however, has assessed the presence or effect of androgen excess earlier in gestation, during the second trimester of human development, when circulating androgen levels in the female fetus can rise into the male range. At this gestational age, amniotic testosterone levels are elevated in female fetuses of PCOS women and therefore could alter the trajectory of fetal growth and development. Understanding how perturbations of the maternal-fetal environment influence the developmental origins of PCOS requires advances in technology that permit safe and accurate measurement of human fetal blood concentrations, or identification of a reliable postnatal biomarker of early-to-mid-gestational androgen exposure.

John C. Marshall, M.B.Ch.B., M.D., was educated in the United Kingdom, obtaining a B.Sc. (honors), M.B.Ch.B. (equivalent to U.S. M.D.) and M.D. (equivalent to U.S. Ph.D.) from the University of Manchester. Subsequent clinical training was in Manchester and London. Fellowship training in endocrinology at Hammersmith was supported by Medical Research Council clinical research awards, before completing a year at the University of California, Los Angeles (Harbor General) on a Medical Research Council Visiting Fellowship. Joining the faculty of the University of Birmingham, he was awarded a Welcome Senior Research Fellowship as Senior Lecturer and Honorary Consultant Physician at Queen Elizabeth Hospital. In 1976, he moved to the University of Michigan, rising to Professor, Chief of Endocrinology, and Associate Chairman, before moving to the University of Virginia as Chair of Medicine in 1991. Since 1996, he has been Director of the Center for Research in Reproduction. His research addresses regulation of gonadotropin-releasing hormone (GnRH) secretion and gonadotropin synthesis with clinical studies focused on hypothalamic function in polycystic ovarian syndrome (PCOS).

Presentation Summary

Role of Postnatal Androgen Exposure. Abnormalities of luteinizing hormone (LH), and by inference GnRH secretion, are integral to the disorder PCOS and manifest during early pubertal maturation in girls. Rapid-frequency GnRH pulse secretion is present in adolescents with PCOS, and the rapid GnRH pulses favor increased synthesis of LH. Pulse frequency in PCOS is persistently one pulse per hour and is resistant to progesterone suppression of GnRH secretion, corrected by pretreatment with an androgen receptor blocker. Thus, abnormal regulation of GnRH pulse secretion is a consequence of elevated androgens in early puberty, and the increase in obesity over the past 40 years is associated with a marked increase in testosterone in 65% of obese pre- and pubertal girls. The source of androgen excess in early puberty is mainly the adrenal with enhanced responsiveness of adrenal androgens to adrenocorticotrophin hormone. During puberty, the ovary becomes the main source of androgens as LH rises.

Early puberty in girls is characterized by low-amplitude, slow-frequency GnRH secretion when awake, with increased pulsatility during sleep. Progesterone rises 2.5-fold overnight, and we propose that this plays a role in suppressing GnRH secretion during the next day. Exogenous progesterone suppresses daytime GnRH pulsatility but does not impair sleep-associated GnRH secretion. We believe excess androgen impairs progesterone suppression of GnRH pulses during the day, so that by midpuberty 24-hour GnRH secretion is present in hyperandrogenemic girls. Fifty percent of hyperandrogenemic girls are resistant to progesterone suppression of GnRH secretion. Studies in mid-to-late pubertal girls suggest a gradual loss of progesterone sensitivity over 12 months. Animal studies confirm the effects of testosterone in impairing regulation of GnRH secretion. After 3 years' exposure to a threefold elevation of testosterone, GnRH frequency was increased almost threefold in pubertal rhesus monkeys. Thus, we propose that the persistent rapid GnRH (LH) secretion in PCOS reflects hyperandrogenemic impairing normal steroid regulation of the GnRH pulse generator.

Teresa Sir-Petermann, M.D., is Professor and Director of the Laboratory of Endocrinology and Metabolism, Department of Medicine, School of Medicine, West Division, at the University of Chile, Santiago, Chile. During the last 30 years, she has developed a line of research regarding the study of the physiopathologic and etiopathogenic mechanisms involved in polycystic ovary syndrome (PCOS). Collaboration with other investigators, several financial support grants for research from national and international agencies, and the development and assembly of different research techniques have allowed her to accomplish these objectives. Her current line of investigation is directed to establishing early hormonal abnormalities in children born to women with PCOS, using the pregnancy/postpartum period as a study model.

Presentation Summary

Early Hormonal Abnormalities in Children Born to Women With PCOS. PCOS is a common endocrine-metabolic condition with a genetic and epigenetic background. We evaluated daughters of PCOS women to determine early reproductive and metabolic markers.

Reproductive markers. The most relevant reproductive feature is an increase in anti-Müllerian hormone (AMH) concentrations since early infancy (2–3 months), throughout childhood (4–7 years), puberty (tanner II to V), and the postmenarcheal period (1 to 3 years postmenarche). Although mean AMH levels are increased in these girls compared with the control group, only 35% of them have high AMH concentrations (over 2 standard deviations of the control mean). This phenomenon persists during puberty and the postmenarcheal period. Interestingly, during these latter stages, only 40% of the PCOS daughters (PCOSd) who fulfill the criteria for PCOS have increased AMH concentrations. This suggests that AMH is a marker of an altered follicular development but not necessarily a marker of PCOS.

Regarding sex steroids, during childhood, there are no significant differences in testosterone, androstenedione, DHEAS, and estradiol levels between PCOS and control daughters. In tanner stage I, basal and ACTH-stimulated DHEAS are increased in PCOSd. From tanner stage IV on, testosterone and 17-OH progesterone levels are increased while sex hormone-binding globulin levels are decreased in PCOSd. In postmenarcheal PCOSd (n=55), testosterone levels are significantly higher compared with control girls (n=35). In pubertal and in postmenarcheal PCOSd, the Ferriman score and free androgen index are higher compared with control girls. Concerning gonadotropins, basal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are always comparable from childhood throughout puberty in both groups. Nevertheless, poststimulated (leuprolide acetate) LH levels increase significantly in PCOSd from tanner stage IV on. In postmenarcheal PCOSd, FSH levels are significantly lower compared with control girls. Ovarian volume, assessed by ultrasound, is increased (twofold) from tanner stage I on, in daughters of PCOS women compared with control daughters. In postmenarcheal PCOSd, the prevalence of PCO morphology is higher in PCSOd (48%) compared with control girls (26%).

Metabolic markers. The most relevant metabolic features are a decline in adiponectin levels during childhood and an increase in poststimulated insulin levels during childhood and throughout puberty. Interestingly, PCOSd show metabolic derangements during childhood (higher insulin levels and lower adiponectin levels), a lower age at pubarche, and an advancement between bone age and chronological age during puberty. In summary, these data address the timing and sequence of the onset of metabolic and reproductive perturbations in the female offspring of PCOS patients.

Marcelle I. Cedars, M.D., is Director of the University of California, San Francisco (UCSF), Center for Reproductive Health and a clinical specialist in the fields of *in vitro* fertilization, perimenopause, and polycystic ovary syndrome (PCOS). As Director of the Division of Reproductive Endocrinology, she coordinates the relationship between science and research being done at UCSF and personalized care for medical center patients. Dr. Cedars received her medical training at the University of Texas Southwestern School of Medicine, completed her residency in obstetrics and gynecology at Parkland Memorial Hospital in Dallas, and did her fellowship in reproductive endocrinology at the University of California, Los Angeles. Her clinical and research interests include PCOS, ovarian aging, and assisted reproduction. She is a National Institutes of Health-funded researcher, has chaired the Food and Drug Administration panel on Obstetrical and Gynecological Devices, and currently serves on the editorial boards of *Fertility and Sterility* and the *Journal of Clinical Endocrinology & Metabolism*.

Presentation Summary

Ovarian Morphology. The topic of ovarian morphology in PCOS is controversial. Not only are the diagnostic criteria still frequently debated (despite the Consensus Conference of Rotterdam in 2003), but it is also debated whether the morphology is a result of, or intrinsic to, the underlying pathophysiology of PCOS. This presentation will discuss available evidence regarding the morphology of the ovary in women with PCOS versus the general population, and if there are specific aspects of this morphology that may be more predictive of the disorder itself and/or the metabolic consequences of the disorder. In addition, we will discuss the physiology and potential pathophysiology associated with variant morphological patterns and introduce concepts about ovarian aging and PCOS.

R. Jeffrey Chang, M.D., is Professor and Director of Reproductive Endocrinology in the Department of Reproductive Medicine at the University of California, San Diego, School of Medicine. His research interests are focused on human ovarian physiology and ovulatory disorders of women. In particular, he has devoted most of his efforts toward understanding mechanisms that may be responsible for hypothalamic-pituitary-ovarian dysfunction in women with polycystic ovary syndrome (PCOS). His current research is directed at abnormalities of ovarian function with respect to excess androgen production.

Presentation Summary

Role of Obesity Prior to Puberty. Obesity is associated with PCOS in about 50% of cases. The consequences of obesity include both reproductive and metabolic abnormalities that commonly worsen symptomatology and increase long-term health risks in this disorder. Obesity is associated with increased adrenal activity in adults and children. In obese prepubertal girls, circulating adrenal androgens are elevated compared with nonobese girls. Clinical examples in adults indicate that excess androgen exposure may induce a PCOS phenotype. In early adolescence, it has been proposed that exaggerated adrenarche leads to initial hyperandrogenemia with subsequent development of PCOS. In addition, girls with premature adrenarche have an increased likelihood of PCOS. Obesity may increase this risk. The mechanism by which obesity may increase risk for PCOS is not completely understood, although acquired insulin resistance and compensatory hyperinsulinemia are likely factors. Whether greater adiposity in prepubertal children increases the prevalence of PCOS has not been examined.

David H. Abbott, Ph.D., is a Professor in the Department of Obstetrics and Gynecology at the University of Wisconsin-Madison, a position he has held since 1998. He is also a Professor in the Wisconsin National Primate Research Center where he has been a faculty member since 1991. He received both his B.Sc. and Ph.D. from the University of Edinburgh in Scotland. He has over 30 years of experience employing animal models of female reproductive endocrinology to determine pathophysiological mechanisms underlying a variety of reproductive health disorders commonly found in women. More recently, he has led the development of a comprehensive nonhuman primate model for polycystic ovary syndrome (PCOS) that was the vanguard for animal and human studies aimed at determining developmental origins of the common endocrinopathy in women. He and his colleagues translated insight gained from the nonhuman primate model to discern pathophysiological mechanisms causing discrete aspects of reproductive and metabolic dysfunction in women with PCOS, including abnormalities at the molecular level. His most recent work identifies metabolic dysfunction as possibly the initial abnormality in early developmental origins of PCOS. Dr. Abbott is a member of the Endocrine Society, Society for Neuroscience, and Society for Behavioral Neuroendocrinology as well as an editorial board member of *Psychoneuroendocrinology, Neuroendocrinology,* and *International Journal of Obesity.* He is President-Elect of the Androgen Excess and PCOS Society. In addition, he has published extensively in the field.

Presentation Summary

Epigenetic Nonhuman Primate Model Demonstrates Metabolic Antecedents to PCOS-Like Traits. Fetal testosterone (T) excess induces PCOS-like reproductive and metabolic traits in female mammals from rodents to primates. Reproductive traits are at least partly due to diminished estrogen action. Fetal female monkey exposure to T provides the most comprehensive PCOS-like epigenetic mimic. Recent studies in female rhesus monkeys demonstrate that maternal glucose intolerance is induced in tandem with T excess. Pancreatic accommodation of dual androgenic and glycemic gestational excess may contribute to adult metabolic pathophysiology in these prenatally T-exposed female monkeys. To gain insight into potential molecular mechanisms involved in fetal T-exposed female monkey pathophysiology, DNA methylation was examined in visceral fat from prenatally androgenized infant and adult females. Pathway and network analyses of differentially methylated genes implicate multiple signaling pathways. Transforming growth factor-beta (TGF-beta) signaling is implicated in the top two pathways identified by gene methylation analyses in both T-exposed infant and adult monkeys. As a potential gene candidate for PCOS, intron 55 of fibrillin 3 is involved in regulating TGF-beta signaling in women; altered function of this signaling pathway may accompany PCOS pathophysiology in fetal T-exposed female monkeys and in women.

Sue Moenter, Ph.D., M.S., is Professor of Molecular and Integrative Physiology, Internal Medicine, and Obstetrics and Gynecology, University of Michigan, and Co-Director of the Reproductive Sciences Program, Faculty Program in Biomedical Sciences, Cellular and Molecular Biology, and Neuroscience Graduate Programs. She received her B.S. in agricultural sciences from the University of Illinois in 1985, M.S. in animal sciences from the University of Illinois in 1986, and Ph.D. in physiology from the University of Michigan in 1991. She did a postdoctoral fellowship at the University of California, San Francisco and joined the faculty in internal medicine at the University of Virginia in 1994. In 2010, she moved to the University of Michigan. Dr. Moenter has served on the Trainee Affairs and Annual Meeting Steering Committee of the Endocrine Society, the Publications and Local Arrangements Committee of the Society for the Study of Reproduction, and the Nominating and Awards Committees of Women In Endocrinology. Her research is in neuroendocrine control of reproduction. Specifically, she studies mechanisms of gonadotropin-releasing hormone (GnRH) pulse generation, mechanisms of estradiol negative and positive feedback, and neuroendocrine changes underlying animal models of human infertility, including polycystic ovary syndrome (PCOS), obesity, and stress.

Presentation Summary

Androgen Effects on the Central Circuits Affecting Fertility. Hyperandrogenemic fertility disorders, such as PCOS, alter GnRH neuron function and other aspects of physiology including metabolism. We study the neuroendocrine and metabolic consequences of prenatal androgenization (PNA) in mice. In PNA mice, vaginal opening is advanced, estrous cycle initiation delayed or absent, and luteinizing hormone (LH) levels, GnRH neuron activity, and excitatory inputs to GnRH neurons are elevated. PNA mice are glucose intolerant, but not insulin resistant, and have normal body composition. Despite the lack of insulin resistance, the insulin sensitizer/AMPK activator metformin restores estrous cyclicity, LH levels, and GnRH neuron activity in PNA mice control values. These data suggest that PNA produces several phenotypes similar to those in women with hyperandrogenemic disorders, and that both androgens and fuel-sensitive factors impact reproductive neuroendocrine function. Preliminary studies of second-generation PNA mice indicate phenotypes may be different from first generation and depend on whether the mother or father was exposed to androgen *in utero*. No animal model perfectly recapitulates all aspects of human disease, but understanding the neurobiological mechanisms in preclinical models narrows the targets for novel therapeutic approaches.

Vasantha Padmanabhan, Ph.D., is Professor of Pediatrics, Obstetrics and Gynecology, Molecular and Integrative Physiology, and Environmental Health Sciences, and Director of Pediatric Endocrine Research at the University of Michigan. She received her Ph.D. in cytogenetics from the Indian Institute of Science, Bangalore, India; completed her postdoctoral fellowship at Michigan State University; and joined the faculty in the Department of Pediatrics at the University of Michigan in 1984. Dr. Padmanabhan has served on the Animal Care, Program, Publication, and Local Arrangements Committees of the Society for the Study of Reproduction. She was a member of the Expert Panel for the 2010 Joint Food and Agriculture Organization/World Health Organization Expert Meeting to review toxicological and health aspects of bisphenol A and a member of the Reproductive Endocrinology and Integrative and Clinical Endocrinology and Reproduction Study Sections. Her research centers on the impact of native and environmental steroids as it relates to the developmental origin of reproductive and metabolic diseases, with emphasis on hyperandrogenic disorders such as polycystic ovary syndrome (PCOS) and metabolic syndrome. She was instrumental in developing the sheep model of PCOS phenotype and is principal investigator of a program grant from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development directed toward identifying prevention and treatment strategies for overcoming reproductive and metabolic dysfunctions in this model.

Presentation Summary

Developmental Programming of PCOS Phenotype: Impact of Maternal/Fetal Environment. PCOS is the most common reproductive disorder affecting several million women worldwide. Using sheep as a model, the studies have found that exposure of female fetuses to excess testosterone at levels seen in male fetuses leads to a PCOS phenotype, which includes oligo-/anovulation, functional hyperandrogenism, luteinizing hormone (LH) excess, neuroendocrine feedback defects, mulitfollicular ovarian morphology, increased ovarian follicular recruitment and follicular persistence, insulin resistance, and hypertension. Importantly, postnatal metabolic compromise from overfeeding was found to amplify the severity of the reproductive phenotype. Recent studies utilize prenatal interventions with androgen antagonist or insulin sensitizer to delineate the relative roles of maternal environment (compromised androgenic, estrogenic, metabolic) in programming the neuroendocrine, ovarian, and metabolic attributes of PCOS. In parallel studies, maternal exposure of sheep to a xenoestrogen, bisphenol A, was found to also induces LH excess, dampening of LH surges, and compromised insulin sensitivity. These findings provide support for the developmental origin of adult reproductive and metabolic diseases, and highlight the risk faced by the developing offspring exposed inadvertently to excess native or environmental steroid mimics and the role of postnatal metabolic environment in amplifying such defects.

Margrit Urbanek, Ph.D., is an Associate Professor in the Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Feinberg School of Medicine, Northwestern University. She received a B.S. in biochemistry from Pennsylvania State University and her Ph.D. in molecular biology from the University of Pennsylvania. Dr. Urbanek's research focuses on the identification of susceptibility genes for complex diseases. Her approach uses family-based and population-based state-of-the-art genetic techniques in conjunction with molecular techniques to identify and verify genes and pathways contributing to the pathogenesis of genetically complex diseases. Specifically, she is carrying out studies to identify susceptibility genes for polycystic ovary syndrome (PCOS) that map to chr19p3.13. She has previously shown that this region shows linkage and association with PCOS in a large set of families. A second project focuses on identifying both maternal and newborn susceptibility genes for glycemic control during pregnancy and pregnancy outcomes. She uses both pathway-driven and genomic approaches in her research. Most recently, her laboratory has focused on applying a combinatorial "omics" approach that uses correlation between genome-wide DNA sequence variation, variation in methylation patterns, and mRNA expression variation in PCOS target tissues to prioritize susceptibility loci.

Presentation Summary

Genetics. PCOS is a genetically complex phenotype. Family studies have provided strong evidence of familial aggregation and a heritability of 0.8 for PCOS. A multitude of single gene association studies have been carried out, but only a limited number of the findings from these studies have been replicated. The first genome-wide association study for PCOS was published in a Chinese cohort in 2011 and identified three reproducible loci: chr2p16.3, chr2p21, and chr9q33.3. The chr2p16.3 locus encodes the genes for luteinizing hormone/choriogonadotropin receptor (*LHCGR/FSHR*); chr22p21 encodes thyroid-associated protein (*THADA*); and chr9q33.3 encodes the DENN/MADD domain containing 1A (*DENND1A*). All three loci have been replicated in both European and Asian ancestry cohorts.

Given the phenotypic overlap between PCOS and diabetes and obesity, multiple studies have asked whether genetic variation impacting these related phenotypes also impacts PCOS. Specifically, the type 2 diabetes susceptibility locus, *TCF7L2*, and the obesity susceptibility locus, *FTO*, have been investigated by multiple investigators. While the diabetes- and obesity-associated variants appear to have at most a modest impact on PCOS, variation in other regions of the two genes may be more relevant to the etiology of PCOS than the diabetes and obesity loci per se.

Traditional genetic analyses have shed some light on the etiology of PCOS, but as is the case for other genetically complex traits, have not explained the bulk of the heritability of PCOS. Rare variants and epigenetic factors may account for this missing heritability. Studies investigating these classes of variation are currently underway and promise to provide interesting insights into the genetics of PCOS and related phenotypes.

Jose C. Florez, M.D., Ph.D., is an Assistant Physician in Medicine (Endocrine Division) at the Massachusetts General Hospital (MGH), an Associate Professor at Harvard Medical School, and an Associate Member at the Broad Institute, where he is active in the Program in Medical and Population Genetics and the Broad Metabolism Initiative. He and his group have contributed to the performance and analysis of genome-wide association studies (GWAS) in type 2 diabetes and related traits, in the Diabetes Genetics Initiative (formed by the Broad Institute, Lund University, and Novartis), in the Framingham Heart Study, and in other international consortia such as MAGIC, GENIE, and DIAGRAM. Dr. Florez leads the genetic research efforts of the Diabetes Prevention Program, where the effects of genetic variants on the development of diabetes can be examined prospectively, and their impact on specific behavioral and pharmacological preventive interventions can be assessed. He is the principal investigator of the Study To Understand the Genetics of the Acute Response to Metformin and Glipizide in Humans (SUGAR MGH) and also conducts other pharmacogenetic studies at MGH. He is an author of more than 90 original publications and more than 30 reviews/book chapters.

In addition to his research and teaching duties, Dr. Florez is clinically active in the MGH Diabetes Center, the Endocrine Inpatient Consultation Service, and the MGH Down Syndrome Program. He serves on the editorial boards for *Diabetes* and for *Human Genetics*, as well as the advisory board for *Diabetologia*; he is also the Editor-in-Chief for *Current Diabetes Reports*. He is the recipient of the MGH Physician Scientist Development Award, a Doris Duke Charitable Foundation Clinical Scientist Development Award, the MGH Department of Medicine Stephen Krane Award, and the 2010 Presidential Early Career Award for Scientists and Engineers, the highest honor bestowed by the U.S. Government on science and engineering professionals in the early stages of their independent research careers.

Presentation Summary

Genome-Wide Association Studies: Predisposition to Comorbidities. Over the past 5 years, there has been an explosion of GWAS for phenotypes related to type 2 diabetes and metabolism. These GWAS have occurred on the background of genotyping arrays populated by common single nucleotide polymorphisms (SNPs), deployed in various cohorts that have coalesced to form large international consortia. As a result, we have begun to accumulate lists of genetic loci that influence type 2 diabetes, related quantitative glycemic traits, adiposity, serum lipid levels, and blood pressure. GWAS findings have typically illustrated novel pathways, pointed toward fundamental biology, confirmed prior epidemiological observations, drawn attention to the role of β-cell dysfunction in type 2 diabetes, explained a fraction of disease heritability, tempered expectations with regard to their use in clinical prediction, and provided possible targets for pharmacotherapy and pharmacogenetic clinical trials. On the other hand, the causal variants have only been identified for a handful of these loci, and a substantial proportion of the heritability of these phenotypes remains unexplained. The latter is likely due to insufficient sample sizes to detect small effects, a nearly exclusive focus on populations of European descent, an imperfect capture of uncommon genetic variants, an incomplete ascertainment of alternate (non-SNP) forms of genetic variation, and the lack of exploration of additional genetic models. As the community embraces complementary approaches

that include systematic fine-mapping, custom-made replication, denser genotyping arrays, platforms that focus on functional variation, next-generation sequencing techniques, and expansion to non-European populations, the coming years will continue to witness exponential growth in understanding of the genetic architecture of metabolic phenotypes. Whether these findings will prove useful in disease prediction or therapeutic decision-making must be tested in rigorously designed clinical trials.

LONG-TERM HEALTH CONSEQUENCES OF PCOS

Adrian S. Dobs, M.D., M.H.S., is Professor of Medicine and Oncology and Vice Chair for Faculty Development in the Department of Medicine of the Johns Hopkins University School of Medicine, in Baltimore, Maryland, and Director of the Johns Hopkins Clinical Research Network of the Johns Hopkins Institute for Clinical and Translational Research. Dr. Dobs is also Interim Director of the Johns Hopkins Center for the Reduction of Cancer Disparities of the Johns Hopkins Bloomberg School of Public Health. Dr. Dobs received a medical degree from Albany Medical College in New York and completed an internship in internal medicine at Montefiore Hospital, Albert Einstein College of Medicine, in the Bronx, New York. She held a fellowship in endocrinology from Johns Hopkins University School of Medicine and earned a master in health sciences degree in cardiovascular epidemiology at the Johns Hopkins University Bloomberg School of Public Health.

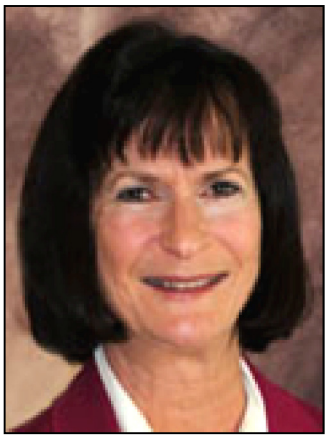
Dr. Dobs is an investigator on several National Institutes of Health-funded studies evaluating the relationship of sex hormones and cardiovascular risk. She lectures in the United States and internationally in these areas, as well as aging and testosterone therapy and testosterone and cardiovascular disease. With book chapters, monographs, and journal articles, as well as television and web contributions, Dr. Dobs has published extensively on topics that include sex hormones and their relationship to metabolic disorders. Journals publishing her research include the *Journal of Clinical Endocrinology and Metabolism, Journal of Acquired Immune Deficiency Syndromes,* and *Journal of Andrology.* She is Co-Chair of the International Registry for Hypogonadal Men. Dr. Dobs is very active in mentoring medical students and postdoctoral fellows and was honored by the Johns Hopkins University School of Medicine with the 2009 David M. Levine Excellence in Mentoring Award.

Presentation Summary

Type 2 Diabetes and Prediabetes in Women With PCOS. Insulin resistance, ranging from impaired glucose tolerance to frank type 2 diabetes mellitus, is common in women with PCOS. It is often observed as part of a full metabolic syndrome with resistance to insulin-mediated glucose uptake into muscle, increased lipolysis, and elevated levels of circulating free fatty acids. The clinical presentation varies, based on the degree of peripheral resistance plus beta cell dysfunction. Regardless, other comorbidities include abdominal obesity, hypertension, dyslipidemia, and an increased risk of cardiovascular disease.

The etiologic mechanism for insulin resistance is unclear and may be due to a postreceptor defect, a phosphorylation defect of the insulin receptor, and/or genetic abnormalities in the receptor. These metabolic abnormalities may result in the abnormal responses of the ovarian follicle to follicle-stimulating hormone, which leads to anovulation and excess androgen secretion.

The diagnosis of insulin resistance and diabetes is based on fasting glucose levels and 2-hour glucose levels after a glucose load. Treatments can include weight loss, lifestyle intervention, as well as pharmacologic intervention with metformin or oral contraceptive pills. Metformin likely works by inhibiting hepatic output of glucose, which results in a lower insulin concentration and reduced androgen production.



Evelyn O. Talbott, Dr.P.H., M.P.H., is a Professor of Epidemiology at the University of Pittsburgh Graduate School of Public Health and an environmental and cardiovascular epidemiologist with more than 25 years of experience in designing and conducting studies in these areas. Until recently, she was principal investigator of a 12-year National Heart, Lung, and Blood Institute-funded study titled, "Cardiovascular Risk in Women With Polycystic Ovary Syndrome." This case control study of 244 women with polycystic ovary syndrome (PCOS) and 244 age-matched controls involved three separate research cycles (1994–1996, 1997–2000, and 2001–2006), during which she investigated cardiovascular risk factors, including measures of subclinical atherosclerosis and inflammatory markers (carotid intima-media thickness, endothelial function, and coronary and aortic calcification). She is currently the principal investigator of the University of Pittsburgh Academic Partner for Excellence in Environmental Public Health Tracking project (2005–2013), funded by the Centers for Disease Control and Prevention, to consider short-term effects of air pollution on inflammatory biomarkers and heart disease. Dr. Talbott is a Fellow of the American Heart Association Council on Epidemiology and Prevention.

Presentation Summary

Cardiovascular Disease. Compared with normal cycling women of similar age, those with PCOS have an adverse lipid profile, as well as an increased prevalence of type 2 diabetes and hypertension. Women with PCOS also appear to have an increase in subclinical atherosclerotic disease as demonstrated by greater carotid intima-media wall thickness and higher levels of coronary calcification. These findings suggest that women with PCOS may be at risk for early-onset cardiovascular disease. A higher incidence of actual cardiovascular events among PCOS women, however, has not yet been demonstrated. Methodological issues may be of importance in this apparent lack of an association between PCOS and coronary heart disease events. Case ascertainment based on anatomic and inpatient discharge records or self-reported anovulation may lead to bias and underestimate the *syndrome* of PCOS. Prospective studies of historical PCOS cohorts—diagnosed by menstrual and endocrine criteria—and age-matched controls are needed to assess more definitively whether women with PCOS actually experience higher rates of cardiovascular events.

David A. Ehrmann, M.D., went to medical school at the University of Michigan where he also completed his internal medicine residency training in 1985. He undertook fellowship training in endocrinology, diabetes, and metabolism at the University of Chicago, where he has been a faculty member since 1998. He currently holds the rank of Professor of Medicine and is Director of the Center for Polycystic Ovary Syndrome (PCOS). Dr. Ehrmann's research and clinical interests focus on the cardiometabolic aspects of PCOS. Specifically, Dr. Ehrmann has investigated the role that defects in insulin secretion and insulin action play in the predisposition to type 2 diabetes among women with PCOS. More recently, Dr. Ehrmann's research has centered on defining causal relationships between obstructive sleep apnea (OSA) and the metabolic disturbances of PCOS. This population of women has a nearly eightfold higher prevalence of OSA compared with control women, even after adjustment for factors such as body weight, age, and sex steroid concentrations. The results of recent investigations indicate that OSA is a major contributor to the pathogenesis of type 2 diabetes in PCOS.

Presentation Summary

Obstructive Sleep Apnea in PCOS: Causes and Consequences. PCOS is one of the most common endocrinopathies in women. It is characterized by androgen excess, obesity, insulin resistance, and significant comorbidities that include early-onset impaired glucose tolerance and type 2 diabetes. We and others have shown that women with PCOS also develop OSA at rates far exceeding those of women without PCOS. In fact, the prevalence of OSA in women with PCOS can equal or exceed that in men, a finding that stands in stark contrast to the well-documented male predominance of OSA in the general population.

Chronic decreases in sleep duration and/or quality have been identified as a risk factor for the development of metabolic derangements identical to those seen in PCOS. Decreased sleep quality due to OSA has been causally linked to insulin resistance, glucose intolerance, hypertension, and most recently even to reduced myocardial perfusion reserve. However, OSA is relatively underappreciated in the pathogenesis of the metabolic derangements in PCOS. We have found that insulin resistance and glucose intolerance in PCOS are strongly predicted by the severity of OSA; thus two subtypes of women with PCOS appear to exist: those with and those without OSA. The former are characterized by metabolic and endocrine alterations that are more frequent and severe. We also found that the plasma-free testosterone levels were virtually identical in PCOS women with and without OSA and that OSA severity did not correlate with the degree of androgen elevation among PCOS women with OSA. This has prompted us to generate new hypotheses concerning the role of sex steroids in the pathogenesis of OSA in PCOS. In particular, a number of studies have shown that progesterone concentrations in women play a role in the pathogenesis of OSA. Progesterone has been reported to directly stimulate respiratory drive via an increased ventilatory response to both hypercapnea and hypoxia, enhance upper airway dilator muscle activity, reduce airway resistance, and augment the relative proportion of slow-wave activity during sleep. The latter, in fact, may be protective against the metabolic consequences of OSA. Women with PCOS have low circulating progesterone concentrations as a result of the oligo/anovulation that defines the disorder and, therefore, would be susceptible to its consequences. Data will be presented that address this issue.

Kurt T. Barnhart, M.D., M.S.C.E., is Assistant Dean for Clinical Research Operations, Associate Director of the Division of Reproductive Endocrinology and Infertility, and the Director of Reproductive Research at the University of Pennsylvania. He is the William Shippen, Jr. Professor in the Department of Obstetrics and Gynecology and Professor of Epidemiology. He received his M.D. at Mount Sinai School of Medicine and his M.S.C.E. (clinical epidemiology and biostatistics) at the University of Pennsylvania. He is board certified in obstetrics and gynecology, as well as reproductive endocrinology and infertility.

Dr. Barnhart's current research interests are focused on clinical and epidemiologic aspects of reproduction, including ectopic pregnancy, miscarriage, infertility, family planning, and prevention of HIV. His research papers have appeared in journals such as *Fertility and Sterility, Human Reproduction*, *Contraception*, *Obstetrics and Gynecology*, *The Journal of the American Medical Association,* and *The New England Journal of Medicine*. He also has served on numerous National Institutes of Health Study Sections and scientific committees of the American Society of Reproductive Medicine and American College of Obstetricians and Gynecologists. Dr. Barnhart is an Associate Editor for *Fertility and Sterility* and *Pharmacoepidemiology and Drug Safety.*

Presentation Summary

Endometrial and Other Cancers. Polycystic ovary syndrome (PCOS) may be associated with an increased risk of reproductive cancer due to its underlying pathophysiology or its association with other common risk factors. It is well accepted that unopposed estrogen, secondary to anovulation, is associated with endometrial cancer. The magnitude of this risk has not been precisely quantitated but is estimated to be increased by two- to threefold. It is unclear if this risk is the same for the development of endometrial cancer in a premenopausal or a postmenopausal woman. There is no agreement on optimum modality or timing to monitor for the development of endometrial cancer.

There is limited information suggesting that women with PCOS have an elevated risk of ovarian cancer (relative risk 2.5). There are limited data to suggest that there is no association with breast cancer, and there are insufficient data to evaluate the risk associated with vulvar, vaginal, or cervical cancer.

Limitations for assessing cancer risk associated with PCOS include lack of precision in the estimates of cancer risk, especially for ovarian cancer, due to a paucity of well-conducted studies; variation in the definition PCOS; lack of validation of self-report data; and inadequate control for confounding factors. A more precise estimate of the association of PCOS and reproductive cancer would be obtained with prospective longitudinal studies controlling for confounding factors, including fertility and fertility treatment.

Silva Arslanian, M.D., a pediatric endocrinologist, is the Richard L. Day Endowed Professor of Pediatrics, University of Pittsburgh School of Medicine. She is the Director of the National Institutes of Health (NIH)-funded Pediatric Clinical and Translational Research Center at the Children's Hospital of Pittsburgh, and Director of the Weight Management and Wellness Center, in addition to having been the principal investigator of the NIH-funded Diabetes Fellowship Training (T32) and Pediatric Diabetes Scholars Program (K12). Dr. Arslanian obtained her medical degree from the American University of Beirut and completed her pediatric residency training at the same institution. She completed her fellowship in pediatric endocrinology at the Children's Hospital of Pittsburgh. Her research focus is the investigation of childhood insulin resistance, which encompasses conditions such as obesity, polycystic ovary syndrome (PCOS), metabolic syndrome, and childhood type 2 diabetes and prediabetes. She has made major contributions to understanding insulin resistance during childhood growth, particularly during the critical period of puberty, race-related differences, and derangements consequent to pathophysiological alterations. Dr. Arslanian was a member of the Maternal and Child Health Study Section, NIH; was on the Board of Directors of the Endocrine Fellows Foundation; and currently is on the Review Board of the American Diabetes Association, among others. She is a consultant to the NIH Office of Human Research Protection, Centers for Disease Control and Prevention, Food and Drug Administration, Endocrine Society, American Diabetes Association, and several international organizations. She serves as an editor, referee, and reviewer for many journals. Dr. Arslanian has been an invited lecturer, keynote speaker, and chairperson at various international congresses and symposia in addition to being the recipient of several prestigious awards.

Presentation Summary

Nonalcoholic Fatty Liver Disease. PCOS is increasingly recognized in adolescent girls seeking treatment for signs and symptoms of hyperandrogenism. PCOS in adolescents is characterized by severe peripheral tissue insulin resistance, hepatic insulin resistance, heightened risk for type 2 diabetes and prediabetes, and a dysmetabolic lipid profile. The linchpin among these is proposed to be insulin resistance. Nonalcoholic fatty liver disease (NAFLD), the pathogenesis of which is also believed to be closely linked to insulin resistance, is escalating in the overall population parallel with the increasing rates of obesity and insulin resistance. NAFLD is present when fatty infiltration affects more than 5% of hepatocytes without evidence of other causes of liver disease. NAFLD is a slowly progressive condition and represents a spectrum of varying severity of liver disease, ranging from simple steatosis to coexistent inflammation with hepatocyte ballooning and necrosis, variable grades of fibrosis, and ultimately cirrhosis. Nonalcoholic steatohepatitis represents the more advanced stages of this disease, which carries a higher risk of cardiovascular disease. Current diagnostic methods for NAFLD include liver enzyme determination, ultrasound imaging, computed tomography scan, magnetic resonance imaging, magnetic resonance spectroscopy, and liver biopsy, all having their advantages and disadvantages, with the latter being the "gold standard." Among adult women with PCOS, the reported prevalence of NAFLD ranges from 30% to 73%. Reports regarding NAFLD in lean women with PCOS are inconsistent, with some showing increased rates and others showing rates comparable to non-PCOS controls. More than 50% of women with proven NAFLD had diagnostic criteria consistent with PCOS. Limited data suggest a beneficial effect of omega-3 fatty

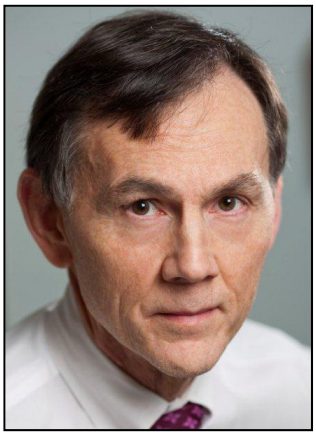
acid supplementation in reducing liver fat in women with PCOS, but controversy continues regarding the benefits of metformin for NAFLD in PCOS women. Data regarding NAFLD in adolescents with PCOS despite their severe insulin resistance are sparse. In conclusion, increased awareness of NAFLD in PCOS women, especially in the presence of risk factors, should prompt early screening and careful follow-up.

Natalie Rasgon, M.D., Ph.D., is Professor in the Department of Psychiatry and Behavioral Sciences and Obstetrics and Gynecology in the Stanford School of Medicine. Before joining Stanford University in 2002, Dr. Rasgon obtained an M.D. from the U.S.S.R. in 1980, a Ph.D. in reproductive endocrinology in 1988 from the Central Institute of Postgraduate Medical Education, and a Ph.D. in pathological physiology from the Central Research Institute of General Pathology and Pathological Physiology Academy of Medical Sciences, Moscow, U.S.S.R. In addition, Dr. Rasgon was a National Research Service Award Research Fellow at the Neuropsychiatric Institute, University of California, Los Angeles (UCLA), School of Medicine from 1995–1996; an Assistant Clinical Professor, Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, Neuropsychiatric Institute and Hospital; and Director of the UCLA Menopause-Related Mood Disorders Program, UCLA Neuropsychiatric Institute and Hospital.

Dr. Rasgon has been involved in neuroendocrine and brain imaging studies for nearly two decades. In addition to her duties as a Professor of Psychiatry and Obstetrics and Gynecology, Dr. Rasgon is also Director of the Stanford Center for Neuroscience in Women's Health. The center's main areas of focus are neuroendocrinology of mood disorders and the role of insulin glucose homeostasis in pathological brain aging.

Presentation Summary

Mental Health. Research of affective disorders has established multiple lines of evidence supporting the dysregulation of the hypothalamo-pituitary axis and various end organ systems as the neuroendocrinological basis for bipolar disorder and major depression. However, neurobiological correlates of emotional and cognitive dysregulation in persons with certain primary endocrine disorders remain to be elucidated. This is particularly important for women with polycystic ovary syndrome (PCOS), the most prevalent reproductive endocrine disorder. Research into comorbid psychopathology among women with PCOS has revealed high rates of depression and negative effects in this population. Studies have found an association between depression and PCOS markers such as obesity, insulin resistance, and hyperandrogenism, thus giving weight to the concept of a common metabolic link between PCOS and affective illnesses. Given that the mean age of onset of PCOS and mood disorders is usually during the reproductive years and the medications used in the treatment of these disorders are often taken for a lifetime, understanding of their pathophysiological overlap stands to critically inform therapeutics and augment current thinking about treatment strategies not only in achieving stable resolution of symptomatology, but in preventing major somatic and neurodegenerative sequelae of both PCOS and mood disorders.



Rogerio A. Lobo, M.D., received his medical degree from Georgetown University Medical School in Washington, DC, and completed his residency in obstetrics and gynecology at the Chicago Lying-in Hospital at the University of Chicago. He completed a clinical research fellowship in the Division of Reproductive Endocrinology and Infertility at the University of Southern California Medical Center in Los Angeles. He has since held numerous teaching positions, including Assistant and Associate Professor in the Department of Obstetrics and Gynecology at the University of Southern California in Los Angeles, where he was later promoted to full Professor. In 1995, he came to the Columbia University College of Physicians and Surgeons in New York City, where he was named the Willard C. Rappleye Professor of Obstetrics and Gynecology, and Chairman of the Department. He also was appointed Director of the Center for Reproductive Sciences at the College of Physicians and Surgeons and Director of the Sloane Hospital for Women, Columbia University Medical Center.

In addition to a successful career in academics, Dr. Lobo has excelled in other aspects of professional medicine, serving as the Director of the Reproductive Endocrinology and Infertility Training Program at the University of Southern California for 11 years. He has provided outside consulting services for many large pharmaceutical laboratories. He has functioned as editor, editorial board member, and/or consultant for over 30 peer-reviewed medical journals in his field, and has authored over 450 articles and 20 books. Dr. Lobo helped found the *Journal of the Society for Gynecologic Investigation* and served as Editor-in-Chief from its inception until July 2006. He was President of the Society for the years 1997–1998. He has contributed chapters to and edited several important medical textbooks. His book, *Treatment of the Post-Menopausal Women,* is in its third edition. Another text, *Menopause*, was published in early 2000. He is also an editor for the seventh edition of *Comprehensive Gynecology*.

Dr. Lobo has done extensive research in various areas of reproductive endocrinology and infertility. His primary research interests are in reproductive endocrinology, specifically in hyperandrogenic disorders and polycystic ovary syndrome (PCOS). He also carried out extensive research in gamete biology, induction of ovulation, *in vitro* fertilization, and estrogen metabolism and the treatment of postmenopausal women. He has excelled in his areas of clinical interest and practice, which include reproductive endocrinology, infertility, and menopause. From 2010 to 2011, he was President of the American Society for Reproductive Medicine.

Presentation Summary

Menopause in Women With PCOS. There are conflicting data regarding the age of menopause in women with PCOS. However, most data suggest that menopause may occur 1–2 years later than the average age of menopause. This seems logical as it has been established that women with PCOS have a larger follicular cohort and higher anti-Müllerian hormone (AMH) levels compared with matched controls, and these decline with age at a slower rate. Androgen levels decline with age, and some studies have suggested that androgen levels reach the normal range in the fourth decade in most women with PCOS. Ovarian size also decreases, as do follicle counts. Levels of AMH and inhibin B decrease, and levels of luteinizing hormone decline, while serum follicle-stimulating hormone tends to rise during the perimenopause. As women enter the perimenopause, prospective longitudinal data suggest that waist circumference increases, reflecting an increase in body weight

with aging. As women with PCOS age, criteria for the diagnosis of PCOS are such that the diagnosis can no longer be made in some women, often by the fourth decade. There is no known phenotype of women with PCOS in menopause.

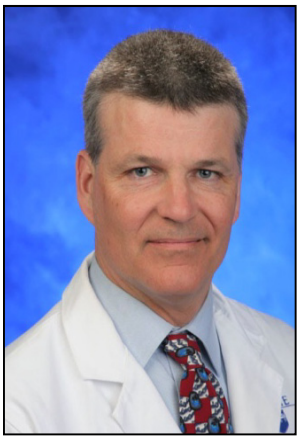
Prior to menopause, a proportion of women with PCOS begin to have more regular cycles. Women who have more regular cycles have been found to have lower follicular counts and lower inhibin B compared with those who remain anovulatory. Further, women who become regular have lower levels of AMH. As women enter menopause, the major health risks are cardiovascular and metabolic diseases as well as cancer. Data suggest that the metabolic concerns of premenopausal women with PCOS persist into menopause despite lower androgen levels. Although androgen levels are lower, it has been suggested that free testosterone levels still may be higher than those of controls in the seventh decade; symptoms of hirsutism may also persist while symptoms of menopause may be less. Most available data are cross-sectional, and prospective longitudinal data are urgently needed.

OPTIMAL MANAGEMENT STRATEGIES FOR THE REPRODUCTIVE AND METABOLIC CONSEQUENCES OF PCOS

Stephen Franks, M.D., FRCP, FMedSci, trained in internal medicine and endocrinology. He is Professor of Reproductive Endocrinology at Imperial College Faculty of Medicine (University of London) and Consultant Endocrinologist at St. Mary's and Hammersmith Hospitals, London. He is a former Chairman of the Society for Endocrinology in the United Kingdom. He is a Fellow of the Academy of Medical Sciences and holds an honorary doctorate from the University of Uppsala, Sweden. He has both clinic and laboratory-based programs of research in the field of normal and disordered function of the hypothalamic-pituitary-ovarian axis. He has a major interest in polycystic ovary syndrome (PCOS). Dr. Franks has published over 200 papers in peer-reviewed journals, mostly on the topic of PCOS. His research includes investigation of the mechanism(s) of anovulation and of the characteristic metabolic abnormalities; it focuses particularly on the interaction between genetic and environmental factors in the etiology of the syndrome.

Presentation Summary

Strategies for Management of Metabolic Phenotypes. PCOS is now recognized to have an important component of metabolic dysfunction, central to which is insulin resistance and the associated hyperinsulinemia. PCOS is a major risk factor for type 2 diabetes mellitus (T2DM), conferring up to a fourfold increase in risk for women who are also obese. Worryingly, the prevalence of metabolic dysfunction among women with PCOS is increasing, a feature of the general increase in the prevalence of overweight and obesity in the population. Particularly alarming is the increasing frequency with which adolescent girls with PCOS are discovered to have impaired glucose tolerance (IGT) or frank T2DM. Early intervention is important, especially in adolescents, to limit the risk of developing complications of metabolic dysfunction in later life. The obvious first step in management of overweight or obese women with PCOS is calorie restriction, complemented by exercise. Even modest weight loss of 5%–10% of body weight has been shown to be effective in improving insulin sensitivity (and indeed reproductive outcome). However, the success of weight-loss and exercise programs has been limited, and both pharmaceutical and surgical strategies may need to be considered, particularly for those women with IGT or T2DM. Metformin treatment is clearly indicated in such patients, if weight-loss/exercise programs have been ineffective, but the utility of metformin in obese women without IGT is unproven. The management of lean women with PCOS and insulin resistance is problematic since there seems little logic in calorie restriction in such subjects. Finally, emerging data suggest that in patients with PCOS and morbid obesity, bariatric surgery is effective in limiting or reversing the metabolic sequelae of PCOS. It can be argued that the most important approach to the management of metabolic consequences of PCOS is early diagnosis and intervention, particularly in adolescent girls.



Richard S. Legro, M.D., FACOG, received his medical degree from the Mount Sinai School of Medicine in New York City, and completed his residency in obstetrics and gynecology at Magee-Womens Hospital at the University of Pittsburgh and a fellowship in reproductive endocrinology and infertility at the University of Southern California in Los Angeles. He is a Professor in the Department of Obstetrics and Gynecology at the Pennsylvania State University College of Medicine in Hershey, Pennsylvania. His research and clinical practice are primarily focused on infertility and polycystic ovary syndrome (PCOS)—diagnosis, treatment, and genetic/environmental causes. At M.S. Hershey Medical Center, he established one of the first clinics devoted to the treatment of women with PCOS.

Presentation Summary

Strategies for Management of Reproductive and Metabolic Consequences of PCOS. This presentation will focus on the management of medical complaints related to reproductive aspects of PCOS. These include complaints related to chronic anovulation such as anovulatory infertility and anovulatory bleeding, as well as the sequelae of peripheral hyperandrogenism, primarily hirsutism, but also acne and androgenic alopecia. The primary treatments that will be addressed are hormonal contraceptives, metformin, anti-androgens, lifestyle, and surgical interventions/procedures.

Amelioration of hirsutism. The primary medical treatment for hirsutism related to androgen excess is ovarian suppression with hormonal contraceptives with/without an oral anti-androgen. There are no hormonal contraceptives that have been shown to be superior to others in this indication. There are concerns about the risk of serious adverse events as well as the potential increased risk profile in women with PCOS that should be considered in prescribing these agents. Topical antimetabolites such as eflornithine cream are also effective. These agents require treatment for 6 months or more to observe a result. In addition, mechanical epilatory methods such as laser or electrolysis are very effective at short-term hair removal, although hirsutism recurs over time. Acne responds well to hormonal contraceptives; however, the treatment of androgenic alopecia and other skin disorders lacks evidence-based methods.

Control of anovulatory bleeding. Anovulatory bleeding (and secondary amenorrhea) should be addressed both as it affects quality of life and as it represents a potential sign of endometrial pathology including polyps, endometrial hyperplasia, and endometrial cancer. Potential methods for treating these complaints include hormonal therapies, mechanical/hormonal with a progestin-containing intrauterine device, or in rare cases with surgery including D and C and endometrial ablation. Metformin and insulin sensitizing agents, while increasing the number of ovulatory events and withdrawal bleeds, are generally inferior to hormonal contraceptives in regulating bleeding. Furthermore, there are no long-term data on their preventive effects on endometrial and other gynecological cancers as there are for hormonal contraceptives. The long-term risks of endometrial ablation in women at increased risk for endometrial cancer, that is, development of endometrial cancer postablation, are unknown.

Treatment of infertility. The first-line treatment for women with PCOS who experience anovulatory infertility is clomiphene citrate (CC). Experts debate whether obese women should first undergo lifestyle therapy, although the benefits of this recommendation have not been clearly demonstrated

in prospective randomized trials. Furthermore, there is no evidence that lifestyle therapy has a role in normal-weight women with PCOS. Women with PCOS are at increased risk for ovarian hyperstimulation syndrome (OHSS), due to increased antral follicles and accordingly multiple pregnancies, compared with other categories of infertility. Thus ovulation induction strategies that lead to monofollicular development may hold interest despite reduced success rates. These include metformin and aromatase inhibitors (letrozole). Metformin is inferior to clomiphene in achieveving live birth in women with PCOS. Metformin also may have a role as an adjuvant therapy for infertility, combined with clomiphene or gonadotropins. Aromatase inhibitors may offer more favorable endometrial effects than CC, but a higher pregnancy rate than metformin. However, there is insufficient evidence to guide treatment with aromatase inhibitors.

Gonadotropin therapy has been reserved for oral medication treatment failures and offers high success rates with increased multiple pregnancy and OHSS rates (though these are user and protocol dependent). Similarly, surgeries or procedures that result in ovarian stromal destruction or reduction have been shown to increase ovulation and pregnancy rates, with the potential for long-term resolution of anovulation. They have become less utilized in the United States due to insurance limitations and practice trends focusing more on antiretroviral therapy for advanced infertility treatment. Women with PCOS who undergo *in vitro* fertilization (IVF) treatment appear to have similar success rates, although potentially higher complication rates (OHSS) than women with other diagnoses. The use of *in vitro* maturation (IVM) in women with PCOS to avoid gonadotropin exposure and OHSS risk is experimental. Although pregnancies have been obtained, the success rates from IVM do not equal those of IVF.

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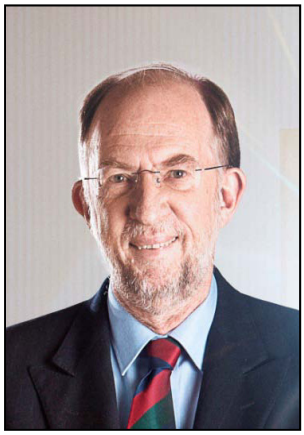
Presentation Summary

Pregnancy and Its Outcomes. Women with PCOS may conceive naturally, or, if they have anovulatory infertility, by ovulation induction. In those treated with ovulation induction, there may be risks associated with the drugs used or with the increased rate of multiple pregnancy. In addition to anovulation, there may be other factors that contribute to subfertility in women with PCOS, including the effects of obesity and metabolic, inflammatory, and endocrine abnormalities on oocyte quality and fetal development. Women who are obese also are more likely to experience miscarriage and pregnancy complications. Oocytes from polycystic ovaries may exhibit reduced developmental competence with a reduced ability to complete meiosis, achieve fertilization, and develop into a normal embryo. Ovarian hyperandrogenism and hyperinsulinemia may promote premature granulosa cell luteinization; furthermore, paracrine dysregulation of growth factors may disrupt the intrafollicular environment, alter granulosa cell-oocyte interactions, and impair cytoplasmic and/or nuclear maturation of oocytes. It has been shown that differences in metabolism exist in oocytes derived from women with PCOS, and this is associated with chromosomal predivision, that is, premature separation of sister chromatids. During early pregnancy, the embryo may be exposed to androgen excess *in utero,* which may have long-term effects particularly on female offspring. Fetal hyperandrogenism may disturb epigenetic programming, in particular those genes regulating reproduction and metabolism. In a meta-analysis in which pregnancy outcomes in 720 women presenting with PCOS were compared with 4,505 controls, women with PCOS demonstrated a significantly higher risk of developing gestational diabetes (odds ratio [OR] 2.94; 95% confidence interval [CI]: 1.70–5.08), pregnancy-induced hypertension (OR 3.67; 95% CI: 1.98–6.81), pre-eclampsia (OR 3.47; 95% CI: 1.95–6.17), and preterm birth (OR 1.75; 95% CI: 1.16–2.62). Their babies had a significantly higher risk of admission to a neonatal intensive care unit (OR 2.31; 95% CI: 1.25–4.26) and a higher perinatal mortality (OR 3.07; 95% CI: 1.03–9.21) unrelated to multiple births. The potential mechanisms for these problems include obesity, altered glucose metabolism, and disturbances in uterine blood flow.



Robert Norman, M.D., holds a personal chair as Professor for Reproductive and Periconceptual Medicine at The University of Adelaide in South Australia and is a subspecialist in reproductive medicine (Certificate of Reproductive Endocrinology and Infertility) and in endocrine biochemistry (Fellow of the Royal College of Pathologists in Australasia). He is Director of the Robinson Institute at The University of Adelaide, a collection of over 450 researchers in reproductive health and regenerative medicine. He has published more than 350 peer-reviewed publications and one book, and he serves on the editorial board of major journals. His major research contributions have been in *in vitro* fertilization and reproductive endocrinology, particularly in polycystic ovary syndrome (PCOS), the effect of lifestyle on reproductive outcomes, and periconception medicine. An active reproductive medicine specialist, he also serves on the Australian National Health and Medical Research Council's research and embryo licensing committees. He is Chair of the Australian PCOS Alliance, which published major international evidence-based guidelines on PCOS in 2011, and has been President of the Androgen Excess and PCOS Society. He is currently President of the Asia Pacific Initiative on Reproduction, which is an emerging influence in Asian Reproductive Medicine.

Presentation Summary

Role of Prevention and Lifestyle Strategies. Treatment of PCOS aims to improve biochemical and clinical hyperandrogenism, reproductive function, psychological features, and metabolic outcomes. Where clinical features of PCOS are worsened by insulin resistance (IR) or obesity, lifestyle (diet, exercise, and behavioral) interventions to reduce weight and/or IR are preferable to drugs, surgery, or other procedures. There is increasing evidence that obesity unmasks a tendency to clinical manifestations of PCOS and also some data suggesting preventive treatments around puberty may be helpful.

There are a large number of small, uncontrolled trials demonstrating that weight loss achieved through lifestyle management decreases abdominal fat, hyperandrogenism, IR, and risk factors for diabetes and heart disease, and improves lipid profiles, menstrual cyclicity, fertility, and psychological health. There are few randomized controlled trials to answer the question of preventive and early lifestyle interventions. The Australian PCOS Alliance evidence-based guidelines recommended that lifestyle interventions (level B) should include reduced caloric intake and exercise, prevention of weight gain (level D), healthy food choices (level C), exercise participation of more than 150 minutes per week (level D), and particular attention to certain ethnic groups.

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Presentation Summary

Role of Family Screening. Family studies of PCOS have consistently shown that clinical and biochemical features of androgen excess, ovulatory dysfunction, and polycystic ovaries on ultrasound cluster in PCOS families. In addition to these features used to define PCOS, metabolic abnormalities are also prevalent in first-degree relatives of women with PCOS. Insulin resistance, varying degrees of glucose intolerance, and dyslipidemia have been reported in mothers, fathers, brothers, and sisters of women with PCOS. The results of the studies on progeny of PCOS are in line with those studies on parents and siblings. Both sons and daughters of women with PCOS show metabolic abnormalities, particularly insulin resistance. Available family data on PCOS are mainly derived from cross-sectional studies. Whether this increased prevalence of metabolic risk factors in first-degree relatives of women with PCOS translates into adverse cardiovascular outcome remains to be determined in follow-up studies.

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