ANDROGEN EXCESS DISORDERS IN WOMEN
CONTEMPORARY ENDOCRINOLOGY

P. Michael Conn, SERIES EDITOR

Evidence-Based Endocrinology, edited by Victor M. Montori, 2006
Stem Cells in Endocrinology, edited by Linda B. Lester, 2005
Office Andrology, edited by Phillip E. Patton and David E. Battaglia, 2005
Androgens in Health and Disease, edited by Carrie Bagatell and William J. Bremner, 2003
Endocrine Replacement Therapy in Clinical Practice, edited by A. Wayne Meikle, 2003
Early Diagnosis of Endocrine Diseases, edited by Robert S. Bar, 2003
Type I Diabetes: Etiology and Treatment, edited by Mark A. Sperling, 2003
Diseases of the Thyroid, 2nd ed., edited by Lewis E. Braverman, 2003
Developmental Endocrinology: From Research to Clinical Practice, edited by Erica A. Engster and Ora Hirsch Pescovitz, 2002
Osteoporosis: Pathophysiology and Clinical Management, edited by Eric S. Orwoll and Michael Bliziotis, 2002
Challenging Cases in Endocrinology, edited by Mark E. Molitch, 2002
Transgenics in Endocrinology, edited by Martin Matzuk, Chester W. Brown, and T. Rajendra Kumar, 2001
Assisted Fertilization and Nuclear Transfer in Mammals, edited by Don P. Wolf and Mary Zelinski-Wootten, 2001
Adrenal Disorders, edited by Andrew N. Margoridis and George P. Chrousos, 2001
Endocrine Oncology, edited by Stephen P. Lother, 2000
Gene Engineering in Endocrinology, edited by Margaret A. Shupnik, 2000
Endocrinology of Aging, edited by John E. Morley and Lucretia van den Berg, 2000
Hormones and the Heart in Health and Disease, edited by Leonard Share, 1999
Autoimmune Endocrinopathies, edited by Robert Volpe, 1999
Hormone Resistance Syndromes, edited by J. Larry Jameson, 1999
Hormone Replacement Therapy, edited by A. Wayne Meikle, 1999
Endocrinology of Breast Cancer, edited by Andrea Manni, 1999
Molecular and Cellular Pediatric Endocrinology, edited by Stuart Handwerger, 1999
Gastrointestinal Endocrinology, edited by George H. Greeley, Jr., 1999
ANDROGEN EXCESS DISORDERS IN WOMEN

POLYCYSTIC Ovary Syndrome and Other Disorders
Second Edition

Edited by

RICARDO AZZIZ, MD, MPH, MBA
Center for Androgen Related Disorders, Cedars-Sinai Medical Center; and Department of Obstetrics and Gynecology, and Department of Medicine, The David Geffen School of Medicine at UCLA, Los Angeles, CA

JOHN E. NESTLER, MD
Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA

DIDIER DEWAILLY, MD
Department of Endocrine Gynaecology and Reproductive Medicine, Lille University Hospital, Lille, France

HUMANA PRESS
TOTOWA, NEW JERSEY
DEDICATION

To Cindy, Ashlee, Jonathon, and Mallory, for their loving and patient support and encouragement.

—RA

To my brother, Gregory, whose love, encouragement, and sense of humor were always a source of comfort.

—JEN

To my family and friends, with love and fondness.

—DD
The field of androgen excess disorders has advanced substantially since the original publication of this book. The Androgen Excess Society (AES) was founded to bring together investigators in the field. A better understanding of the screening, progression, and molecular genetics of nonclassic adrenal hyperplasia (NCAH) has improved the clinical care and diagnostic accuracy of these patients. New criteria for the diagnosis of the polycystic ovary syndrome (PCOS) were proposed in Rotterdam, criteria that have resulted in controversy and, hopefully, initiation of new studies. The association of insulin resistance with PCOS has been strengthened, and the role of metformin in treating the infertility of the PCOS has been validated. Risks for diabetes and, more controversially, cardiovascular disease in women with PCOS have received substantial investigation. Our understanding of the epidemiology and economic impact of these disorders has expanded, emphasizing their critical importance. These are but a few highlights of how the terrain has changed in a relatively brief period of time.

In keeping with these advances, the title of this book has been revised to reflect the growing importance of PCOS as the most prevalent androgen excess disorder in women, and arguably, as the one that might have the most serious adverse consequences for general health. There are fewer chapters to provide a more focused elucidation of the area. Several chapters were penned by new (and young) authors who are conducting cutting-edge research in the field. The time line for publication of the book was intentionally kept tight, so that the information would be fresh and current. Although the editors have grown grayer, and not necessarily wiser, we nonetheless hope that this second edition of Androgen Excess Disorders in Women: Polycystic Ovary Syndrome and Other Disorders will prove to be a helpful guide and resource for all clinicians and researchers in the field of androgen excess.

Ricardo Azziz, MD, MPH, MBA
John E. Nestler, MD
Didier Dewailly, MD
ACKNOWLEDGMENTS

A text of this size and depth cannot be created by only a dedicated few and the authors must, out of fairness, acknowledge the support and assistance of many. We would like to thank our staff who helped in the preparation and formatting of the many drafts involved, particularly acknowledging the expert administrative assistance of Lois Dollar and April Moore. We also greatly appreciate the support, patience, and guidance offered to us by the editorial staff at Humana Press, notably Richard Lansing, Executive Director for Continuing Medical Education and New Project Development; Patrick Marton, Acquisitions Editor; and Robin B. Weisberg, Director of Editorial Services. Our young collaborators, and past and present fellows, deserve special thanks for their generous and enthusiastic intellectual contributions; a notable example is Dr. Daniela Jakubowicz who has played a significant role in furthering our understanding of the therapeutic value of metformin in the polycystic ovary syndrome. We are also deeply indebted to the many authors who gave freely of their time and effort, and who endured our frequent requests for revisions under a tight and unforgiving timeline. Finally, we acknowledge with profound gratitude our many patients who suffer from androgen excess disorders, and who trusted us to care for them, teaching us so much about these disorders and about living gracefully despite their disability.

Ricardo Azziz, MD, MPH, MBA
John E. Nestler, MD
Didier Dewailly, MD
Dedication ............................................................................................................................
Preface ..................................................................................................................................
Acknowledgments ..................................................................................................................
Contributors ..........................................................................................................................

**I. Introduction**

1 A Brief History of Androgen Excess  
*Ricardo Azziz* .................................................................................................................. 3

**II. Physiology of Androgens**

2 Ovarian and Adrenal Androgen Biosynthesis and Metabolism  
*Walter L. Miller, David H. Geller, and Mitchell Rosen* ............... 19

3 Androgens Throughout the Life of Women  
*C. Richard Parker, Jr.* ............................................................................................. 35

4 Physiological Effects of Androgens in Women  
*T. Keta Hodgson and Glenn D. Braunstein* ........................................ 49

5 Androgen Measurements: Methods, Interpretation, and Limitations  
*Frank Z. Stanczyk* ............................................................................................. 63

**III. Uncommon Causes of Androgen Excess**

6 Androgen-Secreting Adrenal and Ovarian Neoplasms  
*Micel Pugeat, Gérard Raverot, Ingrid Plotton, Aude Brac de la Perrière, Pascale Mirakian, Henri Déchaud, Nicole Berger, and Jean Louis Peix* .............................................. 75

7 Cushing’s Syndrome, Acromegaly, and Androgen Excess  
*Anne-Céline Reyss and Didier Dewailly* ...................................................... 85

8 The Nonclassic Adrenal Hyperplasias  
*Didier Dewailly and Ricardo Azziz* ............................................................... 91

9 Pregnancy-Related Androgen Excess  
*Howard D. McClamrock* ............................................................................. 107

10 Drug-Induced Hyperandrogenism  
*Barbara Neraud and Didier Dewailly* .......................................................... 121

11 Severe Insulin-Resistant Hyperandrogenic Syndromes  
*David E. Moller, Antonio Vidal-Puig, and Ricardo Azziz* .......... 129

12 Idiopathic Hirsutism  
*Enrico Carmina* ............................................................................................. 139
<table>
<thead>
<tr>
<th>Section</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV. The Polycystic Ovary Syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Definition and Epidemiology of the Polycystic Ovary Syndrome</td>
<td>Ricardo Azziz</td>
<td>145</td>
</tr>
<tr>
<td>14 Clinical Features of the Polycystic Ovary Syndrome</td>
<td>Walter Futterweit, Evanthia Diamanti-Kandarakis, and Ricardo Azziz</td>
<td>155</td>
</tr>
<tr>
<td>15 Biochemical Features of the Polycystic Ovary Syndrome</td>
<td>Adam H. Balen</td>
<td>169</td>
</tr>
<tr>
<td>16 Ovarian Histology, Morphology, and Ultrasonography</td>
<td>Sophie Jonard, Yann Robert, Yves Ardaens, and Didier Dewailly</td>
<td>183</td>
</tr>
<tr>
<td>17 Hypothalamic–Pituitary–Gonadotrophic Dysfunction</td>
<td>R. Jeffrey Chang and Rinku V. Mehta</td>
<td>195</td>
</tr>
<tr>
<td>18 Ovarian Steroidogenic Abnormalities in the Polycystic Ovary Syndrome</td>
<td>Denis A. Magoffin</td>
<td>203</td>
</tr>
<tr>
<td>19 Hypothalamic–Pituitary–Adrenal Dysfunction</td>
<td>Bulent O. Yildiz, Enrico Carmina, and Ricardo Azziz</td>
<td>213</td>
</tr>
<tr>
<td>20 The Genetic Basis of the Polycystic Ovary Syndrome</td>
<td>Mark O. Goodarzi</td>
<td>223</td>
</tr>
<tr>
<td>21 Pediatric Hyperandrogenism and the Polycystic Ovary Syndrome</td>
<td>Kathleen M. Hoeger</td>
<td>235</td>
</tr>
<tr>
<td>22 Environmental Factors in the Polycystic Ovary Syndrome</td>
<td>Marie-France Hivert and Jean-Patrice Baillargeon</td>
<td>247</td>
</tr>
<tr>
<td>24 Insulin Resistance and Hyperinsulinism in the Polycystic Ovary Syndrome</td>
<td>Paulina A. Essah and John E. Nestler</td>
<td>273</td>
</tr>
<tr>
<td>25 The Endocrine Impact of Obesity and Body Habitus</td>
<td>Renato Pasquali and Alessandra Gamberini</td>
<td>283</td>
</tr>
<tr>
<td>26 Molecular Mechanisms of Insulin Resistance</td>
<td>Theodore P. Ciaraldi</td>
<td>293</td>
</tr>
</tbody>
</table>
27 Menstrual Dysfunction and Endometrial Neoplasia
in the Polycystic Ovary Syndrome and Other
Androgen Excess Disorders
Abdulkadir Wagley and Paul Hardiman .................................... 303

28 β-Cell Dysfunction, Glucose Intolerance, and Diabetes
in the Polycystic Ovary Syndrome
David A. Ehrmann ....................................................................... 319

29 Hypertension and Cardiovascular and Lipoprotein
Abnormalities in the Polycystic Ovary Syndrome
Francesco Orio and Stefano Palomba ........................................ 325

30 Reproductive and Obstetrical Consequences of the Polycystic
Ovary Syndrome
Mary C. Johnson and Richard S. Legro ..................................... 333

31 Psychosocial and Quality-of-life Consequences of Androgen
Excess and the Polycystic Ovary Syndrome
Onno E. Janssen, Susanne Hahn, and Sigrid Elsenbruch ....... 343

32 Overview of Long-Term Morbidity and Economic Cost
of the Polycystic Ovary Syndrome
Ricardo Azziz ................................................................................ 353

V. Evaluation and Treatment of Androgen Excess
33 Clinical and Hormonal Evaluation of Androgen Excess
Ricardo Azziz ................................................................................ 365

34 Ovarian Suppression and Treatment of Hirsutism
Paolo Moghetti ............................................................................. 377

35 Polycystic Ovary Syndrome and Ovulation Induction
Bulent O. Yildiz and Ricardo Azziz ............................................. 389

36 In Vitro Fertilization for the Polycystic Ovary Syndrome
Hanadi Ba-Akdah, Ezgi Demirtas, Hananel Holzer,
William Buckett, and Seang Lin Tan ..................................... 405

37 Surgical Management of the Polycystic Ovary Syndrome
Adam H. Balen ............................................................................. 415

38 Use of Insulin Sensitizers in the Polycystic Ovary Syndrome
Kai I. Cheang and John E. Nestler ............................................. 421

39 Weight Reduction and Lifestyle Modification in the Treatment
of Androgen Excess
Manny Noakes, Lisa J. Moran, Grant D. Brinkworth,
and Robert J. Norman ............................................................. 435

Index ............................................................................................... 445
CONTRIBUTORS

DAVID H. ABBOTT, PhD • National Primate Research Center and Department of Obstetrics and Gynecology, University of Wisconsin, Madison, WI

YVES ARDAENS, MD • Department of Radiology, Hopital Jeanne de Flandre, Centre Hospitalier et Universitaire de Lille, Lille, France

RICARDO AZZIZ, MD, MPH, MBA • Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center; Department of Obstetrics and Gynecology, and Department of Medicine, The David Geffen School of Medicine at University of California, Los Angeles, CA

HANADI BA-AKDAH, MD • Department of Obstetrics and Gynecology, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada

JEAN-PATRICE BAILLARGEON, MD, MSC • Division of Endocrinology, Department of Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada

ADAM H. BALEN, MD • Department of Reproductive Medicine, The General Infirmary, Leeds, UK

NICOLE BERGER, MD • Laboratoire d’Anatomie et de Cytologie pathologiques, Hopital Lyon Sud, Pienne-Benite, France

AUDE BRAC DE LA PERRIÈRE, MD • Fédération d’Endocrinologie, Pole Est des Hopitaux de Lyon, Bron, France

GLENN D. BRAUNSTEIN, MD • Department of Medicine, Cedars-Sinai Medical Center; Department of Medicine, The David Geffen School of Medicine at University of California, Los Angeles, CA

GRANT D. BRINKWORTH, PhD • CSIRO Human Nutrition, Adelaide, Australia

WILLIAM BUCKETT, MD • Department of Obstetrics and Gynecology, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada

ENRICO CARMINA, MD • Department of Clinical Medicine, University of Palermo, Palermo, Italy

R. JEFFREY CHANG, MD • Department of Reproductive Medicine, University of California, San Diego School of Medicine, La Jolla, CA

KAI I. CHEANG, PharmD • Department of Pharmacy, Virginia Commonwealth University School of Pharmacy, Richmond, VA

THEODORE P. CIARALDI, PhD • Department of Medicine, University of California, San Diego, VA San Diego Healthcare System, San Diego, CA

HENRI DECHAUD, MD • Laboratoire de Radioanalyse, Pole Est des Hopitaux de Lyon, Hopital Neuro-Cardio, Lyon, France

EZGI DEMIRTEŞ, MD • Department of Obstetrics and Gynecology, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada

DIDIER DEWAILLEY, MD • Service d’Endocrinologie et Diabetologie, Department of Endocrine Gynaecology and Reproductive Medicine, Hopital Jeanne de Flandre, Centre Hospitalier et Universitaire de Lille, Lille, France

EVANTHIA DIAMANTI-KANDARAKIS, MD • Department of Medicine, Athens University Medical School, Athens, Greece
Contributors

DANIEL A. DUMESIC, MD • National Primate Research Center, University of Wisconsin, Madison, WI and Reproductive Medicine & Infertility Associates, Woodbury, MN

ANDREA DUNAIF, MD • Division of Endocrinology, Metabolism and Molecular Medicine, The Feinberg School of Medicine, Northwestern University, Chicago, IL

DAVID A. EHRRMANN, MD • Section of Endocrinology, The University of Chicago, Chicago, IL

SIGRID ELSENBRUCH, PhD • Institute of Medical Psychology, University Hospital of Essen Medical School, Essen, Germany

PAULINA A. ESSAH, MD • Division of Endocrinology and Metabolism, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA

WALTER FUTTERWEIT, MD, FACP • Division of Endocrinology, Mount Sinai School of Medicine, New York, NY

ALESSANDRA GAMBINERI, MD • Department of Internal Medicine, S. Orsola-Malpighi, Bologna, Italy

DAVID H. GELLER, MD, PhD • Ahmanson Department of Pediatrics Cedars-Sinai Medical Center; Department of Pediatrics, The David Geffen School of Medicine at UCLA, Los Angeles, CA

MARK O. GOODZARZI, MD, PhD • Division of Endocrinology, Diabetes, and Metabolism, Cedars-Sinai Medical Center; Department of Medicine, The David Geffen School of Medicine at University of California, Los Angeles, CA

SUSANNE HAHN, MD • Division of Endocrinology, Department of Medicine, University Hospital of Essen Medical School, Essen, Germany

PAUL HARDIMAN, MBBS, MD, FRCOG • University Department of Obstetrics and Gynaecology, Royal Free and University College of Medical School, London, UK

MARIE-FRANCE HIVERT, MD • Division of Endocrinology, Department of Internal Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada

T. KETA HODGSON, BSN, RN • Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA

KATHLEEN M. HOEGER, MD • Department of Obstetrics and Gynecology, University of Rochester Medical Center, Rochester, NY

HANANEL HOLZER, MD • Department of Obstetrics and Gynecology, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada

ONNO E. JANNSEN, MD • Division of Endocrinology, Department of Medicine, University Hospital of Essen Medical School, Essen, Germany

MOLY C. JOHNSON, BS • Department of Obstetrics and Gynecology, Penn State College of Medicine, Penn State University College of Medicine, M.S. Hershey Medical Center, Hershey, PA

SOPHIE JONARD, MD • Department of Endocrine Gynaecology and Reproductive Medicine, Hopital Jeanne de Flandre, Centre Hospitalier et Universitaire de Lille, Lille, France

RICHARD S. LEGRO, MD • Department of Obstetrics and Gynecology, Penn State College of Medicine, Hershey, PA

JON E. LEVINE, MD • Department of Neurobiology and Physiology, Northwestern University, Evanston, IL

DENIS A. MAGOFFIN, PhD • Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, CA
YANN ROBERT, MD • Department of Radiology, Hopital Jeanne de Flandre, Centre Hospitalier et Universitaire de Lille, Lille, France
MITCHELL ROSEN, MD • Division of Reproductive Endocrinology & Infertility, Department of Obstetrics and Gynecology, UCSF Center for Reproductive Health, San Francisco, CA
FRANK Z. STANCZYK, PhD • Departments of Obstetrics and Gynecology, University of Southern California, Keck School of Medicine, Women & Children’s Hospital, Los Angeles, CA
SEANG LIN TAN, MBBS, FRCOG, FRCSC, MMed (O&G), MBA • Department of Obstetrics and Gynecology, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada
ANTONIO VIDAL-PUIG, MD, PhD • Metabolic Medicine, Addenbrooke’s Hospital, Cambridge, UK
ABDULKADIR WAGLEY, MBChB, MRCOG • Department of Obstetrics and Gynecology, Royal Free & University College Medical School, London, UK
BULENT O. YILDIZ, MD • Department of Medicine, Hacettepe University School of Medicine, and Department of Internal Medicine, Endocrinology & Metabolism Unit Hacettepe, Ankara, Turkey