Ovarian Stimulation
Ovarian Stimulation

Edited by

Mohamed Aboulghar
Cairo University and The Egyptian IVF-ET Center

and

Botros Rizk
University of South Alabama
CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore,
São Paulo, Delhi, Dubai, Tokyo, Mexico City

Cambridge University Press
The Edinburgh Building, Cambridge CB2 8RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9780521197359

© Cambridge University Press 2011

This publication is in copyright. Subject to statutory exception
and to the provisions of relevant collective licensing agreements,
no reproduction of any part may take place without the written
permission of Cambridge University Press.

First published 2011

Printed in the United Kingdom at the University Press, Cambridge

A catalogue record for this publication is available from the British Library

Library of Congress Cataloguing in Publication data
Ovarian stimulation / edited by Mohamed Aboulghar, Botros Rizk.
p. ; cm.
Includes bibliographical references and index.
1. Ovulation—Induction. 2. Fertilization in vitro, Human. 3. Infertility, Female—Treatment. 4. Human
reproduction—Endocrine aspects. 5. Ovaries. I. Aboulghar, Mohamed. II. Rizk, Botros.
RG133.7.O83 2011
618.1’.7806–dc22
2010040405


Cambridge University Press has no responsibility for the persistence or
accuracy of URLs for external or third-party internet websites referred to in
this publication, and does not guarantee that any content on such websites is,
or will remain, accurate or appropriate.

Every effort has been made in preparing this book to provide accurate and up-to-date information
which is in accord with accepted standards and practice at the time of publication. Although case
histories are drawn from actual cases, every effort has been made to disguise the identities of the
individuals involved. Nevertheless, the authors, editors, and publishers can make no warranties that
the information contained herein is totally free from error, not least because clinical standards are
constantly changing through research and regulation. The authors, editors, and publishers therefore
disclaim all liability for direct or consequential damages resulting from the use of material contained
in this book. Readers are strongly advised to pay careful attention to information provided by the
manufacturer of any drugs or equipment that they plan to use.
To a dear friend, an honorable man, a legendary scientist, a Nobel Prize winner and a world renowned leader.
To Professor Robert Geoffrey Edwards, the father of IVF and four million babies worldwide.
We dedicate this book to you in gratitude for your friendship, mentorship and leadership.
The world, East and West, has respected you, and we loved you and honored you.
# Contents

List of contributors   page ix
About the editors   xiii
Foreword by Alan H. De Cherney   xv
Preface   xvi

## Section 1 – Mild forms of ovarian stimulation

1 Oral agents for ovarian stimulation   1
   Mohamed F. Mitwally and Robert F. Casper

2 Ovulation induction for anovulatory patients   14
   Evert J. P. van Santbrink and Bart C. J. M. Fauser

3 Mild ovarian hyperstimulation in combination with intrauterine insemination   27
   Ben J. Cohlen and Astrid E. P. Cantineau

4 Mild approaches in ovarian stimulation   34
   Geeta Nargund and Claire Basille

## Section 2 – Ovarian hyperstimulation for IVF

5 GnRH agonists for ovarian hyperstimulation   42
   Richard Fleming

6 Role of GnRH antagonist in assisted reproduction   49
   Mohamed Aboulghar

7 Gonadotropins in ovarian stimulation   61
   Madelon van Wely and Monique Mochtar

8 Progesterone during controlled ovarian hyperstimulation   67
   Ernesto Bosch

9 Ovarian hyperstimulation for poor responders   77
   William B. Schoolcraft and Eric S. Surrey

10 Polycystic ovarian syndrome   87
   C. Coughlan and W. Ledger

11 Ovarian hyperstimulation syndrome   103
   Botros Rizk and Mohamed Aboulghar

12 How to select ovarian stimulation protocols to avoid difficulties and complications   130
   Ziad Rafic Hubayter and Suheil J. Muasher

## Section 3 – Difficulties and complication of ovarian stimulation

13 Adjuncts for ovarian stimulation   143
   David R. Meldrum

14 Chorionic gonadotropin and luteinizing hormone supplementation during ovarian stimulation   151

15 Ovulation induction for hypogonadotropic hypogonadism   162
   Paraskevi Xekouki and George Tolis
## Contents

### Section 5 – Alternatives to ovarian hyperstimulation

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Natural cycle IVF</td>
<td>Mauro Schimberni, Marco Sbracia, Annalise Giallonardo, and Francesco Morgia</td>
</tr>
<tr>
<td>17</td>
<td>In vitro maturation of oocytes</td>
<td>Baris Ata, Dan Levin, Hananel Holzer, and Seang Lin Tan</td>
</tr>
<tr>
<td>18</td>
<td>Treatment of hyperprolactinemia</td>
<td>Hany F. Moustafa, Botros Rizk, Ahmet Helvacioglu, and Shannon Gilmore</td>
</tr>
<tr>
<td>19</td>
<td>Ovarian cautery for polycystic ovary syndrome</td>
<td>Gabor T. Kovacs</td>
</tr>
</tbody>
</table>

### Section 6 – Procedures before, during, and after ovarian stimulation

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Ultrasound monitoring for ovulation induction: pitfalls and problems</td>
<td>Mona M. Aboulghar</td>
</tr>
<tr>
<td>21</td>
<td>Triggering of final oocyte maturation in ovarian stimulation</td>
<td>Georg Griesinger and Efstratios Kolibianakis</td>
</tr>
<tr>
<td>22</td>
<td>Luteal phase support in in vitro fertilization</td>
<td>Biljana Popović-Todorović and Human Mousavi Fatemi</td>
</tr>
<tr>
<td>23</td>
<td>Ovarian reserve as a guide for ovarian stimulation</td>
<td>Luciano G. Nardo and Lamiya Mohiyiddeen</td>
</tr>
</tbody>
</table>

Index 262
Contributors

Mohamed Aboulghar
Department of Obstetrics and Gynecology
Faculty of Medicine
Cairo University
Cairo
Egypt

The Egyptian IVF-ET Center
Hadayek Al Maadi
Cairo
Egypt

Mona M. Aboulghar
Department of Obstetrics and Gynecology
The Egyptian IVF Center
Cairo
Egypt

A. Arnone
Medicine Unit
Gynepro Medical Centers
Bologna
Italy

Baris Ata
McGill Reproductive Center
Royal Victoria Hospital
Montreal, Quebec
Canada

Claire Basille
Create Health Clinic
West Wimbledon
UK

Ernesto Bosch
Ginecólogo
IVI, Valencia
Plaza Policia
Valencia
Spain

Astrid E. P. Cantineau
Fertility Centre Isala
Isala Clinics Zwolle
The Netherlands

Robert F. Casper
Division of Reproductive Sciences
Department of Obstetrics and Gynecology
Mount Sinai Hospital
Toronto, Ontario
Canada

W. Ciampaglia
Medicine Unit
Gynepro Medical Centers
Bologna
Italy

G. E. Cognigni
Medicine Unit
Gynepro Medical Centers
Bologna
Italy

Ben J. Cohlen
Fertility Care Centre
Isala Clinics Zwolle
Location Sophia
The Netherlands

C. Coughlan
Academic Unit of Reproductive and Developmental Medicine
University of Sheffield
UK

Alan H DeCherney
Branch chief of Reproductive Biology and Medicine
National Institute of Child Health and HumM Development
Bethesda, Maryland
USA
List of contributors

Human Mousavi Fatemi
Centre for Reproductive Medicine
UZ Brussels
Belgium

Bart C. J. M. Fauser
Chair, Division Woman and Baby
University Medical Center, Utrecht
The Netherlands

M. Filicori
Medicine Unit
Gynepro Medical Centers
Bologna
Italy

Richard Fleming
GCRM Ltd
Glasgow
UK

Annalise Giallonardo
Bioroma IVF Center
University of Rome
Rome
Italy

Shannon Gilmore
Gynecology and Infertility Associates
Fairhope, AL
USA

Georg Griesinger
University Hospital of Schleswig-Holstein
Campus Luebeck
Luebeck
Germany

Ahmet Helvacioglu
Gynecology and Infertility Associates
Fairhope, AL
USA

Hananel Holzer
McGill Reproductive Center
Royal Victoria Hospital
Montreal, Quebec
Canada

Ziad Rafic Hubayter
The Johns Hopkins University School of Medicine
Department of Gynecology and Obstetrics

Division of Reproductive Endocrinology and Infertility
Lutherville, MD
USA

Efstratios Kolibianakis
Unit for Human Reproduction
Department of Obstetrics and Gynaecology
Medical School, Aristotle University of Thessaloniki
Thessaloniki
Greece

Gabor T. Kovacs
Monash IVF
Victoria
Australia

W. Ledger
Academic Unit of Reproductive and Developmental Medicine
University of Sheffield
Sheffield
UK

Dan Levin
McGill Reproductive Center
Royal Victoria Hospital
Montreal, Quebec
Canada

David R. Meldrum
University of California at Los Angeles and San Diego
Redondo Beach, CA
USA

Mohamed F. Mitwally
Division of Reproductive Sciences
Department of Obstetrics and Gynecology
Mount Sinai Hospital
Toronto, Ontario
Canada

Monique Mochtar
Center for Reproductive Medicine
Academic Medical Center
University of Amsterdam
Amsterdam
The Netherlands

Lamiya Mohiyiddeen
Department of Reproductive Medicine
<table>
<thead>
<tr>
<th>Contributors</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVF Unit, St Mary’s Hospital, CMFT University Hospitals, Whitworth Park, Manchester, UK</td>
<td></td>
</tr>
<tr>
<td>Francesco Morgia</td>
<td>Bioroma IVF Center, University of Rome, Rome, Italy</td>
</tr>
<tr>
<td>Hany F. Moustafa</td>
<td>Department of Obstetrics and Gynecology, USA College of Medicine, Mobile, AL, USA</td>
</tr>
<tr>
<td>Suheil J. Muasher</td>
<td>The Muasher Center for Fertility and IVF, Fairfax, VA, USA</td>
</tr>
<tr>
<td>Luciano G. Nardo</td>
<td>Department of Reproductive Medicine, IVF Unit, St Mary’s Hospital, CMFT University Hospitals, Whitworth Park, Manchester, UK</td>
</tr>
<tr>
<td>Geeta Nargund</td>
<td>Department of Obstetrics and Gynecology, St George’s Hospital, London, UK</td>
</tr>
<tr>
<td>L. Parmegiani</td>
<td>Medicine Unit, Gynepro Medical Centers, Bologna, Italy</td>
</tr>
<tr>
<td>P. Pocognoli</td>
<td>Medicine Unit, Gynepro Medical Centers, Bologna, Italy</td>
</tr>
<tr>
<td>Biljana Popović-Todorović</td>
<td>Centre for Reproductive Medicine, UZ Brussels</td>
</tr>
<tr>
<td>Belgium</td>
<td></td>
</tr>
<tr>
<td>Botros Rizk</td>
<td>Department of Obstetrics and Gynecology, University of South Alabama College of Medicine, Mobile, AL, USA</td>
</tr>
<tr>
<td>Marco Sbracia</td>
<td>Bioroma IVF Center, University of Rome, Rome, Italy</td>
</tr>
<tr>
<td>Mauro Schimberni</td>
<td>Bioroma IVF Center, University of Rome, Rome, Italy</td>
</tr>
<tr>
<td>William B. Schoolcraft</td>
<td>Colorado Center for Reproductive Medicine, Lone Tree, CO, USA</td>
</tr>
<tr>
<td>Eric S. Surrey</td>
<td>Colorado Center for Reproductive Medicine, Lone Tree, CO, USA</td>
</tr>
<tr>
<td>C. Tabarelli</td>
<td>Medicine Unit, Gynepro Medical Centers, Bologna, Italy</td>
</tr>
<tr>
<td>Seang Lin Tan</td>
<td>McGill Reproductive Center, Royal Victoria Hospital, Montreal, Quebec, Canada</td>
</tr>
<tr>
<td>George Tolis</td>
<td>Department of Internal Medicine, Division of Endocrinology and Metabolism, Hippocratio General Hospital, Athens, Greece</td>
</tr>
<tr>
<td>Evert J. P. van Santbrink</td>
<td>Erasmus Medical Center, Rotterdam, The Netherlands</td>
</tr>
</tbody>
</table>
List of contributors

Madelon van Wely
Center for Reproductive Medicine
Academic Medical Center
University of Amsterdam
Amsterdam
The Netherlands

Paraskevi Xekouki
Clinical Associate
Division of Endocrinology and Metabolism
Department of Medicine
Athens University
Athens
Greece
About the editors

Mohamed Aboulghar

Mohamed Aboulghar, M.D. is Professor of Obstetrics and Gynecology, Faculty of Medicine, Cairo University and Clinical Director and founder of The Egyptian IVF-ET Center, Maadi, Cairo, Egypt, (the first IVF center in Egypt). He is also the founder and first president of the Middle East Fertility Society (MEFS) and Editor-in-Chief and founder of the Middle East Fertility Society Journal (since 1996).

He has published over 200 papers in top international and regional medical journals, and over 20 chapters in international books.

He received the Egyptian National Award for Excellency in Medical Sciences in 2000 and Honorary Membership of the European Society of Human Reproduction and Embryology (Berlin 2004).

For several years, he has been an associate editor for Human Reproduction and the American Journal of Obstetrics and Gynecology. He is also currently a reviewer for Human Reproduction, Human Reproduction Update, Fertility and Sterility and many more international journals.

He has organized 20 international conferences in the Middle East, and chaired 3 pre-congress courses in the American Society for Reproductive Medicine (ASRM) annual conference.

Botros Rizk

Botros Rizk, M.D. is Professor and Chief of the Division of Reproductive Endocrinology and Infertility of the Department of Obstetrics and Gynecology at the University of South Alabama, Mobile, Alabama,
USA. He is also Program Director and Medical and Scientific Director of the USA IVF and ART Program, and Laboratory Director and Clinical Consultant at the Reproductive Endocrinology Laboratory of the University of South Alabama.

Professor Rizk has worked as a research scientist and clinician in reproductive medicine for more than 25 years. His main research interests include the modern management, prediction and the genetics of ovarian hyperstimulation syndrome (OHSS), as well as the role of vascular endothelial growth factor and interleukins in the pathogenesis of severe OHSS. He has authored more than 300 peer-reviewed published papers, book chapters and abstracts. Professor Rizk has edited and authored ten medical textbooks on ovarian hyperstimulation syndrome, infertility and assisted reproduction, endometriosis, ultrasonography in reproductive medicine, ovarian stimulation and the future of ART.

He is past chair of the ASRM international membership committee, member of the scientific advisory board of the Mediterranean Society for Reproductive Medicine, the editorial board of the *Middle East Fertility Society Journal* and reviewer for several national and international journals, as well as for the European Society of Human Reproduction and Embryology Task Force on perinatal outcome and congenital malformations of intracytoplasmic sperm injection.
Foreword

Alan H. DeCherney

National Institute of Child Health and Human Development

Ovarian Stimulation is a text that is comprehensive, insightful, contains a great deal of new information, and is well organized, making it easy to read. The book is divided into 6 sections and 23 chapters and is authored by leaders in the field from the global community, with representatives from such places as Canada, Europe, the United States, Egypt, and Australia, to name a few.

The chapters evolve from ovarian stimulation through procedures before, during, and after stimulation. Oral and injectable agents for ovulation induction are discussed in great depth, incorporating a fair amount of new material. In addition, therapies, such as intrauterine insemination and laparoscopic ovarian drilling are critically evaluated.

Ovarian Stimulation also addresses the utilization of GnRH, for both solitary use in ovarian stimulation and for use in combination with other agents. The occasionally serious adverse effect of ovulation induction (i.e., desecrated hyperstimulation syndrome), is looked at in terms of the diagnosis therapy and the use of novel agents in order to treat the entity, including early aspiration of ascites.

Individual patient scenarios are also addressed, including polycystic ovarian syndrome and the “poor responder.” The discussion of the risk, benefits, and effectiveness of hCG versus LH is included. Of course, much of the data, application, and in-depth understanding come from the author’s experience with in vitro fertilization (IVF), which is covered extensively by looking at natural cycle IVF, in vitro maturation of oocytes, as well as a more traditional approach.

Techniques for monitoring, such as ultrasound and serum estradiol levels are also discussed in depth.

The text is a comprehensive approach for understanding ovarian stimulation. There is no lack of information as far as this topic is concerned. It is up to date with contemporary, excellent and established references. The book is a monumental contribution that enriches our knowledge about a very important topic in reproductive endocrinology and infertility.
Ovarian stimulation has become an integral part of the management of infertility and assisted reproduction. A glance through scientific journals would demonstrate an explosion of publications related to ovarian stimulation. In every world congress and international infertility meeting the ovarian stimulation session is the most popular and lively session of the entire meeting.

This book was authored by the world leaders in infertility and reproductive endocrinology from the United States, Canada, Europe, Australia, the Middle East, and Africa. Each contributor has been the pioneer of the respective area of clinical research and practice.

The book covers in its different sections and chapters all aspects of ovarian stimulation: the different stimulation protocols from which to choose, the management of poor responders and hyper-responders, triggering ovulation and luteal phase support.

We have thoroughly enjoyed putting this book together and we take this opportunity to thank all the authors for their friendship and most valuable contributions.

To our readers, we put into your hands a concise and global book that we hope that you will thoroughly enjoy.