Glenn L. Schattman
Sandro C. Esteves
Ashok Agarwal *Editors*

Unexplained Infertility

Pathophysiology, Evaluation and Treatment

Springer

Glenn L. Schattman • Sandro C. Esteves
Ashok Agarwal
Editors

Unexplained Infertility

Pathophysiology, Evaluation and Treatment

Springer

Editors
Glenn L. Schattman
Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine
Weill Cornell Medical College
New York, NY, USA

Sandro C. Esteves
ANDROFERT, Andrology and Human Reproduction Clinic
Referral Center for Male Reproduction
Campinas, São Paulo, Brazil

Ashok Agarwal
Lerner College of Medicine
Case Western Reserve University
Andrology Center &
Center for Reproductive Medicine
Cleveland Clinic
Cleveland, OH, USA

ISBN 978-1-4939-2139-3 ISBN 978-1-4939-2140-9 (eBook)
DOI 10.1007/978-1-4939-2140-9

Library of Congress Control Number: 2014955347

Springer New York Heidelberg Dordrecht London

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

Infertility, or involuntary childlessness, is customarily defined as the failure of a couple to conceive after 12 months of unprotected regular intercourse. It has been estimated that 10–15 % of couples seek medical assistance for fertility evaluation, and the problem is apparently equally shared between male and female partners. However, after extensive evaluation of both partners by routinely used tests and without physical or endocrine abnormalities, up to 30 % of infertile couples remain childless devoid of identifiable causes—leading to a diagnosis of unexplained infertility.

Potential etiologies of unexplained infertility include couples' miscomprehension of the concept of the female fertile window, improper coital techniques, erectile dysfunction, and molecular and functional causes of male and female infertility. Interestingly, contemporary advanced technologies have demonstrated various ultrastructural, molecular and genetic etiologies in male or female partners with unexplained infertility. Men with unexplained infertility typically have normal semen parameters with no demonstrable abnormalities in their history, physical or endocrinological examination. Possible underlying causes of unexplained male infertility include mainly immune, humoral or cellular sensitization against sperm, genetic defects, sperm dysfunction and fertilization incompetence.

Even more interestingly, highly intricate testing methods provide a great deal of information about the potential contribution of female factors in UI. Cervical hostility, endometrial receptivity problems, fallopian tube dysfunction and oocyte quality may all weaken female fertility potential. Further, immunity against sperm, genetic causes, oxidative stress and subtle foci of endometriosis are some of the conditions that need to be evaluated in a patient with unexplained infertility, in order to understand the underlying cause(s) of unexplained infertility. These conditions may serve as a guide in any future research plans to solve the infertility dilemma.

This book introduces unexplained infertility, its definition and incidence in both males and females. The current use of the 2010 WHO guidelines in semen analysis has an impact on the diagnosis of unexplained infertility. The pathophysiological factors of this type of infertility include physical, immunological and genetic abnormalities. Factors that cause the development of oxidative stress and a variety of environmental factors have a role in the etiology of unexplained infertility. The management of unexplained infertility is complex, as its diagnosis was likely made by exclusion of various potential causes of infertility. Unexplained infertility may be managed through medications that may help normalize the endocrine profile or soothe immunological imbalances. Active interventions and the outcomes of each treatment modality are also considered. Couples dealing with a diagnosis of either male or female factor unexplained infertility very often resort to assisted reproductive technology to achieve conception, and the outcomes of these interventions will be discussed.

This textbook, the first of its kind, is intended to provide the reader with a thoughtful and comprehensive review of the clinical and scientific significance of unexplained infertility. We had invited leading, internationally recognized clinicians and basic scientists with expertise in male and female infertility to contribute their thoughts on these various aspects of

unexplained infertility. The experts from the various sub-specialties have contributed for this textbook. This book puts together information that serves as an invaluable tool both for the basic scientists with an interest in reproductive medicine and for clinicians working in the field of infertility (e.g., urologists, andrologists, gynaecologists and reproductive endocrinologists and embryologists). It is hoped that the topics discussed in this book serves to enlighten the readers regarding unexplained infertility and provide an in-depth perspective of this form of infertility.

Glenn L. Schattman
Sandro C. Esteves
Ashok Agarwal

Contributors

Yapo Guillaume Aboua Division of Medical Physiology, Department of Biomedical Sciences, Stellenbosch University, Cape Town, South Africa

Ashok Agarwal Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA

Alfredo Guillén Antón Department of Reproductive Medicine IVI Madrid, Rey Juan Carlos University, Madrid, Spain

Michael S. Bloom Obstetrics, Gynecology and Reproductive Sciences, University of California at San Francisco, San Francisco, CA, USA

Jamin Brahmbhatt Department of Urology, University of Florida & Winter Haven Hospital, Winter Haven, FL, USA

Spyridon Chouliaras Reproductive Medicine and Gynecology, Gynehealth, Manchester, UK

Marcello Cocuzza Department of Urology, University of Sao Paulo (USP), Sao Paulo, SP, Brazil

Ali A. Dabaja Department of Urology, Weill Cornell Medical College, New York-Presbyterian Hospital, New York, NY, USA

Anderson Sanches de Melo Department of Obstetrics and Gynecology, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

Marcello Desgro Department of Gynecology and Division of Gynecology and Reproductive Medicine, IRCCS Istituto Clinico Humanitas, Rozzano (Milano), Italy

Richard P Dickey The Fertility Institute, Mandeville, LA, USA

Sejal B. Doshi Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA

Stefan S. du Plessis Division of Medical Physiology, Department of Biomedical Sciences, Stellenbosch University, Parow, Western Cape, South Africa

Damayanthi Durairajanayagam Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA

Sandro C. Esteves ANDROFERT, Andrology and Human Reproduction Clinic, Referral Center for Male Reproduction, Campinas, Sao Paulo, Brazil

Fathy Ezzeldin Department of Obstetrics and Gynaecology, Alexandria University, Alexandria, Egypt

Rogério de Barros Ferreira Leão ANDROFERT, Andrology and Human Reproduction Clinic, Referral Center for Male Reproduction, Campinas, SP, Brazil

Rui Alberto Ferriani Department of Obstetrics and Gynecology, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

Victor Y. Fujimoto Obstetrics, Gynecology and Reproductive Sciences, University of California at San Francisco, San Francisco, CA, USA

Daniela Galliano Department of Reproduction, Instituto Valenciano Iinfertilidad (IVI), Barcelona, Spain

Bhushan K. Gangrade Center for Reproductive Medicine, Orlando, FL, USA

Juan Antonio García Velasco Department of Reproductive Medicine IVI Madrid, Rey Juan Carlos University, Madrid, Spain

Jaime Gosálvez Biology Department, Genetics Unit, Universidad Autónoma de Madrid, Madrid, Spain

Lawrence Grunfeld Department of Obstetrics, Gynecology, & Reproductive Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Ahmet Gudeloglu Department of Urology, University of Florida & Winter Haven Hospital, Winter Haven, FL, USA

Brent M Hardin Division of Urology, Department of Surgery, University of Tennessee Graduate School of Medicine, Knoxville, TN, USA

Avner Hershlag Department of Obstetrics, Gynecology and Reproductive Medicine, North Shore-Long Island Jewish Hospital of Hofstra University School of Medicine, Manhasset, NY, USA

Roy Homburg Fertility Centre, Homerton University Hospitals NHS Trust, Homerton, London, UK

Edward D Kim Division of Urology, Department of Surgery, University of Tennessee Graduate School of Medicine, Knoxville, TN, USA

Walter K.H. Krause Deptartment of Dermatology and Allergology, University Hospital, Philipp University, Marburg, Germany

Pieter Johann Maartens Division of Medical Physiology, Department of Biomedical Sciences, Stellenbosch University, Cape Town, South Africa

Avinash Maganty Department of Urology, New York—Presbyterian Hospital, Weill Cornell Medical College, New York, NY, New York, USA

Ricardo Miyaoka ANDROFERT, Andrology and Human Reproduction Clinic, Referral Center for Male Reproduction, Campinas, SP, Brazil

Ben Willem Mol Department Gynecology/Obstetrics, Academic Medical Center at the University of Amsterdam, Amsterdam, The Netherlands

Fabiana Y. Nakano Androfert, Campinas, SP, Brazil

Anupa Nandi Fertility Centre, Homerton University Hospitals NHS Trust, Homerton, London, UK

Luciano G. Nardo Reproductive Medicine and Gynecology, Gynehealth, Manchester, UK

Paula Andrea de Albuquerque de Salles Navarro Department of Obstetrics and Gynecology, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

Rajesh K. Naz Department of Obstetrics and Gynecology, West Virginia University School of Medicine, Morgantown, WV, USA

Darius Paduch Department of Urology, Weill Cornell Medical College, New York-Presbyterian Hospital, New York, NY, USA

Sijo Parekattil Department of Urology, University of Florida & Winter Haven Hospital, Winter Haven, FL, USA

Sejal Dhana Patel Center for Reproductive Medicine, Orlando, FL, USA

Zamip Patel Center for Reproductive Medicine, Orlando, FL, USA

Pasquale Patrizio Department of Gynecology and Division of Gynecology and Reproductive Medicine, IRCCS Istituto Clinico Humanitas, Rozzano (Milano), Italy

Antonio Pellicer Department of Reproduction, Instituto Valenciano Iinfertilidad (IVI), Barcelona, Spain

Ranjith Ramasamy Department of Urology, New York—Presbyterian Hospital, Weill Cornell Medical College, New York, NY, New York, USA

Patricia Rekawek Department of Obstetrics, Gynecology, & Reproductive Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

A. K. Rengan Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA

Edmund S. Sabanegh Department of Urology, The Cleveland Clinic, Cleveland, OH, USA

Hassan Sallam Department of Obstetrics and Gynaecology, Alexandria University, Alexandria, Egypt

Nooman Sallam Department of Obstetrics and Gynaecology, Alexandria University, Alexandria, Egypt

Glenn L. Schattman Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medical College, New York, NY, USA

Peter N. Schlegel Department of Urology, New York—Presbyterian Hospital, Weill Cornell Medical College, New York, NY, New York, USA

Thalia R. Segal Department of Obstetrics, Gynecology and Reproductive Medicine, North Shore-Long Island Jewish Hospital of Hofstra University School of Medicine, Manhasset, NY, USA

Lucky H. Sekhon Department of Obstetrics, Gynecology, & Reproductive Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Paolo Emanuele Levi Setti Department of Gynecology and Division of Gynecology and Reproductive Medicine, IRCCS Istituto Clinico Humanitas, Rozzano (Milano), Italy

Rakesh K. Sharma Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA

Christopher L. Starks The Urology Group of Virginia, Glickman Urologic and Kidney Institute, The Cleveland Clinic Foundation, Cleveland, Suite 112 Leesburg, USA

Bruno Camargo Tiseo Department of Urology, University of Sao Paulo (USP), Sao Paulo, SP, Brazil

Alberto Vaiarelli Department of Gynecology and Division of Gynecology and Reproductive Medicine, IRCCS Istituto Clinico Humanitas, Rozzano (Milano), Italy

N. M. van den Boogaard Gynaecology and Obstetrics and Reproductive medicine, VU medical centre and AMC medical centre, Amsterdam, Pieter Lodewijk Takstraat 31, The Netherlands

Michelle van der Linde Division of Medical Physiology, Department of Biomedical Sciences, Stellenbosch University, Parow, Western Cape, South Africa

Fulco van der Veen Department of Gynecology, Academic Medical Center, Amsterdam, The Netherlands

Fatma Ferda Verit Department of Obstetrics & Gynecology, Infertility Research & Treatment Center, Suleymaniye Maternity, Research &Training Hospital, Istanbul, Turkey

Sidney Verza Jr. ANDROFERT, Referral Center for Male Reproduction, Andrology and Human Reproduction Clinic, Campinas, Sao Paulo, Brazil

Irene Zerbetto Department of Gynecology and Division of Gynecology and Reproductive Medicine, IRCCS Istituto Clinico Humanitas, Rozzano (Milano), Italy

About the Editors

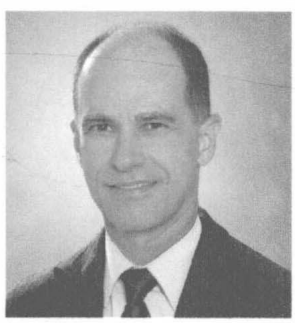
Dr. Glenn L. Schattman MD is an Associate Professor of Clinical Obstetrics and Gynecology and Clinical Reproductive Medicine at the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine (CRM) of Weill Cornell Medical College. Dr. Schattman is board certified in Obstetrics and Gynecology and Reproductive Endocrinology and Infertility. He is a noted specialist in in vitro fertilization (IVF), fertility preservation, minimally invasive reproductive surgery and problems of sexual development in girls and young women.

Dr. Schattman is a leading minimally invasive surgeon. He was one of the first gynecologic surgeons to perform robotic surgery for reversal of tubal ligation and excision of uterine fibroids.

Dr. Schattman earned a Bachelor of Science from St. Lawrence University in Canton, New York, in 1983 and his medical degree from the State University of New York, Downstate Medical Center, in Brooklyn, New York, in 1987. He completed his residency training in Obstetrics and Gynecology at The George Washington University Medical Center in 1991. He finished his training with a fellowship in Reproductive Endocrinology and Infertility at the Center for Reproductive Medicine and became a CRM faculty member in 1993.

He was the 2011–2012 President of the Society for Assisted Reproductive Technology (SART), the leading association of in vitro fertilization-specialized physicians. Dr. Schattman was the Chair of SART's Practice Committee from 2004 to 2009 and is a member or fellow of numerous medical associations, including the American Society for Reproductive Medicine and the American Association of Gynecologic Laparoscopists.

Dr. Schattman has authored numerous articles and textbook chapters and lectures both nationally and internationally on a wide range of topics in reproductive medicine.



Sandro C. Esteves MD, PhD is Director of ANDROFERT—Andrology and Human Reproduction Clinic in Campinas, Brazil.

Sandro Esteves graduated in 1990 at the University of Campinas Medical School (UNICAMP), Brazil, where he accomplished a residency program in General Surgery and Urology (1991–1995). He received his Master Degree in Surgery in 1996 from UNICAMP, and a PhD in Medicine in 1998 from the Federal University of São Paulo (UNIFESP). He did his post-residency training in Andrology and Male Infertility under a fellowship from the Cleveland Clinic Foundation International Center at the Center for Reproductive Medicine of the Glickman Urological & Kidney Institute in Cleveland, Ohio (1995–1996). Dr. Esteves is a board-certified Urologist by the Brazilian Society of Urology,

and member or office bearer of several professional societies, including the Brazilian Society of Urology (SBU), Brazilian Society of Human Reproduction (SBRH), Brazilian Society for Assisted Reproduction (SBRA), American Society for Reproductive Medicine (ASRM), Society for the Study of Male Reproduction and Urology (SMRU). He is an 'ad hoc' consultant in the area of germinative tissues at the Brazilian National Agency of Sanitary Surveillance.

Dr. Esteves is the founder of ANDROFERT, the first Center dedicated to male reproduction in Brazil. ANDROFERT has become a Referral Center for Male Infertility, and was the first Brazilian Human Reproduction Clinic to obtain full ISO 9001:2008 certification.

Dr. Esteves has authored and edited medical textbooks on human reproduction and published over 200 peer-reviewed articles and book chapters over the past 20 years (http://www.researchgate.net/profile/Sandro_Esteves/publications/). He serves as Associate Editor of the International Brazilian Journal of Urology and Area Editor of Clinics (Sao Paulo), International Urology and Nephrology, and MedicalExpress. Dr. Esteves' major interest areas are clinical male infertility, reproductive endocrinology, microsurgery, cryobiology, andrology and IVF laboratory technique, and quality management applied to Fertility Centers.

Dr. Esteves is a Research Collaborator and External Faculty at the Cleveland Clinic's Center for Reproductive Medicine, a Clinical Tutor in the College of Medicine at the University of Edinburgh.

Ashok Agarwal PhD is a Professor at Lerner College of Medicine, Case Western Reserve University and the head of the Andrology Center. He is the Director of Research at the Center for Reproductive Medicine, Cleveland Clinic, USA. He has researched extensively on oxidative stress and its implications on human fertility and his group has published over 500 research articles. Ashok is an editor of over 26 medical text books/ manuals related to male infertility, ART, fertility preservation, DNA damage and antioxidants. Dr. Agarwal serves on the editorial boards of several key journals in human reproduction. His current research interests are the study of molecular markers of oxidative stress, DNA fragmentation and apoptosis using proteomics and bioinformatics tools, as well as fertility preservation in patients with cancer, and the efficacy of certain antioxidants in improving male fertility.

Contents

Part I
Definitions and Epidemiology

Definitions and Relevance of Unexplained Infertility in Reproductive Medicine

1

Sandro C. Esteves, Glenn L. Schattman and Ashok Agarwal

Infertility is customarily defined as the inability of a sexually active couple with no contraception to achieve natural pregnancy within one year [1]. The American Society for Reproductive Medicine (ASRM) considers infertility as a disease, which by definition is "any deviation from or interruption of the normal structure or function of any part, organ, or system of the body as manifested by characteristic symptoms and signs; the etiology, pathology, and prognosis may be known or unknown" [2, 3].

It has been estimated that 15% of couples seek medical assistance for infertility, and the origins of the problem seem to be equally distributed between male and female partners [1]. Taking into account a global perspective and a world population of 7 billion people, these figures indicate that approximately 140 million people (2.2%) face infertility [4, 5].

Infertility depends at large on the age of the female partner. As such, the ASRM states that an early evaluation and treatment is warranted after 6 months for women aged 35 years or older [3].

In men, about 8% seek medical assistance for fertility-related problems [6]. In its most updated version (2010) on "the optimal evaluation of the infertile male," the American Urological Association (AUA) recommends that the initial screening should be done if pregnancy has not occurred within one year of unprotected intercourse, or earlier in cases of known male or female infertility risk factors [7]. Male infertility can result from congenital or acquired urogenital abnormalities, urogenital tract infections, increased scrotal temperature such as a consequence of varicocele, endocrine disturbances, genetic abnormalities, immunological factors, lifestyle habits (e.g., obesity, smoking, and use of gonadotoxins), systemic diseases, erectile dysfunction, and incorrect coital habitus. Unfortunately, owed to limitations in our understanding of the events that take place during natural conception, and in view of the crude diagnostic tests available to identify potential abnormalities, the cause of infertility is not determined in nearly half of the cases. Moreover, approximately 5% of couples remain unwillingly childless despite multiple interventions [1, 8, 9].

Infertility of unknown origin comprises both idiopathic and unexplained infertility. Men presenting with idiopathic infertility have no obvious history of fertility problems, and both physical examination and endocrine laboratory testing are normal. However, semen analysis as routinely performed reveals sperm abnormalities that come alone or in combination. The reported prevalence of men with unexplained reduction of semen quality ranges from 30 to 40% [1, 10].

In contrast to idiopathic infertility, the term "unexplained infertility" is reserved for couples in whom routine semen analysis is within the reference values, and a definitive female infertility factor has not been identified [11]. In females with unexplained infertility, no definitive abnormality can be identified, but a reduced fecundity potential may be suspected in ovulatory woman with evidence of diminished ovarian reserve testing, including elevated follicle stimulating hormone (FSH) or low anti-Mullerian hormone (AMH) levels. In addition, direct evidence of diminished ovarian reserve can be determined by low antral follicle counts or lack of response to exogenous gonadotropins despite normal ovarian reserve testing. This category of 'poor ovarian response (POR)' or 'diminished ovarian response (DOR)' is difficult to define and the leading experts in the field were still unable to arrive at a conclusive definition [12].

The reported prevalence of unexplained infertility ranges from 6 to 30% [1, 8, 9, 11, 13], and this highly variable

S. C. Esteves (✉)
ANDROFERT, Andrology and Human Reproduction Clinic, Referral Center for Male Reproduction, Avenida Dr. Heitor Penteado, Campinas 1464, Sao Paulo, Brazil
e-mail: s.esteves@androfert.com.br

G. L. Schattman
Center for Reproductive Medicine, Weill Cornell Medical College, 1305 York Avenue, 10021 New York, NY, USA
e-mail: glschatt@med.cornell.edu

A. Agarwal
Center for Reproductive Medicine, Cleveland Clinic, 10681 Carnegie Avenue, Desk X-11, Cleveland, OH, 44195 USA
e-mail: agarwaa@ccf.org

G. L. Schattman et al. (eds.), *Unexplained Infertility*, DOI 10.1007/978-1-4939-2140-9_1,