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## OVARIAN HYPERSTIMULATION SYNDROME

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Ovarian Hyperstimulation Syndrome (OHSS) is a condition that can occur in women undergoing in vitro fertilization, after having follicle stimulating hormone (FSH) injections to stimulate egg growth and maturation. Some patients respond excessively to the drug and dose given. If large numbers of eggs mature, the high hormone levels coming out of the hyperstimulated ovaries, combined with the increased size of the ovaries, can cause extremely serious, and sometimes lethal, side effects. Moderate-to-severe OHSS requires admission to a hospital. Dr. Rizk is one of the world's top experts on managing OHSS.

This is the first published book dedicated to all aspects of OHSS. The pathophysiology, prevention and management of this syndrome have been revolutionized over the past decade, and it is important for reproductive practitioners and infertility specialists to understand the latest findings about this potentially deadly condition. The author reviews in depth the classification, epidemiology, pathophysiology, complications, and prediction, prevention and treatment options for OHSS. This book is intended for infertility specialists, reproductive medicine specialists and assisted reproduction specialists.

Botros R. M. B. Rizk is Professor and Chief, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology at the University of South Alabama School of Medicine. He is also Medical and Scientific Director of the University of South Alabama in vitro fertilization program.

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Botros R. M. B. Rizk

Frontmatter

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# OVARIAN HYPERSTIMULATION SYNDROME

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**Epidemiology, Pathophysiology, Prevention and Management**

BOTROS R. M. B. RIZK

*University of South Alabama*

*School of Medicine*



**CAMBRIDGE**  
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*This book is dedicated to my very dear and beloved parents, Dr. Isis Mahrous Rofail, my mother, and Mitry Botros Rizk, my father. Their unlimited true love, genuine sacrifice, care and support have filled my life with happiness, fulfilment and gratitude. Their memories, wisdom and thoughts will stay with us forever to guide us.*

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## FOREWORD

### A COMPLICATED COMPLICATION

The subject of this book continues to attract serious medical attention. Ovarian hyperstimulation was a problem from before the days of in vitro fertilization (IVF), when it was noted by an Israeli group among their patients being stimulated for ovulation induction. It also emerged when IVF created the need to apply ovarian stimulation to produce, say, 10 mature oocytes for fertilization in vitro. Today, the condition is well known and heavily researched as it spreads with every practising IVF centre, where there is a constant need to produce a medium number of follicles per patient. Unfortunately, as originally discovered in laboratory animals, there is a very weak correlation between the dose of gonadotrophins and the number of ovulated oocytes, indicating that unknown numbers of follicles may begin their growth and expansion. Numerous attempts have been made to introduce useful therapies for this condition, and these are effective to varying degrees of efficiency.

Botros (Peter) Rizk is highly talented and presents a text that is well balanced between the description of OHSS, its causes and effects, and means of controlling its very serious complications. His own opinions come through very clearly and will help professionals involved in assisted reproduction to keep up-to-date with current therapies. Available therapies are assessed in detail, which is certain to be of help to many clinicians. He gives his own clear opinions on the risks and the means of prevention. Since he writes simply and informatively, it is a pleasure to read the various sections of this book. The clear layout, good illustrations and numerous references in the book should help to clarify the causes of this condition. Every point made in the book has several associated references, providing clear pointers to further reading. The numerous illustrations help to carry the reader through this exhaustive evaluation of the causes of and, hopefully, cures for OHSS. Overall, the text is so clear and authoritative that attention must be given in this Foreword to the aspects of ovarian hyperstimulation covered.

Successive chapters cover the classification of the syndrome, its epidemiology, pathophysiology and genetics. These are followed by chapters on the complications of hyperstimulation, its prediction and patient education to help with this disorder. The book is completed with chapters on the prevention and treatment of hyperstimulation. The layout is very simple and attractive, such as in the opening classification where the objectives of classification are considered, including a description of its first classification

by Rabau et al. in 1967, followed by successive modifications (e.g. the division of its symptoms into mild, moderate and severe as successive investigators modified the original protocol), until workers today go into such detail as suspecting hypothyroidism or FSH receptors may be involved. Discussing the epidemiology of ovarian hyperstimulation, the author stresses the effects of IVF on our understanding of ovarian hyperstimulation, the need for milder treatments, the relationships with polycystic ovarian disease and the roles of hyperinsulinism. The accompanying endocrine revolution led to the introduction of human menopausal gonadotrophin (hMG) and then recombinant preparations of gonadotrophins and the introduction of GnRH, its agonists and antagonists. The complex problems of the short luteal phase in relation to the use of ovarian stimulation in cyclic women is discussed in detail and assessed for spontaneous and recurrent situations.

Extensive attention is naturally paid to the pathophysiology of hyperstimulation and its associated massive ovarian enlargement and circulatory disorders. These highly serious conditions have, fortunately, attracted the attention of many investigators who have steadily characterized their successive stages. A glance at the work of Van Beaumont in 1872 introduces the problems of osmoregulation, capillary permeability, the roles of various steroids and the ovarian renin–angiotensin system. This section also stresses the genetic nature of OHSS, with references to the actions of prostaglandins, Von Willebrand factor and of vascular endothelial growth factor (VEGF) as an agent affecting capillary permeability. Its actions in follicular fluid are presented in detail and in relation to the ratio between total and free VEGF. Analyses of the roles of interleukins, selectins and intercellular adhesion molecule (ICAM) follow in succession.

Not surprisingly, the genetics of OHSS occupies the succeeding chapter, opening with descriptions of recent work on the follicle stimulating hormone (FSH) receptor, its mutations and the origin of spontaneous OHSS. Extensive detail is considered in this and the previous chapter, as the slow but certain clarification of the background genetics is assessed. Reaching the molecular level is certain to open new leads, such as the higher sensitivity to human chorionic gonadotrophin (hCG) to specific forms of the FSH receptor mutants. This polymorphic system may determine the severity of many systems reliant on FSH activity and the threshold effects of the various mutants.

The complications of OHSS also attract, quite correctly, the detailed attention of the author. Fatalities are very rare, yet nevertheless have attracted considerable attention ever since the first case was described by Lunenfeld and his colleagues. Cerebrovascular complications include thromboembolic complications and hypercoagulable states, and their early and later effects are assessed. The detailed discussion of these states and their related effects leads to a most authoritative analysis by the author. Family histories, rare vascular complications, myocardial infarction and respiratory complications are all described. The details of these complications are so numerous as to demand a close reading of this chapter. Predicting OHSS is not easy, and is considered in

Chapter VI. Classical approaches involve estrogen assays, yet their value is still questioned today despite exhaustive studies. The author discusses the value of assessing the rising levels of VEGF from granulosa cells and in blood. Assays for Von Willebrand factor, especially near the time of implantation, and for inhibin are mentioned, together with the use of ultrasound for scoring the sizes of the numerous follicles, measuring ovarian volume and low intravascular ovarian resistance. Risk factors include rapidly rising plasma oestrogen levels and young women with polycystic ovaries with excessive follicular response, especially soon after the hCG injection (early OHSS).

The author clarifies the risks to patient health and provides help to increase awareness of this distressing disorder. ‘Ten Commandments’ for preventing OHSS initiate Chapter VII, and these are soon doubled. The first set includes the use of low doses of stimulatory gonadotrophins, and ovarian diathermy prior to stimulation. The second list proposes delaying hCG, avoiding it by using GnRH to induce ovulation and progesterone for luteal phase support. Risks of polycystic ovary syndrome (PCOS), the use of metformin and weight reduction are essential reading, although the consequences of changing gonadotrophin levels have always been somewhat unpredictable, while results with metformin, aromatase inhibitors, pentoxifylline and other formulations require much more analysis. Ovarian drilling and the use of GnRH antagonists are discussed at some length, although more data are clearly needed. Likewise, by using natural cycle IVF, single-embryo transfer may help, although the author concludes that no single protocol has yet proved effective.

Adjusting the effects of ovarian stimulation by “coasting” HCG has been in use for many years now, and the author gives much space to its practice. Summarizing numerous reports, he concludes there is still a paucity of randomized trials, and that coasting risks decreases in oocyte numbers and pregnancy rates. Using GnRH antagonists, and recombinant luteinizing hormone (rLH) does not lead to firm conclusions, although rLH may offer the best alternative. Injecting albumin or starch are of doubtful value, and reducing follicle numbers, or cryopreserving oocytes for a later cycle seem to offer little. The author suggests a combined approach is best, involving decreasing gonadotrophins, coasting, reducing HCG levels to induce ovulation, and giving progesterone for luteal support.

The final chapter deals with treatments for OHSS. This has attracted detailed attention and the author recommends thorough check-up and follow-up. Moderate forms may be treated on an outpatient basis, with ultrasound, blood counts, liver function and coagulation monitoring, and perhaps too with rehydration, culdocentesis and albumin injections. Severe forms involve aspirating ascitic fluid, giving intravenous fluids, hydration, paracentesis, liver function tests, investigating respiratory compromise, anticoagulants to preserve renal function, and also treating many other symptoms. Ascitic fluid and pleural effusions may be aspirated, many clinicians considering this a matter of priority. Abdominal paracentesis has been questioned but is now regarded as essential. The author covers the basics of these studies and concludes by describing novel forms of blocking VEGFR-2.

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This book has several very attractive advantages. It is well written and maintains a momentum that carries the reader with the text. It is clearly authoritative and written by a clinician with considerable experience. The detailed references set the scene for further reading, give credit to workers in the field and display the immense amounts of effort put into hyperstimulation research. It will be a very handy tome on a clinician's bookshelf, and should also attract the attention of non-clinical scientists and researchers and those practising IVF. And in the future, it could be updated fairly quickly as the saga of ovarian hyperstimulation enters new fields of scientific awareness.

*Professor Robert G. Edwards, C.B.E., Ph.D., D.Sc., F.R.C.O.G., F.R.S.  
Emeritus Professor, Cambridge University, Cambridge, England  
Editor-in-Chief, Reproductive Biomedicine Online*

## PREFACE

Ovarian hyperstimulation syndrome (OHSS) presents a unique challenge in the practice of medicine in general and reproductive medicine in particular. There is no other situation where a “healthy” patient seeks medical assistance and may end up with serious medical complications. About 20 years ago, when I was working at Northwick Park Hospital in London, UK, a young patient presented to the emergency department a few days after a Gamete Intra-Fallopian Transfer (GIFT) procedure with severe OHSS, shortly followed by stroke. Amazingly, she completely recovered and delivered a healthy girl. The acute developments in this patient had an extraordinary effect on me, and since then I have dedicated a significant part of my career to this iatrogenic complication.

Worldwide, more than 500 000 in vitro fertilization (IVF) cycles are performed every year, and five to six times this number of superovulation cycles are performed. Therefore, severe OHSS will be encountered in small numbers by individual centers, although large numbers of cases will occur worldwide. This has led to lack of expertise in dealing with the myriad of complications of OHSS, especially because of their multisystem effects. Furthermore, the emphasis has been on how to maximize the success of IVF. This emphasis should shift to how to maximize its safety, and this is the ultimate goal of this book.

Writing this book, I was driven by a desire to provide a clinical guide that will help those practicing in the field of assisted reproduction and infertility. Both clinicians and scientists were in my mind. The infertility specialist will find the book a resource on how to evaluate patients before starting fertility treatment, with keen attention on to how to avoid the development of OHSS by a series of well-chosen decisions. The success of this book should be judged by a decline in the incidence and severity of OHSS seen in IVF centers and by infertility specialists. The scientist reading this book will immediately realize that recent discoveries in receptor mutations emphasize that only systematic scientific research can provide real understanding of the pathophysiology of OHSS and the potential for change. I hope this book boosts their enthusiasm to make further discoveries. The IVF nurse coordinator who is directly involved in ovarian stimulation will find this book helps her understand what is going through the minds of the IVF team during the cycle, and so helps her to serve her patients better.

The structure of the book is simple, with eight chapters covering all important areas. It was essential to start with classification in Chapter I – categorizing patients makes it possible to decide who can be treated as an outpatient and who needs to be admitted to hospital or intensive care. Chapter II on epidemiology emphasizes which groups of patients are at risk, taking into consideration patient characteristics and treatment protocols. The call to establish an international registry should be a priority of the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology. The pathophysiology of OHSS is where all the recent research developments have occurred, and in Chapters III and IV in-depth discussion of the molecular biology research over the last decade complements our understanding. These developments should stimulate basic science researchers to advance our knowledge not only of hyperstimulation but also of routine ovulation induction. In Chapter V the detailed discussion of the complications of OHSS should prepare clinicians for difficulties they may encounter. Prediction, prevention and treatment are covered in the final three chapters. There has been an extraordinary effort to prevent OHSS. Eventually, this should mean that we all have extensive experience of prevention and less experience of treatment. Chapter VIII focuses on outpatient and inpatient treatment, as well as intensive care and novel medical therapies that we may see in the next few years.

The work presented in this book has been the result of tremendous research and contributions from clinicians and scientists all over the world. The fight against OHSS has been global, with important contributions from Europe, the USA and the Middle East. While early work is quoted in detail in this book, the recent advances in the last five years are emphasized. The wonderful stimulation, leadership and guidance provided by Bob Edwards has been extraordinary and could have never been replaced. I have also greatly enjoyed my extensive collaboration over the last two decades with Dr. Johan Smits from Belgium, Dr. Mohamed Aboulghar from Egypt, and Dr. Melanie Davies, Dr. Charles Kingsland and Dr. Sam Abdalla from the UK. I would also like to thank Dr. Bridgett Mason and Professor Howard Jacobs from London and Professor Steve Smith from Cambridge for the magnificent opportunities they gave me in those two great cities in the UK. Working with skilled clinicians, such as Dr. Dudley Mathews from Kent and Dr. Roger Martin and Simon Crocker from Norwich provided great enjoyment. I thank Miss Julie Hazelton for her dedication and assistance in typing the manuscript of this book. I believe that our collaboration with investigators from Spain, Greece and Italy will open the way to more innovations. I have tried my best to present impartially the evidence on every issue that is open for debate, while making my personal views clear. I hope that clinicians will identify much useful experience, and that scientists will maintain their eagerness for research that will enlighten our understanding; and ultimately that our patients will benefit from all our efforts.

*Botros Rizk, M.D., M.A., F.R.C.O.G., F.R.C.S.(C.), H.C.L.D., F.A.C.O.G., F.A.C.S.  
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