

Human Semen Analysis

From the WHO Manual
to the Clinical Management
of Infertile Men

Ashok Agarwal
Florence Boitrelle
Ramadan Saleh
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Editors



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ISBN 978-3-031-55336-3 ISBN 978-3-031-55337-0 (eBook)
<https://doi.org/10.1007/978-3-031-55337-0>

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In memory of my father, Professor RC Aggarwal, whose legacy of integrity, dedication, and hard work remains a guiding light. To my wife, Meenu, and sons, Rishi and Neil-Yogi, whose unwavering love sustains me. Gratitude to Professor Kevin Loughlin (Harvard Medical School), the late Professor Anthony Thomas (Cleveland Clinic), and Dr. Rupin Shah (India) for their invaluable friendship, guidance, and profound impact on my journey. To over thousand researchers, students, and the countless patients who entrusted me over four decades—your collaboration and trust have been my greatest inspiration.

*—Ashok Agarwal, MSc, PhD, HCLD
(Andrology)*

The idea for this book was born a few years ago. While the WHO manual is part of our day-to-day work as andrologists, we felt it was important to understand it better in order to use it more effectively. To improve international research in Andrology, Prof. Agarwal created the

Global Andrology Forum. For me, becoming a member of this group has enabled me to get to know andrologists who are passionate about their profession, whether they live in France, Europe, or the rest of the world. I would like to thank him warmly for inviting me to edit this book with him. Dear Ashok, dear co-editors (Rupin and Ramadan), thank you for this wonderful adventure.

—Florence Boitrelle (MD, PhD, France)

To my family for your constant love and support. You have always been there for me.

To Professor Ashok Agarwal (Global Andrology Forum, USA) for your guidance and support. Thank you for believing in my dream. You were the first person to encourage me to be part of this achievement.

To the late Professor Kamal Abdel Hafez (Assiut University, Egypt) for his mentorship and guidance.

—Ramadan Saleh, MD

This book is dedicated to my wife Urvashi, for her patient understanding; to my patients, who have been my true teachers; to my co-editors, Florence and Ramadan, who have been wonderful partners in this journey; and to Ashok Agarwal, who made this book possible and has been a great friend and inspiration in my academic journey.

—Rupin Shah

Foreword

This is much more than a reference book. Many experts have collaborated to explain why such a fundamental biological test (semen analysis) fails to define the most important of human conditions—fertility.

Previous editions of the WHO manual sought to define reference limits, but the sixth edition describes a continuum of parameters which, at the extremes, predict either a fertile or an infertile state. Once reference values have been removed, semen analysis can no longer be used as a gateway to some kind of artificial reproductive technology (ART) because abnormalities require explanation by further tests and most significantly, as nearly every chapter states, by clinical examination and scrutiny.

Male fertility has moved from a largely laboratory-based definition to the more traditional realm of clinical input and further clinically directed tests. Diagnosis therefore replaces diktat, and proper treatment with measured improvement replaces the former solution, which was so often some form of ART.

Overall, this excellent commentary has recalibrated the status of male infertility, which can now be regarded as a disease, a major health issue, with many associations with significant other medical conditions.

Considering that repeated studies have shown that standard semen analysis, according to WHO guidelines, is very limited in predicting male fertility potential, and leaves a large proportion of men either undiagnosed or not correctly diagnosed, situations which lead to inappropriate treatment. Therefore, by elegantly combining clinical aspects and future developments, clinicians and researchers are provided with directions for further developments in how andrological diagnostics will improve in the years to come.

This book highlights the implementation of artificial intelligence (AI) into automated CASA systems to improve the determination of sperm count, motility, and normal morphology to make semen analysis faster, more accurate, and reliable. Other areas of research include the better understanding and determination of redox stress and sperm DNA fragmentation with robust clinical cut-off values since these fields have recently been recognized by the WHO as important and recommended for advanced examination. The book also underscores the importance of genetic screening for sperm aneuploidy as many aspects of male infertility have genetic causes.

This book explains why, and how, semen analysis is merely the first step in a diagnostic journey which may lead us to understand the basis of disordered spermatogenesis.

Eventually, all these research efforts must lead not only to a better understanding of male fertility with better diagnostic and treatment, and improved pregnancy rates in vitro and in vivo, but also to novel methodologies for male contraception. In this sense, this book will also lead the way to change the perception by recognizing the man as a patient who should be treated, rather than his sperm.

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Preface

The *WHO laboratory manual for the examination and processing of human semen* is the most widely referenced document in the evaluation of male infertility. It provides a detailed description of a variety of semen tests that are considered relevant to the evaluation and management of an infertile male. However, its clinical utility is severely limited by the fact that it is, indeed, as its name suggests, a laboratory manual and does not provide a clinical context for the various tests described.

Hence, the clinician is left with a range of tests to prescribe but with no guidance as to when to ask for a specific test, how to interpret the test results, and what subsequent clinical action to take. As a result, many of the tests described in the manual, especially the extended and advanced tests, remain underutilized, and even the interpretation of some components of the basic semen analysis is unclear.

The purpose of this book is to bridge this gap between the laboratory manual and the clinician by explaining in detail the test indication, its clinical utility, interpretation of results, and presenting a decision algorithm based on the test results. Even the cost-effectiveness and future perspectives of the tests are discussed where relevant.

The book has 19 chapters grouped under seven parts that follow the chapters of the sixth edition of the WHO manual. Each chapter is written and reviewed by a team of senior clinicians, thus bringing a perspective that is truly clinically relevant. This book will be of great value to all clinicians involved in the management of male infertility and will also be of interest to laboratory scientists involved in semen testing by providing them with clinical perspectives of the test they perform.

Our book is poised to become an indispensable guide for clinicians, medical laboratory technologists, scientists, embryologists, researchers, and healthcare professionals dedicated to the care of infertile couples. It also stands as a valuable resource for students and residents eager to deepen their understanding of this critical subject, making it a significant addition to the realm of male infertility literature.

A heartfelt appreciation goes out to the impressive collaboration of experts—35 authors from 20 countries—who have dedicated their efforts to provide the latest, well-written, and meticulously researched manuscripts. Without their unwavering support, this book would not have been possible. Special thanks are extended to the organizational prowess of Lillie Mae Gaurano, Springer Editor, Clinical Medicine (Books), and the day-to-day support of Production Editor Janakiraman G.

In honor of our families, mentors, and patients, this book is a dedication to those who inspire and motivate us in the pursuit of advancing knowledge in the field of male infertility.

Moreland Hills, OH, USA
Poissy, France
Sohag, Egypt
Mumbai, India

Ashok Agarwal
Florence Boitrelle
Ramadan Saleh
Rupin Shah

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About the Editors



Ashok Agarwal is a highly regarded andrologist and researcher who has made significant contributions to the field of male infertility. As the founder and current President of the Global Andrology Forum (GAF) headquartered in Moreland Hills, Ohio, he leads an international coalition of 700 members from 84 countries, tirelessly propelling the advancements in male reproductive health. For nearly three decades (1993–2022), Ashok served as the Director of the Andrology Laboratory and Research in Urology at Cleveland Clinic, concurrently holding the position of Professor of Surgery at Case Western Reserve University, Cleveland. His prolific contributions encompass over 950 scientific articles and the editing of 55 medical textbooks, earning him numerous accolades in andrology and male infertility research. Beyond his groundbreaking research and clinical expertise, Ashok’s dedication extends to education and mentorship. He has shared his knowledge with over 1000 clinicians and scientists from 65+ countries, shaping the future of andrology. Recognized as a foremost authority in male infertility research, Ashok has been a featured speaker at countless national and international conferences, showcasing his leadership in the global dialogue on male reproductive health.



Florence Boitrelle is a doctor specializing in andrology and assisted reproduction. She is head of department, head of a MPA center, former president of the Société d'Andrologie de langue Française, and a member of various learned societies in France and internationally (ESHRE, Global Andrology Forum...). Passionate about clinical andrology and research, she is the author of over 100 articles referenced in Pubmed and has participated in over 80 communications in France and abroad.



Ramadan Saleh is a Professor of Dermatology, Venereology and Andrology, in Sohag University, Egypt. He is the founder of Ajyal IVF Center, Ajyal Hospital, Sohag, Egypt. He is a co-founder of Global Andrology Forum established in December 2021. He is a member of several professional societies and a reviewer in many international journals in the field of reproductive medicine. He has published more than 150 research articles in peer-reviewed scientific journals and co-edited three books.



Rupin Shah is a senior uro-andrologist practicing male infertility and sexual dysfunction in Mumbai at the Lilavati Hospital & Research Centre. He is Founder-President of the South Asian Society of Sexual Medicine, Chairman of the Post-Doctoral Fellowship in Andrology of the National Board of Examinations of India, Co-Chair of the International Consultation on Sexual Medicine-2024, Associate Editor of the journal *Fertility and Reproduction*, and Senior advisor to the Global Andrology Forum.