Recurrent Pregnancy Loss: Causes, Controversies, and Treatment

Editor: Howard J.A. Carp

The publication of the third edition of this book shows the progress made in the clinical and scientific approaches to managing recurrent pregnancy loss (RPL). This book, first published in 2007, and the second edition of 2014, became the leading and most comprehensive work on RPL. An unusual feature of the previous editions was the inclusion of debates on controversial issues argued by leading authorities. Fortunately, a consensus has been reached on most of the former debates. In the third edition, there are only two debates: on the use of progestogens and pre-gestational testing. Both issues are highly controversial. The controversies are fully discussed and often help the reader decide which line of management to take in different patients.

The third edition is divided into five sections:

Section 1 reviews the basic principles. It is interesting that the editor has introduced a chapter on "Personalised vs. evidence based medicine". In this chapter, the author argues very convincingly that treating RPL as one homogeneous whole and using a trial to determine effect in a large number of patients, while still considered by many to be the gold standard, may be passé and should be replaced by a paradigm based on accurate diagnosis. The personalized approach is now possible as accurate diagnosis can be achieved, when the abortus is subjected to accurate genetic diagnosis using molecular techniques. In addition, the conclusions of negative trials are questioned, as positive results may be obtained when trials are restricted to appropriate patients.

Section 2 examines the etiology of RPL. The major advances in genetics, immunology, endocrinology, and thrombotic mechanisms are described in depth. There are new chapters on the role of the endometrium in RPL and immune testing. The chapter on the male factor has been completely rewritten to stress the new developments. There is also a new chapter on fetal anomalies, which integrates genetic and embryoscopic diagnoses and the implications for genetic counseling. The chapter contains important insights and shows the multi-disciplinary approach in action.

Section 3 discusses the developing pregnancy, including ultrasound follow-up, threatened miscarriage complicating early pregnancy, and screening to avoid anomalies in an RPL population.

Section 4 assesses clinical management. Again different patients are described, with an approach not to be "over aggressive" in good prognosis patients and not to use "masterly inactivity", in poor prognosis patients. The roles of progestogens, hCG, anticoagulants, empirical in vitro fertilization, pregestational testing and third party reproduction are fully featured.

As in many clinical situations, there are guidelines from professional organizations regarding appropriate management. The discrepancies between the different guidelines leave the clinician in a quandary as to the optimal management. The editor has contrasted the guidelines from three organizations: the Royal College of Obstetricians and Gynaecologists, the American Society of Reproductive Medicine, and the European Society of Human Reproduction and Embryology. Today, the International Federation of Gynecology and Obstetrics (FIGO) is preparing guidelines and the Israel Fertility Association has approved Israel guidelines. In view of the different recommendations in the various professional guidelines, it is reassuring to have the benefit of the author’s vast experience when treating patients.

Section 5 includes a section on immunotherapy. Immunotherapy has always been controversial, and the ongoing debate is discussed. The reader is asked whether immunotherapy requires reassessment in the 2020s.

The 3rd edition of Recurrent Pregnancy Loss: Causes, Controversies, and Treatment, like the past editions, is in-
tended for general gynecologists and specialists working in the field. The editor, Howard J.A. Carp, has assembled an impressive list of contributors from Israel, the United States, United Kingdom, Canada, Greece, Belgium, India, and Italy. Each contributing author is an authority on a specific area of recurrent pregnancy loss. Their views summarize years of research in their own fields and make compelling reading. This reference book is highly recommended.

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**Capsule**

**SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies**

The coronavirus disease-2019 (COVID-19) pandemic presents an urgent health crisis. Human neutralizing antibodies that target the host ACE2 receptor-binding domain (RBD) of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike protein show promise therapeutically and are being evaluated clinically. To identify the structural correlates of SARS-CoV-2 neutralization, Barnes and colleagues solved eight new structures of distinct COVID-19 human neutralizing antibodies in complex with the SARS-CoV-2 spike trimer or RBD. Structural comparisons allowed us to classify the antibodies into categories: (1) neutralizing antibodies encoded by the VH3-53 gene segment with short CDRH3 loops that block ACE2 and bind only to ‘up’ RBDs; (2) ACE2-blocking neutralizing antibodies that bind both up and ‘down’ RBDs and can contact adjacent RBDs; (3) neutralizing antibodies that bind outside the ACE2 site and recognize both up and down RBDs; and (4) previously described antibodies that do not block ACE2 and bind only to up RBDs. Class 2 contained four neutralizing antibodies with epitopes that bridged RBDs, including a VH3-53 antibody that used a long CDRH3 with a hydrophobic tip to bridge between adjacent down RBDs, thereby locking the spike into a closed conformation. Epitope and paratope mapping revealed few interactions with host-derived N-glycans and minor contributions of antibody somatic hypermutations to epitope contacts. Affinity measurements and mapping of naturally occurring and in vitro-selected spike mutants in 3D provided insight into the potential for SARS-CoV-2 to escape from antibodies elicited during infection or delivered therapeutically. These classifications and structural analyses provide rules for assigning current and future human RBD-targeting antibodies into classes, evaluating avidity effects and suggesting combinations for clinical use, and provide insight into immune responses against SARS-CoV-2.

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**Capsule**

**SARS-CoV-2-derived peptides define heterologous and COVID-19-induced T cell recognition**

T cell immunity is central for the control of viral infections. To characterize T cell immunity, but also for the development of vaccines, identification of exact viral T cell epitopes is fundamental. Nelde and colleagues identified and characterized multiple dominant and subdominant SARS-CoV-2 HLA class I and HLA-DR peptides as potential T cell epitopes in COVID-19 convalescent and unexposed individuals. SARS-CoV-2-specific peptides enabled detection of post-infectious T cell immunity, even in seronegative convalescent individuals. Cross-reactive SARS-CoV-2 peptides revealed pre-existing T cell responses in 81% of unexposed individuals and validated similarity with common cold coronaviruses, providing a functional basis for heterologous immunity in SARS-CoV-2 infection. Diversity of SARS-CoV-2 T cell responses was associated with mild symptoms of COVID-19, providing evidence that immunity requires recognition of multiple epitopes. Together, the proposed SARS-CoV-2 T cell epitopes enable identification of heterologous and post-infectious T cell immunity and facilitate development of diagnostic, preventive and therapeutic measures for COVID-19.

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