

Recurrent Pregnancy Loss: Causes, Controversies and Treatment

Editor: Howard Carp

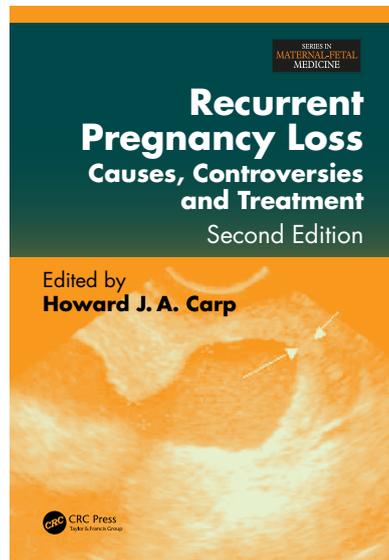
2nd Edition, CRC Press, 2014, London, £99

IMAJ 2015; 17: 461–2

This book, first published in 2007, became the foremost and most comprehensive work on recurrent pregnancy loss (RPL). An unusual feature of the book was the inclusion of debates on controversial issues argued by experts in their respective fields. The second edition has the same feature, the controversial issues being immunotherapy, fetal karyotyping, use of anticoagulants etc., which are debated in depth. The hot topic regarding the use of pregestational screening (PGS) in recurrent miscarriage is passionately debated by the two leading authorities in the field, Carlos Simon and Marriette Goddijn. This debate provides the reader with firm evidence on the efficacy of the treatment. Moreover, the second edition shows that fetal structural malformations and chromosomal aberrations may confound the results of maternal therapy such as immunotherapy, hormone supplementation, etc.

There are chapters devoted to the various causes of RPL. The chapter on Genetics, written by Joe Leigh Simpson, discusses the new information available from molecular genetic techniques – not available with the older karyotyping and FISH techniques – which may explain miscarriage. There is also information suggesting that second-trimester abortions may also have a genetic basis which, although less common than in first-trimester miscarriages, was not previously recognized. The issue of parental karyotypic inversions, translocations and their effect on subsequent pregnancies is described, showing accurate prognoses that are possible today due to genetic counseling.

In the antiphospholipid syndrome (APS), which is known to lead to pregnancy loss, new concepts have emerged regarding its etiology. The primary concept to-day is that of an autoimmune reaction to an infective agent due to molecular mim-



icry. The most common infective agents serving as the trigger include parvovirus B19, cytomegalovirus, hepatitis C virus, toxoplasma, rubella, varicella, human immunodeficiency virus, streptococcal and staphylococcal infections, gram-negative bacteria, *Mycoplasma pneumoniae*, urinary tract infection and *Helicobacter pylori*. The section on APS continues with information regarding which antibodies are relevant. In addition to lupus anticoagulant, β 2-glycoprotein-1 and anticardiolipin antibody, other antibodies such as antiphosphatidyl serine and antiphosphatidyl ethanolamine may be more relevant in pregnancy loss. Antiphospholipid syndrome is an autoimmune condition affecting almost all organ systems in the body. One of its manifestations is pregnancy loss. In 1999, the American Society of Reproductive Immunology defined a broad clinical entity: reproductive autoimmune syndrome (RAS). The different features of APS and RAS are clearly defined, which is useful for physicians treating pregnancy loss.

Immunotherapy for RPL has been extremely controversial, and the debate continues. This edition of the book contains a new chapter describing immunotherapy with granulocyte colony-stimulating factor (G-CSF). The authors report on their pilot study and a randomized controlled study assessing women with RPL and losses of a eukaryotypic embryo. The results of 35 women who received recombinant G-CSF until nine weeks gestation were compared to 33 controls treated with saline. The rate of live births in women treated with G-CSF was 82.8%, as compared to 48.5% in the controls ($P = 0.0061$). The opposing debate concludes that there is insufficient evidence for recommending this treatment and that further trials are required since there have been no confirmatory trials.

The new chapter on the male factor in recurrent miscarriage, by Richard Bronson of New York, casts a new light on a subject that has scarcely been touched in the medical literature. The chapter summarizes the subject of sperm aneuploidy, microdeletions, and the difficulties in diagnosis. Additionally, evidence for the epigenetics of abnormal sperm DNA methylation is discussed, with strong data demonstrating that hypermethylation may block the access of DNA polymerase and inhibit gene expression. There is a fascinating section on sperm RNA. Sperm RNA was previously assumed to be degraded leftovers following expulsion of the residual body during spermiogenesis. Newer evidence, however, indicates that sperm retain specific coding and non-coding RNAs and serve a potential functional role after fertilization. Of note, miR-34c is essential to early embryo development, being required for the first cellular division. Some non-coding RNAs may also act as epigenetic modifiers, inducing histone modifications and DNA methylation.

Disagreements concerning the guidelines of the Royal College of Obstetricians, the American Society of Reproductive Medicine, and ESHRE are contrasted and discussed. It is interesting that the three leading sets of guidelines differ in their recommendations. The disagreements, however, are confusing for the clinician who would like a clear set of rules for treating the patient. However, the differences in the various guidelines show that guidelines are only recommendations and not a set of instructions to be followed in all circumstances.

Many other topics appear in the second edition, such as autoimmunity and recurrent pregnancy loss, third-party reproduction, and Chinese medicine. Alternative medicine is not usually discussed in a conventional medical book, and it is fascinating to recognize that some of the traditional Chinese classifications are not so different from current Western classifications.

The book also offers many practical clinical points from the editor's vast experience, including protocols of investigation and the different prognoses for different

groups of patients. There are also case descriptions illustrating the wide clinical presentations and different management strategies for different patients. This book is intended for general gynecologists and specialists. It will be most useful and may be essential reading for any physician counseling or treating women with recurrent pregnancy loss.

Yehuda Shoenfeld MD FRCP MaACR

Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Israel