Recurrent Pregnancy Loss: Causes, Controversies and Treatment

Editor: Howard Carp

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 Godijn. 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 mimicry. 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, β2-glycoprotein-1 and antipcardiolipin 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.

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**Capsule**

**Finding better immunosuppressants**

The immunosuppressant cyclosporin A (CsA) prevents organ rejection in transplant patients. CsA inhibits the phosphatase calcineurin and prevents the activation of the NFAT transcription factors, both of which are required for T cell proliferation. However, CsA also prevents calcineurin from binding to other targets, leading to many side effects. Matsoukas and team identified compounds that displaced NFAT from calcineurin-NFAT complexes without inhibiting the activity of the phosphatase. Four of these compounds blocked the expression of NFAT target genes and inhibited the proliferation of human CD4+ T cells, and may be good leads for further testing as immunosuppressants.

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Eitan Israeli

**Capsule**

**How bladder cells kick out unwelcome intruders**

The bladder epithelium acts as the front line of the urinary defense system against microbial infection. Miao and co-authors examined urine samples from humans and mice and the extracellular medium of cultured bladder epithelial cells after infection by uropathogenic *Escherichia coli*. Remarkably, they found numerous viable bacteria encased in host-derived membrane-bound vesicles. Intracellular bacteria were initially taken up by autophagosomes and targeted to lysosomes. The bacteria raised the normally low lysosomal pH, which might be expected to protect them from lysosomal degradation. However, the bladder cells sensed the neutralized lysosomes and exocytosed them, expelling the membrane-encased bacteria. The bacteria were thus incapable of reinfection, and the bladder cells defended against their unwelcome visitors.

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Eitan Israeli

**Capsule**

**Calming the cytokine storm**

The innate immune response is poised to act quickly in the face of pathogenic invaders. However, this priming can incite a cytokine storm: excessive production of inflammatory cytokines that harm the host. Coon et al. report that HECTD2, a ubiquitin E3 ligase, can degrade the anti-inflammatory protein PIAS1, enhancing this inflammatory effect. People with a polymorphism in the *HECTD2* gene exhibit lower inflammation and are protected from acute respiratory distress syndrome. Moreover, a small-molecule inhibitor of HECTD2 reduced lung inflammation in mice. These observations pinpoint HECTD2 as a therapeutic target for inflammation-induced lung injury.

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