Symposium: Embryo implantation failure and recurrent miscarriage

Guest Editors: Luciano G Nardo, Tin-Chiu Li, Robert G Edwards

Introduction: human embryo implantation failure and recurrent miscarriage: basic science and clinical practice

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There is increasing evidence that uterine natural killer (uNK) cells have a role in reproductive failure. Quenby and Farquharson discuss the origin and contribution of uNK cells in controlling trophoblast invasion. Increased numbers of CD16+CD56dim leukocytes have been associated with idiopathic recurrent miscarriage and repeated implantation failure. In previous studies, the authors have demonstrated that preconceptual treatment with prednisolone reduces the number of uNK cells and improve pregnancy outcome in women with recurrent early pregnancy loss. Immunomodulation of the preimplantation endometrium is not recommended at present. Couples with recurrent implantation failure after IVF should be made aware of the lack of evidence supporting the use of immunotherapy to improve pregnancy outcome.

Stern and Chamley detail the mechanisms and clinical associations between antiphospholipid antibodies (APA), prothrombotic disorders and adverse pregnancy outcome. Experimental animal models suggest that APA have a deleterious effect on preimplantation embryonic development and can cause fetal loss. APA can reduce the proliferation, invasion and syncytialization of trophoblast, and can negatively affect the transformation of the endometrium into the decidua. While some researchers report an increased prevalence of autoantibodies in infertile patients, the evidence with respect to unsuccessful IVF outcome is unclear. Treatment with aspirin and heparin may reduce early pregnancy loss but does not seem
to improve pregnancy rates in patients with implantation failure after IVF.

Findikli and colleagues comment on the association between chromosomal abnormalities and both repeated implantation failure and recurrent miscarriage. They also discuss the possible benefits of preimplantation genetic diagnosis for aneuploidy screening (PGD-AS) in such cases. Early reports have shown that assessment of the chromosomal pattern of cleavage day-3 embryos increases the chance of successful pregnancy. Recent studies show that PGD-AS improves IVF pregnancy outcome in young women, but not in women ≥40 years of age. Nevertheless more studies are required to define subgroups of patients who may benefit from this diagnostic and therapeutic approach. The role of PGD-AS in idiopathic recurrent miscarriage needs to be further investigated before this invasive and expensive technique can be routinely offered in clinical practice.

Nardo and Sallam review the literature about the use of progesterone supplementation to prevent recurrent miscarriage and to reduce implantation failure in ART cycles. Luteal phase defect has been recognized for a long time as a cause of inadequately developed endometrium and pregnancy failure. It is well established that progesterone down-regulates Th1 cytokines and stimulates Th2 cytokines, resulting in a shift towards humoral immunity. By modulating the immune activity at the endometrium level, progesterone therefore plays an important role in the establishment and maintenance of pregnancy. A recent meta-analysis showed that administration of progesterone in patients treated with human menopausal gonadotrophin improves significantly pregnancy rates.

A large body of evidence demonstrates that altered immunological function is central to the pathogenesis of endometriosis. Although it would be plausible to postulate an immunological link between this common gynaecological condition and both embryo implantation failure and recurrent miscarriage, conclusive data are lacking. As outlined by D’Hooghe and colleagues, most of the studies are retrospective, non-randomized and inadequately designed. In their article, the authors discuss thoroughly the immunomodulatory mechanisms that could explain the association between endometriosis and reproductive failure, and also summarize the findings from the available literature.

The new Italian law on assisted reproduction technology (number 40/2004), approved in February 2004, became far more than a contested argument about how the 21st century bioethical arguments should be legislated. The controversial clause of the law limits to three the number of oocytes to be fertilized in vitro and imposes that all resulting embryos must be transferred at one time. Fertility experts worldwide voiced concerns about the clinical consequences of the new fertility legislation. La Sala and colleagues compared pre- and post-law outcomes and found a significantly reduced rate of early pregnancy losses in the latter period. A lower number of embryos were transferred after the law. Possible influences of oocyte quality and selection are discussed. These preliminary data do not seem to support early concerns about the decreased IVF fertility outcome post-legislation.

Finally, Christiansen and colleagues give an overview of the different causes of repeated implantation failure after IVF and recurrent miscarriage. The authors discuss some of the future directions of research that may contribute to consolidate our understanding and establish new therapeutic strategies. It is emphasized that numerous questions related to genetics, endocrinology, thrombophilia and immunology in infertility and recurrent early pregnancy loss remain still unanswered. Despite the vast amount of research carried out in the last decade, our understanding of the mechanisms involved in repeated implantation failure after IVF and recurrent miscarriage remains somewhat limited. This symposium is timely because of the increasing clinical trends in prescribing unproven and costly therapies for women with poor fertility outcome. Further research exploring basic science and clinical aspects of reproductive failure has to be of high quality and without flaws.