



IMMUNOLOGICAL TESTING AND INTERVENTIONS FOR REPRODUCTIVE FAILURE

This is the second edition of this Opinion Paper, which was originally published in October 2003.

1. Background

The traditional immunological perspective of pregnancy is that the semi-allogeneic fetus will be rejected unless the mother's immune system is suppressed. To date, there is no convincing evidence that reproductive failure occurs as a result of immune rejection. Contemporary concepts in reproductive immunology now emphasise the cooperative nature of the interaction between the maternal immune system and the fetoplacental unit in governing pregnancy outcome.¹

An aberrant immune response – either auto- or alloimmune – has been postulated to underlie some cases of 'unexplained' infertility, *in vitro* fertilisation (IVF) failure and recurrent miscarriage. Despite a paucity of evidence, a variety of immune tests and treatments for reproductive failure have been introduced into clinical practice.

2. Immune tests

2.1 Natural killer cell testing

Natural killer (NK) cells are lymphocytes which are part of the innate immune system. NK cells are found in both peripheral blood (PBNK) and the uterine mucosa (uNK), where they promote trophoblast invasion and angiogenesis. There are important phenotypic and functional differences between NK cells present at the two sites.^{2,3} Hence, measurement of PBNK cell numbers or activity as a surrogate marker of events at the maternal–fetal interface is inappropriate. PBNK cell levels and activation are subject to a number of variables including the time of day a sample is taken and parity of the mother. There is no agreement on what is a raised PBNK cell level. While several small observational studies have reported an association between PBNK cell numbers and/or activity and IVF outcome, a recent large UK study reported PBNK cell levels in predicting IVF cycle outcome to be 'little better than tossing a coin'.⁴

Several studies have reported that women with recurrent miscarriage have a raised uNK cell number in a preconception cycle and that these levels may be decreased with prednisolone.⁵ While a small study ($n = 16$) reported a raised uNK cell level to be associated with future pregnancy loss, a larger study ($n = 51$) reported no such association.⁶ This discordance may be attributed in part to the difficulty in accurately quantifying uNK cell numbers which vary throughout the secretory phase of the menstrual cycle and in different endometrial compartments. An association between uNK cell number and function has not been demonstrated.

2.2 Autoantibody screening

Antiphospholipid antibodies (aPL) are a family of approximately 20 antibodies directed against phospholipid-binding plasma proteins. Two members of this family, lupus anticoagulant (LA) and anticardiolipin antibodies (aCL), are an important treatable cause of recurrent miscarriage.⁷ The prevalence of these two antibodies is increased among those with infertility and implantation failure following IVF embryo transfer. However, a meta-analysis reports no relationship between LA and aCL status and implantation or clinical pregnancy rate among those undergoing IVF.⁸ In respect to IVF treatment, other aPL family members (in particular, antiphosphotidyl ethanolamine and serine) may be of more relevance than LA and aCL. The relationship between other autoantibodies (such as nuclear, thyroid, ovarian, sperm) and reproductive failure is unproven.

2.3 Alloimmune testing

It has been suggested that increased sharing of human leucocyte antigen (HLA) between partners can lead to failure of the woman to mount a protective immune response leading to miscarriage. The arguments against this theory have been well rehearsed.⁹ In essence, there is no increased HLA sharing between partners with recurrent miscarriage; production of the putative 'blocking' antibody occurs after 28 weeks of gestation and successful pregnancies can occur despite failure of production of the 'blocking' antibody.

3. Immune treatments

Few randomised placebo-controlled studies have addressed the efficacy of immune interventions in the treatment of reproductive failure. Meta-analyses have reported that (a) aspirin in combination with heparin significantly increases the livebirth rate among those with antiphospholipid syndrome;¹⁰ (b) the routine use of periimplantation glucocorticoids does not increase the live birth rate among those undergoing IVF;¹¹ (c) white cell immunisation does not increase the livebirth rate among those with recurrent miscarriage;⁹ and (d) intravenous immunoglobulin (IVIG) does not improve the livebirth rate among those with unexplained recurrent miscarriage.¹² In addition to a short-term increased risk of infection, there are no published data on the use of anti-tumour necrosis factor (TNF) agents such as infliximab and etanercept to improve IVF outcome. Certain immune therapies can have significant adverse effects. Anti-TNF-alpha agents are associated with the development of granulomatous disease, lymphoma and demyelinating disease and intravenous immunoglobulin may cause anaphylaxis.

4. Opinion

With the exception of aPL testing among women with recurrent miscarriage, there is little evidence to support any particular test or immunomodulatory treatment in the investigation and treatment of couples with reproductive failure. These tests and treatments should be restricted to those entered into formal research studies.

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