DEBATE concluded

Potential health hazards of assisted human reproduction

Possible immunological complications

Meenakshi Narayanan1, P.S.R. Murthy, S.A. Munaf and M.D. Kini

IVF and Infertility Unit, Almana General Hospital, P.O.Box 2366, Dammam–31451, Saudi Arabia

1To whom correspondence should be addressed

Articles in previous issues of this journal have addressed several important potential health hazards of assisted reproduction. This debate series has dealt with genetic (Benagiano and Rowe, 1995; Kaminski and Garel, 1995) and embryological aspects (Ménezó and Dale, 1995; Tarin and Cano, 1995), antenatal and postnatal outcome (Seamark and Robinson, 1995), and clinical complications and psychological effects (Amso, 1995) associated with assisted reproduction treatments.

We wish to highlight yet another complication of assisted reproduction, associated with the immune system. This particular complication, which has been identified in recent years, is the production of autoantibodies against the ovarian antigens.

Vallonton and Forbes (1966) were the first to report on the presence of anti-ovarian (AOAb) antibodies. Since then they have been described in patients with idiopathic adrenal failure (Irvine et al., 1967), premature ovarian failure (De Moraes Ruehsen et al., 1972; Coulam et al., 1981; Damewood et al., 1986; Luborsky et al., 1990), endometriosis (Mathur et al., 1982; Confino et al., 1990), polyglandular autoimmune disorder (Ahonew et al., 1987) and systemic lupus erythematosus (Moncayo et al., 1989a; Moncayo and Moncayo, 1995). Thus AOAb have been found to be associated with conditions that are considered to represent non-organ specific immune disease.

Cameron et al. (1988) described the presence of AOAb in cases of subclinical ovarian failure after hormone stimulation for in-vitro fertilization (IVF). Similar observations have come from other groups. Moncayo et al. (1989b, 1990; see also Moncayo and Moncayo, 1990) have proposed that continual hormonal stimulation for repeated IVF cycles leads to the production of AOAb. A French group (Barbarino-Monnier et al., 1991; Gobert et al., 1992) has shown that repeated follicular puncture during IVF cycles releases ovarian antigens into the circulation, resulting in the production of AOAb. It has been shown that such antibody production is due to a humoral immune response (Barbarino-Monnier et al., 1991). Our own studies (Narayanan et al., 1995) have shown that: (i) 46% of infertile patients who had had no previous treatments for infertility were highly positive for AOAb by enzyme-linked immunosorbent assay (ELISA); (ii) patients undergoing repeated intra-uterine insemination (IUI) treatments (hence no follicular puncture) had undergone sero-conversion and become positive for AOAb; (iii) repeated IVF attempts also resulted in patients producing AOAb, the activity increasing with each additional treatment.

However, production of AOAb was not seen in all patients undergoing repeated treatments. A similar group of 'immune responders' was described by Gobert et al. (1992). We therefore conclude that certain infertile patients probably have the genetic propensity to form autoantibodies directed against the ovarian antigens. Hormonal treatments or follicular puncture during repeated IVF cycles probably aggravate an already existing problem.

Our results (Narayanan et al., 1995) have shown that patients who are positive for AOAb have significantly lower fertilization rates, cleavage rates and pregnancy rates following IVF, in comparison with AOAb-negative patients. Significantly, we observed very high abortion rates among AOAb-positive patients after IVF treatment. Other groups have reported similarly (Barbarino-Monnier et al., 1991; Gobert et al., 1992). AOAb may interfere with implantation and pregnancy by (i) cross-reacting with components of the ovary, e.g. the corpus luteum, resulting in its functional impairment (Moncayo and Moncayo, 1995); (ii) cross-reacting with placental components which may result in an altered maternal immune tolerance to the fetal allograft. It is possible that mature ovarian structures which do not develop until adulthood have not been subjected to the thymic education to recognize self antigens.

Though the use of luteinizing hormone-releasing hormone (LHRH), LHRH analogues, and gonadotrophins has been widely accepted as a treatment modality for IVF, little has been done to determine any detrimental effect on human subjects. Marchetti et al. (1989) have shown that LHRH can influence thymic function. Despite this evidence, the clinical use of LHRH and LHRH analogues has not been considered in relation to the immune system.

In the light of this new information, AOAb should be considered a potential candidate to be included in the risk associated with assisted reproduction. A routine assessment of these autoantibodies among infertile patients may be a useful method of monitoring IVF and investigating immunological infertility.

The normal functioning of the ovary results from a balanced interaction between the endocrine, neurological, immunological and genetic factors. Intervention in any of these factors may upset the balance and cause an adverse response. High concentrations of steroids in IVF patients may potentiate an immune cascade. AOAb may interfere with steroid hormone synthesis, which would probably also involve other organs. The long-term effects of these autoantibodies is difficult to predict. However, clinicians should consider these possibilities before embarking on repeated superovulation treatments. Clearly, more research is required to provide a better insight into this problem.
References


Marchetti, B., Guarcello, V., Murale, M.C. et al. (1989) Luteinizing hormone-releasing hormone (LHRH) agonist restoration of age associated decline of thymus weight, thymic LHRH receptors and thymocyte proliferative capacity. Endocrinology, 125, 1037-1045.


