Detection of antisperm antibodies: an argument against therapeutic nihilism

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I concur with many of the statements in the first debate (Helmerhorst et al., 1999), yet cannot agree with their conclusions that ‘... it is difficult to consider the routinely used antisperm antibody (ASA) tests as an essential procedure in the fertility work-up nor that it is even more difficult to justify a treatment on the basis of such tests’. As Helmerhorst et al. note, large prospective studies are needed to scientifically prove that ASA cause infertility. We have offered a similar opinion (Bronson and Tung, 1997). I believe, however, that this opinion does not justify, on several counts, a recommendation not to routinely test and to treat. Given the low incidence of significant immunities to spermatozoa in men and women (which are found in ~5% of unselected infertile couples), many centres will need to participate in a prospective study of the effects of ASA on fertility, and patient acquisition will be slow. From a practical point of view, results will be long in coming. In addition, we have determined by retrospective analysis the chance of pregnancy in women treated for infertility, whose husbands were found to exhibit an auto-immunity to spermatozoa but were not themselves treated (Ayvaliotis et al., 1985). Pregnancy rates varied from 15.3 to 66.7%, depending upon the proportion of spermatozoa coated with immunoglobulin. The results suggest that the number of cases needed to obtain sufficient power to detect differences in fertility between antibody-positive and antibody-negative groups will be large.

Current tests also do not identify those sperm-associated antigens to which ASA are directed. Antibodies directed against different antigens would be expected to play differing roles in impairing processes leading to successful fertilization. This appears to be the case. When transferred to spermatozoa of known fertile men, ASA detected in sera of infertile couples have varying effects on gamete interactions in vitro, as judged by both hemi-zona assays (Bronson et al., 1982a; Mahoney et al., 1991) and sperm penetration of zona-free hamster eggs (Haas et al., 1980; Bronson et al., 1981; Aitken et al., 1988). Significant impairment of sperm binding to the zona pellucida as well as oocyte penetration was observed in certain, but not all, cases. In some instances, ASA paradoxically enhanced oocyte penetration (Bronson et al., 1981; Aitken, 1988) through promotion of sperm adherence to the oolemma (Bronson et al., 1990). It is then currently difficult to select homogeneous groups of couples with immunities to spermatozoa for study of their fertility. For these reasons, I do not believe that such a study is possible at this time, nor will it be performed in the near future. This in itself should not be sufficient reason to abandon tests for ASA and to declare them not useful.
Examination of the evidence garnered from prior work supports the thesis that ASA impair human reproduction.

As regards which test to utilize to detect ASA, many in the US would consider immunobead binding the best available, both in terms of its sensitivity, the low incidence of false positive tests, and its ability to localize antibodies of all three immunoglobulin classes on the spermatozoan surface (Bronson et al., 1984). This became apparent at the World Health Organization (WHO) Workshop on Clinically Defined Sera, held in Tokushima more than a decade ago. Participating laboratories analysed >100 samples in a blinded manner, utilizing their own particular assays to detect antibodies directed against human spermatozoa, and a comparison of results was then carried out (Bronson et al., 1985). Evidence has also been presented that immunobead binding is more sensitive than the MAR test (mixed anti-globulin reaction) in its ability to detect immunoglobulins (Ig) of the IgA class present on the spermatozoan surface (Meinertz and Bronson, 1988).

Complement-dependent sperm immobilization is dependent upon the isotype of ASA and its location on the spermatozoan surface (Bronson et al., 1982b). When motile spermatozoa of fertile men were sensitized by incubation in ASA-containing sera, complement-dependent immobilization occurred only when the majority of the sperm tail principal piece was coated with immunoglobulin, but not with lesser degrees of tail binding. There was no loss of sperm motility when ASA of the IgA class, a non-complement fixing immunoglobulin, bound to the sperm tail despite the presence of complement. Complement-fixing antibodies of the IgG class that were directed solely against the spermatozoan head did not promote significant loss of sperm motility as well. In contrast, the detection of immunoglobulins on the spermatozoan surface by immunobead binding is independent of the action of complement. The relatively large size of the immunobeads limits their resolution (Helmerhorst et al., 1999), and the number of antibody molecules bound to the sperm surface necessary for bead binding is not known. We have discussed these and other limitations of immunobead binding previously (Bronson, 1988a), yet much clinically useful information can still be gained utilizing this assay.

Analysis of post-coital test results in couples where men exhibited auto-immunity to spermatozoa has also demonstrated that sperm entry of cervical mucus is impaired. This impairment correlated with the proportion of spermatozoa in the ejaculate coated with ASA, as detected by directed immunobead binding (Bronson et al., 1984). Treatment of such spermatozoa with proteases, to degrade the bound immunoglobulins, resulted in their improved cervical mucus penetrating ability in vitro (Bronson et al., 1987). These studies suggest that a major locus of action of ASA on fertility, in addition to their effects at the level of gamete interaction, is on sperm entrance of the female reproductive tract, where they also become liable to complement-mediated damage.

Clinical evidence has also accumulated that the ASA-related impairment of sperm transport suggested by the prior studies can be circumvented in the majority of cases by laboratory assisted reproduction. In the absence of saturating levels of sperm head-directed antibodies (where >80% of spermatozoa are coated with immunoglobulin), fertilization and pregnancy rates following in-vitro fertilization (IVF)/embryo transfer are high, in the face of ASA (Lahteenmaki, 1993). Conversely, when the vast majority of spermatozoa are coated with immunoglobulin over their heads, fertilization is often impaired (Daitoh et al., 1995; Yeh et al., 1995). In addition, the techniques utilized to recover spermatozoa within the laboratory for intrauterine insemination (IUI) or IVF differ whether ASA are present or not. Following the detection of ASA in semen, we request that the semen specimen be collected within the hospital, directly into buffered medium, prior to Isolate density centrifugation, to minimize post-ejaculatory sperm antibody binding (Bronson, 1988b; Jeulin et al., 1989; Elder et al., 1990). The immunobead binding test also allows one to determine whether antibodies are present on all spermatozoa in an ejaculate, a situation that may be associated with substantially lower fertilization rates. In this case, ICSI has been shown to be associated with enhanced fertilization rates in vitro and should be recommended (Lahteenmaki et al., 1995; Nagy et al., 1995; Clarke et al., 1997). When women are found to possess ASA in their serum, it should not be used to supplement IVF tissue culture media, as lower fertilization rates have been documented in this case (Mandelbaum et al., 1987; Vasquez-Levin et al., 1991). While the argument has been made that the routine use of ASA testing is not cost effective in the use of ART, this is a value judgement. Should one wait for the occasional case of failed fertilization to perform ASA retrospectively, as has been suggested? How does one judge the emotional cost to the couple who has gone through these procedures and failed to conceive? Had an immunobead binding test been performed, for a very small individual cost relative to the total cost of an IVF cycle, they could have been placed in a high risk category for failed IVF and alternate treatment strategies discussed.

The near future holds promise for the development of more specific tests that will allow one to detect ASA directed against an array of defined fertilization-related antigens. Several of these specific antigens have now been detected utilizing sera of infertile men and women (Shetty et al., 1999). They will be sequenced, cloned, and recombinant protein made available in the not too distant future. Their availability will lead to the development of ELISA-based tests utilizing purified fertilization-related antigens that may allow one to identify the specific locus of fertilization blockade for individual couples. I would argue, however, that we do not have to wait for such future assays of ASA or for absolute proof that they cause infertility, if our current tests have clinical value in helping to make decisions and to alter our practice. I believe that this is the case.

References

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