Letters to the Editor

Present options for treating sperm autoimmunity before proteomic analysis is available

Dear Sir,

I would like to commend Drs Bohring and Krause for their excellent treatise of sperm autoimmunity and the value of proteomic analysis. This article provides a detailed clear elucidation of the knowledge concerning this potential infertility factor and provides good insight into where the future is headed in making a specific diagnosis as to which sperm protein is the antibody directed and thus its clinical significance. Once this is known, more specific recommendations for therapy can be made.

As far as present treatment options are concerned, the authors state that currently the first choice is ICSI to overcome the effects of antisperm antibody (ASA) on fertilization. But they also imply that certain autoantibodies may inhibit cervical mucus penetration but not adversely affect fertilization. If the specific antibody and antigen could be identified for this problem then ‘this kind of infertility may be overcome by intrauterine insemination (IUI)’ (Kuthe et al., 1996).

I have some observations to share and then have a question to the authors. They referred to a study showing that treating sperm with autoantibodies by an ASA protease from N. gonorrhoeae was able to overcome the block to mucus penetration (Bronson et al., 1987). We have also found that treating sperm bound with autoantibodies with the protein digestive enzyme chymotrypsin followed by IUI was more effective in achieving pregnancies than IUI with sperm ejaculated into albumin (Bollendorf et al., 1994). Others have also found that IUI with untreated sperm with significant amounts of antibodies attached rarely results in pregnancies (Francavilla, 1992). Chymotrypsin treatment of sperm bound with autoantibodies was found to improve both fertilization rates and pregnancy rates following conventional insemination of oocytes (Katsoff et al., 1995). Thus, chymotrypsin treatment seems to neutralize to some degree antibodies to proteins that inhibit the fertilization process. But we have also seen that treatment of sperm bound with autoantibodies with chymotrypsin can result in normal sperm progression ≥8 h after intracervical insemination in women with previously poor post-coital tests. Thus chymotrypsin may be a treatment that can neutralize to some degree antibodies to proteins that prevent sperm mucus penetration and antibodies to those affecting fertilization. One final observation: though <25% of women whose husbands test positive for ASA demonstrate sperm in cervical mucus with progressive forward motion on post-coital testing, nevertheless these patients are likely to conceive without any treatment for the sperm (Check et al., 1992).

The question I pose to the authors is whether they are aware of complement existing in the biological fluids beyond the cervical mucus. If not, then our observations are consistent with the possibility that most sperm autoantibodies that inhibit mucus penetration also inhibit fertilization and that antisperm antibodies that allow mucus penetration may usually also allow oocyte fertilization. If the authors are aware of data suggesting that complement is present throughout the biological fluids up to the oocyte beyond the mucus, then typical failure of IUI only without enzyme treatment (Francavilla, 1992) could be explained on the basis of these sperm not reaching the oocyte, but if they could, then perhaps conventional insemination rather than ICSI would be effective. Under these circumstances there could well be ASA that inhibit fertilization but not mucus penetration and vice versa. This would be the circumstance where proteomic analysis would be most important.

We have recently demonstrated that ICSI is more effective than chymotrypsin galactose treatment but it may be partially related to transfer of multiple embryos versus single oocyte ovulation (Hourani et al., 2003). However, it may be that chymotrypsin treatment does not negate sperm autoantibodies in all women, possibly depending on concentration or type of antibody. Chymotrypsin treatment does not seem to change the percentage of sperm detected with sperm immunoglobulin by immunobead testing (Pattinson et al., 1990; Bollendorf et al., 1994). Thus it may damage the antibody and neutralize its effect without eluting them. The possibility exists that the success rate following chymotrypsin treatment followed by IUI could be improved even more if the IUI were limited to those demonstrating sperm with progressive motion in the mucus ≥8 h after insemination of treated sperm.

To be cost-effective and safety conscious, IUI with enzyme-treated sperm should be the first therapeutic option for patients who want to take the least expensive and safest treatment. However, if the couple only wants this safe treatment, and if there is reason to believe it will be effective, we inseminate the sperm treated with chymotrypsin intracervically at the appropriate time in the cycle and evaluate sperm progression in the mucus ≥8 h later. If progressively motile sperm are present, we continue IUI for 4–6 cycles; if no conception, we proceed to IVF with ICSI. However, for those couples with limited financial resources or fearful of complications from IVF, we continue with IUI with chymotrypsin-treated sperm in the hope that despite its failure to neutralize sufficiently the antibodies that inhibit motility, there has been neutralization of the antibodies blocking fertilization. Thus it is hoped that by bypassing the cervical mucus, a pregnancy may ensue. For those patients anxious to achieve the quickest pregnancy, we advise them that just because we have neutralized antibodies that inhibit sperm progression in the mucus, we may not have neutralized those causing fertilization failure, so they can start with IVF with ICSI. We advise them that IVF with ICSI has been quite effective even in those failing with IUI with chymotrypsin-treated sperm (Check et al., 2000; Hourani et al., 2003).
One final point and a question for the authors. Many years ago corticosteroid treatment of the male was found to be an effective treatment for ASA (Shulman et al., 1986). In fact, before the days of IVF and ICSI, it was considered the treatment of choice (Isidori et al., 1988). I stopped administering corticosteroids many years ago because of the fear of complications from therapy. However, I wonder sometimes if the woman undergoing IVF with ICSI may be subjected to greater risks than the male treated with corticosteroids. Anecdotally at the time I used such treatment, it seemed as though some males improved, as evidenced by sperm progressing in the mucus following intercourse and achievement of pregnancies. The authors, however, state that ‘the favorable response to immunosuppression was not demonstrable in ASA. This may be because it is impossible to treat patients seeking fertility with cytotoxic drugs but not because of the ineffectiveness of the treatment.’ My question to the authors is as follows: do this statement imply that corticosteroids were subsequently not proven to be effective and that more potent immunosuppression would theoretically work but is not safe? Do the authors believe that corticosteroid treatment of the male would be a consideration for patients in whom IVF and ICSI are not options, personal or religious reasons? If they agree that corticosteroids can be used, what regimen do they think is the most effective with the least side-effects and long-term risks?

Though I write this letter to possibly add some therapeutic options at the present time and provide some questions, I whole-heartedly agree with the authors’ premise that the future lies with the identification of functionally relevant antigens with the eventual development of therapies aimed at specific antibodies rather than therapies aimed at general antibody production (unless it is found that a given male usually makes antibodies rather than therapies aimed at general antibody production).


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