Letters to the Editor

Antiphospholipid antibodies and reproductive failure

Dear Sir,

We read with interest the paper by Eldar-Geva et al. (1999) in which the authors report finding no association between antiphospholipid antibodies and recurrent fertility treatment failure. This finding is at odds with several previous reports (Birdsall et al., 1992, 1996; Birkenfeld et al., 1994; Stern et al., 1998) and we wish to raise some concerns we have with aspects of the paper by Eldar-Geva et al. (1999).

Our first concern relates to the statistics employed. Small negative studies are often misleading because they do not have sufficient statistical power to show even quite large effects. This study involved only a small number of patients; 81 patients who were negative and 92 who were positive for any of the tested antibodies, with low pregnancy rates reported in both groups. We were unable to obtain any information regarding confidence limits from the paper, but the fact that the pregnancy wastage rates of 45% in the patients who were positive, 36.6% in those who were borderline and 27% in the negative group were not statistically significant indicates the lack of power in this study. Thus, failure to show an association in a small study does not prove antiphospholipid antibodies are not involved in adverse outcomes of ART.

Our second concern is with the high incidence of antiphospholipid antibodies in the control series (33% with one or more positive antibodies) reported by Eldar-Geva et al. (1999). Eldar-Geva et al. (1999) tested their samples for aPL reactivity using published methodology (Matzner et al., 1994). However, the method used defines antiphospholipid antibody levels as being positive if they are greater than 2 standard deviations above the mean for a normal population. This normal population appears to consist of 43 people without known immunologic or rheumatologic abnormalities (Matzner et al., 1994). Studies examining aPL in large populations have indicated that the distribution of these antibodies is non-parametric (Pattison et al., 1993). As these populations are not normally distributed it is inappropriate to determine negative/positive cutoff points based on standard deviations from the mean, nonparametric statistics e.g. multiples of the mean, should be used instead if standards are not available (Kutteh et al., 1994). We also wonder about the validity of determining cutoff points based on population statistics derived from a normal population of only 43, as appears to have been the case in the antiphospholipid antibody assays used (Matzner et al., 1994). As there are a number of questions regarding the validity of the ELISA method used to evaluate antiphospholipid antibodies we question whether it is possible to draw any valid conclusions regarding the relevance of antiphospholipid antibodies to infertility based on the data presented by Eldar-Geva et al. (1999).

Interestingly, in a recent study we found that autoantibodies reactive with $\beta_2$ glycoprotein I were significantly associated with unsuccessful IVF treatment (Stern et al., 1998). $\beta_2$ glycoprotein I has recently been demonstrated to be the antigen for many antiphospholipid antibodies and we believe that this antigen should be included in the panel of antigens screened when testing for antiphospholipid antibodies (Roubey et al., 1995; Chamley et al., 1999). Unfortunately, Eldar-Geva et al. (1999) did not test their series of women for antibodies reactive with $\beta_2$ glycoprotein I.

In accordance with the results of Eldar-Geva et al. (1999), who did not find any patients in their series with lupus anticoagulant, we also found no cases of lupus anticoagulant in plasma from 360 women (including women with recurrent miscarriage, women undergoing IVF and fertile women) attending the Royal Women’s Hospital, Melbourne (Stern et al., 1998). Based on published prevalence data we would have expected to find 3–6 patients with this antibody in our group of 360. Given that Eldar-Geva et al. (1999) were also working with a Melbourne based population we wonder whether these two independent studies indicate that there is a lower prevalence of lupus anticoagulant in this population than elsewhere. It has been previously shown, for example, that the incidence of antiphospholipid antibodies, including lupus anticoagulant, is different in Israelis and Europeans (Levy et al., 1996). Melbourne has large ethnic Greek and Asian populations that have distinct HLA haplotypes (Robinson et al., 1996). It is possible that genetic differences in this population affect the prevalence of lupus anticoagulant.

References


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