Antiphospholipid antibodies and reproductive failure: what they do and what they do not do; how to, and how not to treat!

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Birdsall et al. (1996) recently published a very interesting article in this journal in which they reported associations with the evaluation of antiphospholipid antibodies in women undergoing in-vitro fertilization (IVF). This paper is of considerable interest because it confirms certain published associations with the presence of abnormal values of antiphospholipid antibodies, while at the same time denying others. It therefore calls for a brief review of what antiphospholipid antibodies may or may not be accused of doing.

Association is not causation

‘Association is not causation’ has been a standard dictum in medical education. Nowhere seems a reminder more appropriate than in relationship to the volume of literature on the presence of antiphospholipid antibodies (Gleicher et al., 1993).

First of all, it is important to note that antiphospholipid antibodies are present in virtually every individual. They are so called ‘natural’ antibodies which can be found in females as well as males, though they appear at higher levels in females (El-Roeiy et al., 1988a; El-Roeiy and Gleicher, 1988). Moreover, puberty and/or exposure to semen appears to affect at least the isotype of antiphospholipid antibodies produced, if not their quantity (Ober et al., 1993). Pregnancy per se does not result in increased antiphospholipid antibody titres. However, antibody production is, in fact, greatly increased in relation to total immunoglobulin (Ig) concentrations and their titres are maintained at normal values only because plasma volume in pregnancy increases considerably, and therefore, dilutes the absolute quantity of antibody produced by B lymphocytes (El-Roeiy et al., 1990). In fact, the acute reactant autoantibody of IgM isotype will frequently exceed normal non-pregnancy concentrations, and such abnormal values will characteristically occur in the peripartum period in normal patients (El-Roeiy et al., 1990).

What all of this teaches us is that the definition of what represents ‘normal’ autoantibody concentrations cannot be made without a qualifier as to in whom antibody concentrations are measured and at what time in that person’s life cycle those measurements are taken.

This should not be surprising since it has been known for decades that the sexes vary in antibody concentrations and production and that, for example, autoantibody concentrations increase with age (Moulias et al., 1984). Increased autoantibody concentrations cannot, however, automatically be equated with the presence of a disease state. In fact, it is probably reasonable to assume that a majority of women with raised antiphospholipid antibody concentrations are perfectly healthy. A good example are relatives of patients with established autoimmune diseases. While first degree relatives of patients with autoimmune diseases have an increased incidence of elevated autoantibodies, and while they also experience an increased risk of autoimmune disease, a majority, even amongst those with elevated autoantibodies, will never develop an autoimmune disease (Shoenfeld et al., 1987).

The mere presence of autoantibodies does, therefore, only denote a risk of disease and not necessarily the presence of disease itself. One therefore has to question the notion that the presence of elevated antiphospholipid antibodies per se causes disease and has to raise the possibility that the presence of abnormal autoantibody concentrations is only indicative of either abnormal B cell production or abnormal antibody clearance, while the truly pathognomonic effect, leading to disease, may be at a completely different level within a complex and intertwined immune system (Gleicher, 1994).

The mere presence of abnormal autoantibodies does therefore not necessarily suggest that those autoantibodies cause concomitantly observed disease phenomena. Association is not necessarily causation, and abnormal autoantibodies may be nothing but an epiphenomenon in such a circumstance.

Antiphospholipid antibodies and infertility

We reported as early as 1989 that infertile females demonstrated increased antiphospholipid antibody values (Gleicher et al., 1989) This has since been confirmed by a number of investigations (Kim et al., 1996). Even earlier, in 1987, we had reported that women who reached IVF demonstrated a surprisingly high incidence of antiphospholipid antibody abnormalities which, in turn, appeared to reduce their pregnancy chances with IVF (El-Roeiy et al., 1987). Studies by Sher et al. (1994), Dmowski et al. (1995) and others (Birkenfeld et al., 1994; Geva et al., 1994, 1995) more recently seemed to support the contention that the presence of elevated antiphospholipid antibodies reduces the chance of conception with IVF. Sher et al. (1994) and Dmowski et al. (1995) further strengthened this conclusion by apparently demonstrating that therapies directed at suggested pathophysiological effects of antiphos-
phospholipid antibodies reversed their effect on pregnancy outcome. A conclusion that antiphospholipid antibodies caused IVF failure therefore seemed tempting. However, Birdsall et al. (1996) in their current paper suggest that, as so often, the obvious may not necessarily be the truth.

There can be no doubt at this point that women who reach IVF are preselected for a high incidence of antiphospholipid antibodies. This was first reported by us (El-Roeiy et al., 1987) but has now been demonstrated in innumerable studies (Fish et al., 1991; Sher et al., 1994; Dmowski et al., 1995; Gleicher et al., 1994). Birdsall et al. (1996) fully confirm this finding, even though their incidence of 15% is low in comparison with other studies due to the fact that they tested only for anticardiolipin and antiphosphatidyl serine antibodies (while others tested for up to six antiphospholipids) and only for IgG and IgM isotypes (while others also included IgA isotypes). However, these authors were unable to demonstrate an association with pregnancy failure in IVF. One could easily argue that their failure to test for more autoantibodies or the small sample size of their study prohibited them from finding a statistical association. While both of these arguments may, in fact, be correct, it is equally likely that their findings are factual. After all, in a large, fully blinded follow-up to the initial study that had suggested an association (El-Roeiy et al., 1987), we, too, had been unable to find a statistical association between the presence of antiphospholipid antibodies and IVF failure (Gleicher et al., 1994).

How is it, then, that some patient populations do seem to demonstrate such an apparent association (El-Roeiy et al., 1987; Sher et al., 1994; Dmowski et al., 1995) and others do not (Gleicher et al., 1994; Birdsall et al., 1996)? The explanation of this puzzle may lie in the fact that, in regards to IVF failure, autoantibodies may represent only an epiphenomenon. Since they represent only an epiphenomenon, they may be detectable or they may not, depending on possibly unrelated conditions. What cannot, however, be in dispute at this point is that IVF patients (and for that matter female infertility patients in general) demonstrate an unusual incidence of immunological abnormalities. And it is, in fact, quite likely that whatever lies at the core of these patients’ immune dysfunction, also contributes to their infertility, to the fact that they reach IVF and, quite likely, also to IVF failure itself. At the same time it seems unlikely that an antiphospholipid antibody abnormality per se contributes to IVF failure.

Why is a differentiation between these two concepts at all important? If autoantibody abnormalities contribute directly to IVF failure, then treatment should be geared at suppressing autoantibodies or counteracting their theoretical effects. If, however, a more basic immune defect causes the IVF failure, then a more generalized immune therapy may be indicated.

Both Sher et al. (1994) and Dmowski et al. (1995) reported success with treatment options which at least superficially seem to be geared at autoantibody suppression and/or suppression of alleged (and never proven) pathophysiological effects of those autoantibodies. Both of their treatment protocols have, however, considerable systemic effects that go beyond the narrow treatment goal originally intended by those authors (Shoenfeld and Isenberg, 1989; Flescher et al., 1991). Therefore, one cannot preclude the possibility that this reported treatment success took place because of systemic immune effects of their treatment regimens, rather than the suggested specific effect on antiphospholipid antibodies. The mere fact that they were successful therefore does not indicate that the correct medication was chosen for the right reason. In fact, the correct medication may have been chosen for wrong reasons, not dissimilar to danazol, historically chosen for the treatment of endometriosis based on its endocrine activity, when its true benefit may have been derived from its immunological effects (El-Roeiy et al., 1988b).

If the concept outlined here is correct, then more systemic immunological treatment options can be expected to give better results. This is obviously only a hypothesis but Coulam’s results after the treatment of IVF failure with intravenous immunoglobulin (IVIg) should be viewed with considerable interest in this context (Coulam et al., 1994).
Antiphospholipid antibodies and intrauterine growth retardation (IUGR)

While unable to find a correlation to IVF failure, Birdsall et al. (1996), noted, for them, a surprising statistical association between the presence of abnormal antiphospholipid antibodies and IUGR. This association does not come as a surprise to us since we reported this association already in 1991 (El-Roeiy et al., 1991). Since then, similar observations have also been made by Polzin et al. (1991), Kajino (1991), Out et al. (1992) and Yasuda et al. (1995).

Antiphospholipid antibodies are highly predictive of IUGR in normal pregnancies, women with chronic hypertension, in pre-eclampsia and in women with superimposed pre-eclampsia (El-Roeiy et al., 1991; Yasuda et al., 1995). In fact, the association between antiphospholipid antibodies and IUGR carries over independently into an association between antiphospholipid antibodies and perinatal risk due to hypertensive conditions of pregnancy (Figure 1). The risk for perinatal morbidity increases with increasing amounts of antiphospholipid antibodies (El-Roeiy et al., 1991; Gleicher et al., 1993).

Birdsall et al. (1996) have now carried this observation into IVF. We already know that IVF patients have an increased incidence of antiphospholipid antibodies. There have been a number of recent reports which have shown conclusively that IVF pregnancies are at greater increased perinatal risk, even if controlled for patient age (Tan et al., 1992; Nurat et al., 1994; Olivennes et al., 1996). The conclusion from this observation therefore seems obvious: an immunological defect, that leads to an increased incidence of autoantibody abnormalities in IVF patients, also exposes patients who conceive to an increased IUGR risk and, probably, therefore, to an increased perinatal risk, if they are lucky enough to conceive. An increased perinatal risk due to antiphospholipid antibodies was first reported by Lockshin et al. (1985).

In contrast to the IVF failure risk, the IUGR and perinatal risks seem, however, phospholipid antibody mediated since an undisputed statistical correlation seems to exist. This should not be surprising because placental antibody deposits have been suggested as a cause of IUGR (Katsuragawa et al., 1995). In contrast to IVF failure, antiphospholipid antibodies here may be the direct culprit, and treatment with directed therapy, such as aspirin and heparin, may therefore in fact represent the treatment of choice.

Conclusion

There is much to be learned about the effects of antiphospholipid antibodies on reproduction. Birdsall’s study brought this once more to our attention. For example, it is curious that pregnancy selectively increases the production of antiphospholipid antibodies over other antibodies (El-Roeiy et al., 1990), an observation that strongly suggests that antiphospholipid antibody production in the pregnant female occurs in response to fetal stimulation. It therefore seems tempting to speculate that, in analogy to the experience reported in women with rheumatoid arthritis (Nelson et al., 1993), paternally derived fetal alleles may determine the rate of maternal antiphospholipid antibody production (or whatever immunological process they represent as an epiphenomenon).

It is equally curious that women with abnormally high peripheral values of antiphospholipid antibodies concentrate these antibodies at incredibly high amounts in follicular fluid, while other immunoglobulins demonstrate standard clinical gradients between blood and follicle (El-Roeiy et al., 1987). In consideration of this observation, one has to wonder whether many more cases of unexplained infertility than are usually expected may not be due to an immunological cause. In fact, one can almost conclude that this is the case.

A picture seems thus to emerge that suggests that the immune system can cause infertility. Maybe more importantly, however, if we outwit the immunological cause of infertility and succeed in nevertheless establishing a pregnancy, this pregnancy is at considerable excessive risk. This risk involves an increased chance of pregnancy loss (Gleicher et al., 1989; Geva et al., 1994), intrauterine growth retardation (El-Roeiy et al., 1991; Kajino, 1991; Polzin et al., 1991; Out et al., 1992; Yasuda et al., 1995) and increased perinatal morbidity as well as mortality (Lockshin et al., 1985; Tan et al., 1992; Nurat et al., 1994; Olivennes et al., 1996).

While antiphospholipid antibodies, as previously noted, may not be the direct culprit for all of these findings, they seem to represent excellent markers of risk in all circumstances. Therefore, one cannot but conclude that infertile females, and especially those undergoing ART procedures, should be screened for antiphospholipid abnormalities not only in order to potentially improve their conception chance through appropriately directed therapy but to reduce their pregnancy risk once they conceive.

References


El-Roeiy, A., Dmowski, P. and Gleicher, N. (1988b) Danazol but not lipid antibody over other antibodies (El-Roeiy et al., 1990), an observation that strongly suggests that antiphospholipid antibody production in the pregnant female occurs in response to fetal stimulation. It therefore seems tempting to speculate that, in analogy to the experience reported in women with rheumatoid arthritis (Nelson et al., 1993), paternally derived fetal alleles may determine the rate of maternal antiphospholipid antibody production (or whatever immunological process they represent as an epiphenomenon).

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Received on August 28, 1996; accepted on October 30, 1996