Pregnancy and antibodies to phospholipids

There is an association between the presence of antibodies that bind to anionic phospholipids and the occurrence of repeated spontaneous abortions,\(^1\sim^7\) often during the second and third trimesters of pregnancy.\(^2\sim^6\) These antibodies have been identified in women with recurrent unexplained miscarriages using, in order of increasing sensitivity, the Venereal Disease Research Laboratory reagent,\(^1\sim^6\) the test for the lupus anticoagulant,\(^1\sim^3\) and radioimmunoassay or enzyme linked immunosorbent assay (ELISA) with cardiolipin\(^9\) or other negatively charged phospholipids\(^13\) as the antigen. The antigen binding properties of the antiphospholipid antibodies identified with these assays are heterogeneous, and it is an oversimplification to equate the results from each assay.\(^12\sim^15\) That much can be stated contentiously about the association of antiphospholipid antibodies with pregnancy failure. No causal link has been established between these two findings and the relevant antibody specificity has yet to be defined. The association of these antibodies with abnormalities of coagulation in vivo has led to the hypothesis that the cause of pregnancy failure is a coagulopathy within the placenta, and some pathological studies have shown placentas to be small and infarcted, with vascular thrombosis,\(^2\sim^6\) though placental infarction was only a minor feature of the placentas described by Lockshin and colleagues.\(^18\)

What is the extent of the clinical problem? Most of the excess pregnancy failure encountered among patients with systemic lupus erythematosus, compared with healthy women, is probably associated with the presence of these antibodies. In one series 50 patients with systemic lupus erythematosus without anticardiolipin antibodies had 129 pregnancies with 27% resulting in miscarriage, compared with 12 patients with very high levels of anticardiolipin antibodies who had 37 pregnancies with 89% miscarrying.\(^9\) Both retrospective\(^9\) and prospective studies\(^18\) of pregnant patients with systemic lupus erythematosus have shown correlations between the level of antiphospholipid antibodies and the incidence of pregnancy failure. The IgG rather than the IgM anticardiolipin antibody isotype seems to be more closely linked to disease,\(^9\)\(^11\)\(^13\) though there have been conflicting reports.\(^20\)\(^21\) The incidence of miscarriages is higher in women with antiphospholipid antibodies who have had a previous miscarriage than amongst primigravidae with these antibodies.\(^19\) The data presented in each of the series quoted above are almost certainly skewed towards overestimation of the association of anticardiolipin antibodies with recurrent pregnancy failure owing to bias in the ascertainment of patients. The overall prevalence of fetal loss among unselected women with anticardiolipin antibodies is not known.

What percentage of women without systemic lupus erythematosus, but with recurrent abortions which are otherwise unexplained, have these antibodies? Figures of 8% (of 24 women with three or more consecutive abortions),\(^4\) 11% (of 44 women with three or more consecutive abortions),\(^22\) 13% (of 61 women with two or more abortions),\(^13\) 27% (of 55 women with two or more abortions),\(^11\) and 42% (of 68 women with three or more consecutive abortions)\(^23\) have been reported.

How should these women be treated? This is a highly contentious subject and the paper in this issue of the Annals\(^24\) is an addition to a number of uncontrolled studies reporting favourable pregnancy outcomes in women treated with large doses of prednisolone and low dose aspirin, a result first described by Lubbe and his colleagues.\(^6\) This form of treatment, however, is associated with considerable maternal morbidity, particularly in the form of iatrogenic Cushing’s syndrome with prominent hypertension.\(^8\) One patient treated with high doses of prednisolone died of miliary tuberculosis.\(^25\) Other groups have reported favourable pregnancy outcomes in similar patients after no treatment,\(^22\) low dose aspirin,\(^29\) treatment with full dose subcutaneous heparin,\(^5\) treatment with low dose aspirin,\(^30\) low dose aspirin plus high dose prednisolone,\(^6,\) low dose prednisolone,\(^26\) low dose prednisolone plus azathioprine,\(^25\) and intravenous high dose immunoglobulin.\(^31\) Framp ton and colleagues described a patient treated with plasma exchange plus low dose steroids,\(^32\) but a subsequent pregnancy in this woman, while she was taking only low dose steroids, resulted in a live infant (G Frampton, D G Williams, and J S Cameron, personal communication).
Similarly, treatment failures have been reported with most of these therapeutic regimens.\(^7\)\(^9\) Probably obsessive attention to fetal monitoring is one of the most important factors in the improved outcome of pregnancy, rather than the varying protocols for drug treatment.\(^8\)\(^18\)\(^26\)\(^33\) There is presently no consensus view on the optimum management of pregnancy in this group of patients, and the cautious views of Lockshin\(^33\) are fully justified.

It is also important to take into account that many of these women are otherwise entirely well, and it is therefore particularly important to identify the most effective treatment which causes the least maternal morbidity. It is encouraging, in this context, that arrangements are well underway for an international multicentre trial of treatment of at-risk subjects. It is planned to compare the results of aspirin plus high dose prednisolone with anticoagulation with full doses of heparin in patients with a previous history of recurrent miscarriages and the presence of a lupus anticoagulant.\(^36\) It is disappointing, however, that neither of the proposed treatments in this trial are innocuous to the mother, and in view of the lack of data showing an advantage of one treatment over another it would have seemed more prudent to conduct a trial comparing aspirin alone with aspirin plus low dose steroids, or even of aspirin alone against placebo. A consoling feature of the study design is that primigravidae with the lupus anticoagulant will be entered into a trial comparing aspirin with placebo.

There are few data to enable a rational choice of steroid dose for treatment of these women. Normalisation of the lupus anticoagulant test has been the goal of several groups, but this is not necessarily associated with loss of antiphospholipid antibodies measured by anti-cardiolipin antibody assays.\(^15\) It is not clear that normalisation of this assay, performed in vitro, bears any relation to the putative pathophysiological activities of antiphospholipid antibodies in vivo. The pathogenesis of most of the tissue lesions in patients with systemic lupus erythematosus is inflammatory, and it is easy to see that steroids may have a therapeutic effect through their 'anti-inflammatory' activities. By contrast, the complications associated with the presence of antiphospholipid antibodies appear to be mainly thrombotic, and an important role for leucocytes and the complement system in the mediation of these effects has not been established.

The association of antiphospholipid antibodies with pregnancy failure appears to be genuine—but not necessarily causal. There is unacceptable therapeutic anxiety in the management of these unfortunate patients. A controlled, prospective study is badly wanted, which will need to be conducted at many centres to enrol sufficient patients to obtain valid results. Unfortunately, it is not clear whether the Kingston antiphospholipid study will be asking the right therapeutic question.\(^34\)

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