The association of antiphospholipid antibodies with severe early-onset pre-eclampsia

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Objective. To confirm the association of antiphospholipid antibodies with early onset of severe pre-eclampsia before 30 weeks' gestation.

Study design. Thirty-four patients with diastolic blood pressure levels ⩾ 110 mmHg and at least 2+ proteinuria before the 30th week of pregnancy were randomly chosen for inclusion in the study. Blood samples were taken for assessment of anticardiolipin antibodies (ACAs), lupus anticoagulant, syphilitic serology and antinuclear antibodies. Fifteen normal antenatal patients matched for age, parity and gestational age acted as control subjects.

Results. Four of the 34 women (11,7%) in the study group had elevated levels of both ACAs and lupus anticoagulant, compared with none in the control group. This was not found to be statistically different.

Conclusion. Given the low incidence of positive ACAs in early-onset severe pre-eclampsia it is unlikely that they are implicated in its pathogenesis. It is possible that they represent a small subset of patients with alternative or combined pathology.

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Antibodies, in particular those directed at negatively charged phospholipids such as cardiolipin and phosphatidylinositol, have been implicated in placental dysfunction. Several mechanisms have been proposed to explain the association of high titres of antiphospholipid antibodies (APAs) and pregnancy loss. One hypothesis is that these maternal antibodies decrease prostacyclin production by placental tissue, with resultant thrombosis.[1,2] Other possibilities are that antibodies can bind platelet and endothelial cell membranes, affect cell function and promote thrombosis. Because there are similarities in placental pathology in patients with APAs and those with pre-eclampsia, viz.

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microthrombi and infarcts, some authors have suggested an association between pre-eclampsia and anticardiolipin antibodies (ACAs).[3,4] These reports, however, included many patients on large doses of corticosteroids, a potential cause of hypertension. The purpose of our study was to confirm the association of APAs with severe early-onset pre-eclampsia.

Methods

Following institutional ethical approval and informed consent, 34 patients with severe pre-eclampsia prior to the 30th week of gestation were admitted to the study. All had singleton pregnancies, diastolic blood pressures of 110 mmHg or higher and proteinuria of ++ or more (detected semiquantitatively by Testape (Ames)). Patients with essential hypertension or on corticosteroid therapy were excluded, as were patients who were seropositive for syphilis and antinuclear factor. ACAs were analysed by a modified enzyme-linked immunosorbent assay (ELISA) technique described by Harris.[5] No attempt was made to differentiate between IgG and IgM antibodies; only IgG antibodies were sought. Results were recorded as an ACA index and a value of > 1,3 was regarded as significant. The index is calculated as the mean optical density of the sample divided by 1,5 x optical density of a standard negative. Lupus anticoagulant antibodies (LACs) were detected by the activated partial thromboplastin time (PTT), the 50:50 PTT and the Exner test. LACs were reported as a ratio of the normal and a value of > 1,35 was regarded as abnormal. Fifteen normal antenatal patients, matched for age (± 5 years), parity and gestational age (± 2 weeks), acted as control subjects.

Results

Results are reported as means and the ranges are given. The chi-square test was used to compare differences between groups and, where necessary, Fisher's exact test was used.

Four of the 34 women (11,7%) with early onset of severe pre-eclampsia (study group) had elevated levels of both ACAs and LAC compared with none in the control group. This, however, was not found to be statistically different (Table I). The mean values of ACA and LAC in the 4 patients were 4,7 (1,5 - 12; SD 5,3) and 1,6 (1,4 - 2,1; SD 0,35) respectively.

Table I. Clinical data (means and ranges)

	Study	Control
No. of patients	34	15
Maternal age (yrs)	25,1 (19,34)	24,6 (20 - 28)
Parity	1,4 (0 - 4)	1,6 (0 - 3)
Gestational age (wks)	23,9 (15 - 30)	24,4 (16 - 30)
Blood pressure on admission to study		
Systolic (mmHg)	185,3 (160 - 250)	111,6 (105 - 120)
Diastolic (mmHg)	128,2 (110 - 160)	66,6 (60 - 80)
No. of ACA positive	4	0
No. of LAC positive	4	0

ACA — anticardiolipin antibodies; LAC — lupus anticoagulant.

Details of the 4 patients with significant APAs are shown in Table II. Two of the patients with APAs delivered premature neonates at 32 weeks' gestation. The other 2 patients had spontaneous intra-uterine deaths. None of the patients in the control group suffered a perinatal loss, while the perinatal loss in the 30 patients in whom APAs were not detected was 70%. Maternal signs of pre-eclampsia regressed within a week of delivery.

Discussion

Conflicting reports[6-8] on the association of APAs and pre-eclampsia have been published. Rajah *et al.*[8] and Scott[7] found no significant difference in ACA levels between study and control groups. Rajah *et al.*[8] studied patients in late pregnancy while Branch *et al.*[6] reported that one-third of women with severe pre-eclampsia occurring before 34 weeks' gestation had high titres of ACA. Our study shows that although 4 of 34 women with severe pre-eclampsia, a clinically important proportion (11,7%), had elevated APAs before 30 weeks, statistical significance was not achieved. Reports on studies involving large numbers of patients however also found no differences in APA levels between patients with severe early-onset pre-eclampsia and controls.[9,10] Further, Kilpatrick *et al.*[10] state that even Branch *et al.*[6] found ACAs in only 16% of their patients.

In the present study, both ACA and LAC levels were assayed, and all 4 patients had significantly raised APA levels with elevated titres on both antibody tests. The ACA test is generally accepted as the most sensitive.[5] In addition tests for nuclear antibodies and smooth-muscle antibodies, as well as syphilitic serology, were negative in all patients. Nuclear antibodies were sought by testing patients' sera on

Table II. Details of APA-positive patients

Patient	Gestational age (wks)	Parity	Blood pressure (mmHg)	ACA index	LAC ratio	Neonatal outcome	Maternal complications
6	21	3	190/140	2,2	1,49	IUD (450 g)	Nil
14	18	1	180/120	2,5	1,35	Preterm delivery (1 200 g)	Renal damage
24	28	0	170/110	1,5	1,4	IUD (1 100 g)	HELLP syndrome
33	26	3	160/120	12,6	2,1	Preterm	Severe uncontrollable hypertension

ACA — anticardiolipin antibody; LAC — lupus anticoagulant; IUD — intra-uterine death; HELLP — haemolysis, elevated liver enzyme levels, low platelet levels

a composite block of mouse liver, kidney and stomach substrate. Anti-smooth-muscle antibodies were, however, not sought. The ELISA for ACA was standardised in our laboratory according to the Rayne Institute (London, UK) standard serum samples.

The actual significance of increased titres of APA in patients with pre-eclampsia is not known. Although the perinatal outcome in the 4 patients with ACA was poor, the perinatal outcome in patients who had no antibodies was similar. The pathogenic role of ACA is undefined as low titres in normal pregnancies elicited either as a physiological response to normal pregnancy or as a general response to tissue injury have also been reported.[11,12] Given the low incidence of positive ACAs in severe pre-eclampsia it is unlikely that they are implicated in the pathogenesis of pre-eclampsia. It is possible that they represent a small subset of patients with alternative or combined pathology. The clinical importance of detection is that these patients may have a poor pregnancy outcome. Further study is indicated.

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