Anticardiolipin antibodies in pre-eclampsia and intrauterine growth retardation

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Summary

Objective: to establish an association of anticardiolipin antibody (ACA) levels and pre-eclampsia or intrauterine growth retardation (IUGR).

Methods: twenty-eight patients with pre-eclampsia, 28 with IUGR and 28 normotensive control group were matched for maternal age, race, weight, cigarette smoking, and parity. All had plasma anticardiolipin antibodies (GPL and MPL) detected by the modified enzyme- linked immuno-absorbent assay (ELISA) technique.

Results: no statistical significant difference in ACA values, both GPL and MPL, was found among the three groups studied. Furthermore, none reached a value of ACA that could be considered clinically relevant (>15).

Conclusion: no association was found in anticardiolipin antibody levels between pre-eclamptic and IUGR versus the control group.

Key words: Anticardiolipin antibodies; Pre-eclampsia; IUGR.

Introduction

Anticardiolipin antibodies (ACA), as lupus anticoagulants, are antiphospholipid antibodies (APA) which are involved with the so-called "antiphospholipid syndrome". Arterial and venous thrombosis, recurrent fetal losses or neurologic disorders characterize this syndrome.

Antiphospholipid antibodies, and in particular anticardiolipin antibodies, seem also to be involved with pre-eclampsia and intrauterine growth retardation (IUGR) [1-3].

These findings would suggest that an autoimmune abnormality is implicated in the pathogenesis of such pregnancy complications.

It would be interesting to ascertain whether antiphospholipid antibodies always play a role in the pathophysiology of adverse outcomes in pregnancy or if the presence of such autoantibodies only selects a population at risk for pre-eclampsia and IUGR.

For this purpose, in our study, we have investigated the incidence of anticardiolipin antibodies in cases of pre-eclampsia and intrauterine growth retardation.

Material and Methods

The study was performed over a two year period and 84 pregnant women were recruited as follows: 28 in-patients with severe pre-eclampsia, 28 in-patients with IUGR, and a control group of 28 healthy pregnant women. Each blood sample was taken within ten minutes before delivery, via an indwelling venous catheter. All women gave their written informed consent to participate in the study. Gestational age was confirmed by ultrasoundy (Kranzbuler, Sonoscope 3) and was referred to the first day of the last menstruation.

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Patients with IUGR were defined as having growth patterns of 2 SD or less as identified by ultrasound scan in accordance with Italian growth patterns [4] and abnormal Doppler flow of the umbilical vessels with an elevated systolic-diastolic ratio >2 SD. Nobody suffered from any other systemic disease.

Patients with severe pre-eclampsia were defined as having blood pressure levels of at least 160/100 mmHg or more with a presence of proteinuria equal or more than 3 g/l. None of this group had a history of chronic hypertension, renal disease or collagen vascular disease; and nobody had received long term therapy with aspirin, heparin or steroids.

For each woman with pre-eclampsia or IUGR included in the study group, a normotensive patient matched for maternal age, race, weight, cigarette smoking, parity and gestational age was recruited to form the control group.

Anticardiolipin antibodies were detected by modified enzyme-linked immunoabsorbent assay (ELISA) technique, described by Harris [5]. All samples were blind tested and in duplicate. Antibody plasma levels of both IgG (GPL) and IgM (MPL) classes were tested. The recommendations of the Second International Anticardiolipin Standardization Workshop [6] are that only moderately positive (16 to 80 units) and highly positive (>80 units) anticardiolipin levels should be considered as clinically relevant.

Statistics

Results are presented as means ± SD throughout the study. Data were analyzed by using one- or two-way analysis of variance (ANOVA).

Significance was accepted for P values <0.05.

Results

No significant statistical difference in ACA values for both GPL and MPL was found among the three groups studied (Mean ± SD): IUGR (GPL: 6.6±3.3 SD; MPL: 7.8±2.3 SD), pre-eclamptic women (GPL: 6.3±3.2 SD;

MPL: 7.2±3.8 SD) and control group (GPL: 5.8±2.4 SD; MPL: 6.7±2.7 SD) (p>0.05) (Fig. 1-2).

Pre-eclampsia

In the 28 pre-eclamptic patients the median age was 28 years (range 19-36). The median gestational age at delivery was 32 weeks (range 25-40).

Five patients had HELLP syndrome and two patients eclamptic seizures.

All patients had lower segment Caesarean sections; some a selected one, others an emergency one for serious fetal hypoxia assessed with cardiotocographic equipment.

The median infant weight at delivery was 1,550 grams (range 650-2,600).

Five babies died after delivery due to severe prematurity.

Neonatal death did not correlate with severity of pre-eclampsia, proteinuria or ACA levels.

The mean GPL level was 6.3±3.2 SD (Fig. 1); the mean MPL level was 7.2±3.8 SD (Fig. 2), but none could be considered as clinically relevant.

Intrauterine growth retardation (IUGR)

In the 28 IUGR patients the median age was 28 years (range 20-37); the median gestational age at delivery was 34 weeks (range 28-40).

All patients but one (stillbirth) had a selected lower segment Caesarean section.

The median infant weight at birth was 1,690 grams (range 540-2,360), and all the babies but one (stillbirth) survived.

The mean GPL level was 6.6±3.3 SD (Fig. 1); the mean MPL level was 7.8±2.3 SD (Fig. 2), but none could be considered as clinically relevant.

The control group

In the control group the median age was 28 years (range 19-37), the median gestational age at delivery was 40 weeks (range 38-42), and blood sampling took place at 33 weeks (range 28-40). The median infant weight at delivery was 3,380 grams and all the babies were in good health.

The mean GPL level was 5.8±2.4 SD (Fig. 1); the mean MPL level was 6.7±2.7 SD (Fig. 2).

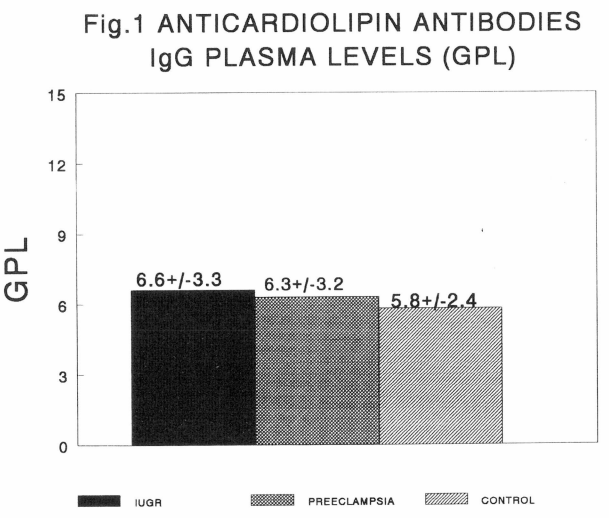

Figure 1. — Anticardiolipin antibodies IgG plasma levels (GPL).

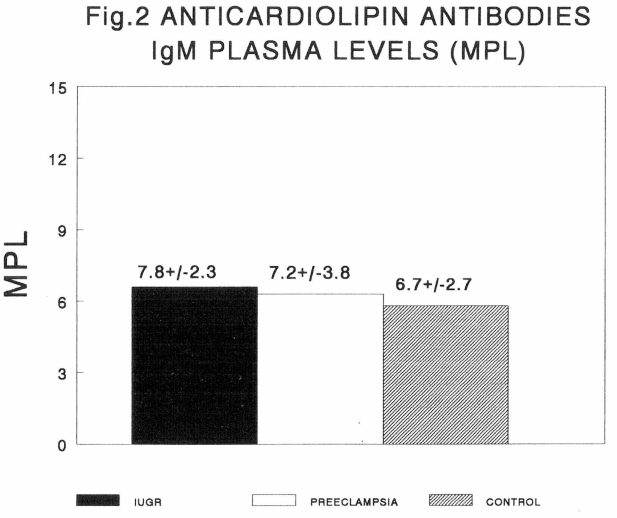

Figure 2. — Anticardiolipin antibodies IgM plasma levels (MPL).

Discussion

In this prospective study we attempted to identify the relationship between ACA, IUGR and pre-eclampsia.

Of the 84 patients examined none reached a value of ACA that could be considered clinically relevant: >15 GPL [6] and no significant statistical difference in ACA values, both GPL and MPL, was found in the IUGR, pre-eclamptic and control groups.

It is quite surprising that none of the patients or healthy controls had raised ACA levels as these autoantibodies are reported to occur in 2.2% [7] to 7% [3]. One possible explanation for this discrepancy may be the small number of patients studied.

However, our results are in accordance with Scott [8] who did not find any significant difference in ACA levels in women with mild to moderate pre-eclampsia when compared to a control group of normotensive pregnant women. Also Out *et al.* [9] did not see any significant statistical difference in the incidence of pre-eclampsia in 59 pregnancies with antiphospholipid antibodies compared to 54 pregnancies without these antibodies.

On the other hand, Branch [1] studied 43 women with severe pre-eclampsia and found that 7 (16%) had elevated APA levels.

Yasuda *et al.* [3], in a large prospective study carried out with 860 patients, reported that the rates of pre-eclampsia and IUGR in the anticardiolipin antibody-positive group were significantly higher than those in the ACA-negative group.

Moodley *et al.* [10] reported elevated ACA levels in eclamptic women with HELLP syndrome; instead, Lockshin *et al.* [11] found that pre-eclamptic women with

HELLP syndrome had similar ACA levels to those with pathologic or non-pathologic pregnancies.

Thus, the association of ACA with pre-eclampsia and IUGR is still controversial.

It is quite obvious that if ACA were implicated in pathogenesis of pre-eclampsia or IUGR there should always be raised ACA levels in these pathological pregnancies. However we cannot exclude, as some Authors [1, 2, 3, 12] suggest, that women with ACA are especially predisposed to pre-eclampsia and IUGR, although it is not known, at the moment, why.

An explanation for this particular condition could be the role of the coagulation system, which is a target both in antiphospholipid syndrome (arterial and venous thrombosis) with elevated ACA levels and in pre-eclampsia. In fact, Out *et al.* have reported [13] similiar thrombosis damage in the placental vessels of women with ACA and those with pre-eclampsia and IUGR. Therefore a patient suffering from antiphospholipid syndrome, who has an affected coagulation system, could be predisposed to pre-eclampsia.

In conclusion, our data suggests that no difference exists in ACA levels between patients with pre-eclampsia or IUGR and normotensive pregnant women. Probably, autoimmune disorders are not really involved with the pathogenetic mechanism of pre-eclampsia and IUGR, but the presence of raised ACA levels could select a population at risk for these pregnancy complications. However, further research is needed to confirm this hypothesis.

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