Prevalence and Significance of Persistently Positive Antiphospholipid Antibodies in Women with Preeclampsia

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ABSTRACT. ***Objective.*** To determine the prevalence of antiphospholipid antibodies (aPL) and their association with obstetric outcomes in women with preeclampsia.

Methods. The study included 150 patients. Clinical variables, risk factors, and severity criteria for preeclampsia and aPL were analyzed.

Results. We found aPL in 4% of patients without risk factors for preeclampsia and in no women with risk factors (p = 0.03). Fifty percent of aPL-positive patients had a fetus with intrauterine growth restriction versus 13.9% (p = 0.04). No relation between aPL and severe preeclampsia was found.

Conclusion. The prevalence of aPL among women with preeclampsia is low. aPL can predispose women without risk factors to preeclampsia. (J Rheumatol First Release Dec 15 2014; doi:10.3899/jrheum.140737)

Key Indexing Terms:
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Preeclampsia complicates 2%–8% of pregnancies[1]. The antiphospholipid syndrome (APS) is associated with a large spectrum of thrombotic and obstetric manifestations, including preeclampsia[2]. However, the association between antiphospholipid antibodies (aPL) without full-blown APS and preeclampsia is disputed[3]. We aimed to analyze the prevalence of aPL among unselected women with preeclampsia and to determine the effect of aPL on the severity of the disease.

MATERIALS AND METHODS

Study design and objectives. Ours was a cross-sectional study with the primary objective of determining the prevalence of aPL in women with preeclampsia. The secondary objective was to analyze the association between aPL, the severity of preeclampsia, and the obstetric outcomes.

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Study population and variables. One hundred fifty consecutive women were studied at the Internal Medicine Department, Hospital Universitario Cruces, between January 2011 and September 2013. They were all recruited during admission to the obstetrics ward with the diagnosis of preeclampsia. Patients with known positivity for aPL, known congenital thrombophilia, or a diagnosis of systemic autoimmune disease (including APS) were excluded.

The local institutional review board of the Hospital Universitario Cruces approved the study protocol in compliance with the Helsinki Declaration. All patients signed informed consent at the time of enrollment.

Just after delivery, several variables were recorded: age, race, family or personal history of preeclampsia or thrombosis, cardiovascular risk factors (body mass index > 30, smoking, diabetes mellitus, gestational diabetes, arterial hypertension, hypercholesterolemia), number of pregnancies, number of miscarriages and/or stillbirths, use of assisted reproduction techniques, single/multiple pregnancy, gestational age at the onset of preeclampsia, gestational week at delivery, occurrence of fetal loss, weight of the newborn, and presence of intrauterine growth restriction (IUGR), defined as a fetus under the 10th percentile with an umbilical artery Doppler showing decreased end-diastolic flow, reflected by a high pulsatility index[4,5].

Blood samples were tested for anticardiolipin antibodies (aCL), immunoglobulin G (IgG), and immunoglobulin M (IgM), anti-β_2 glycoprotein I antibodies (anti-β_2-GPI), and lupus anticoagulant (LA). aCL were measured using a commercial β_2-GPI–dependent standardized kit (Cheshire Diagnostics, Chaser Diagnostics Ltd.). Titers below 13 G phospholipid units (GPL) and 11 M phospholipid units (MPL) were reported negative. Titers between 13–18 GPL and 11–16 MPL were reported as low-positive. For the purposes of our study, we considered aCL levels ≥ 20 GPL or MPL as significant. These limits were suggested by the manufacturer and have been clinically validated in previous studies by our group[6]. The Aeskulisa β_2-glyco-GM kit (AESKU.Diagnostics GmbH & Co. KG) was used for the detection of anti-β_2-GPI. Normal cutoff values were set at 17 U/ml. LA was diagnosed according to the recommendations of the International Society of Thrombosis and Hemostasis, using the diluted Russell's viper venom time and the silica clotting test[7].

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Anticoagulants were not used at the time of testing. All positive tests were confirmed after 12 weeks; only patients testing positive twice were classified as aPL-positive.

Severe preeclampsia was defined according to the American College of Obstetricians and Gynecologists[8]. Patients fulfilling criteria for HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome according to the University of Tennessee criteria[9] or eclampsia were also classified as severe cases for the purpose of our study.

Risk factors for preeclampsia were defined according to the American College of Obstetricians and Gynecologists[8]: primiparity, previous preeclampsia, chronic hypertension or chronic renal disease, multiple pregnancy, *in vitro* fertilization, family history of preeclampsia, diabetes mellitus, obesity, systemic lupus erythematosus (SLE), and advanced maternal age.

Statistical analysis. Clinical descriptors of the cohort were generated using means with SD or proportions. The relation between the severity of preeclampsia and aPL was tested either by the chi-square test or Fisher's exact test. The following adverse obstetric outcomes were also tested using chi-square or Fisher's exact tests: IUGR, fetal loss, prematurity under 34 weeks, and onset of preeclampsia before 34 weeks. In addition, backward stepwise logistic regression models, including clinical meaningful variables, were constructed.

All statistical analysis was done using the software SPSS 20.0.0 statistical package for Mac OS X (SPSS Inc.).

RESULTS

Demographic variables, risk factors, and severity of preeclampsia. Demographic characteristics and risk factors for preeclampsia are shown in Table 1. Preeclampsia was classified as severe in 121 women (80.7%; Table 2).

Frequency and associations with aPL. Six patients (4%) tested repeatedly positive for aPL, 3 were LA-positive (2%), and 4 were aCL-positive (2.7%): 2 of them were aCL IgG-positive (GPL 30 and 33, GPL 25 and 23, respectively) and 2 were aCL IgM-positive (MPL 21 and 27, MPL 29 and 29, respectively). One patient was double-positive LA/aCL.

Table 1. Demographic and clinical characteristics of the cohort. Values are expressed as range (%) unless otherwise specified.

Characteristics	Values
Ethnicity	
White	137–145 (91)
Latin American	5–145 (3.3)
Afro Caribbean	3–145 (2)
Age over 40 at the onset of preeclampsia	14–150 (9.3)
Family history of preeclampsia	8–150 (5.3)
Personal history of preeclampsia	7–150 (4.7)
Personal history of arterial hypertension	5–150 (3.4)
BMI > 30	25–139 (18)
Diabetes mellitus	2–150 (1.3)
Smoking	12–150 (8)
Hypercholesterolemia	3–150 (2)
Nulliparity	97–150 (64.7)
Previous miscarriage	31–150 (20.7)
More than 1 miscarriage	4–150 (2.7)
Previous fetal loss	4–150 (2.7)
Assisted reproduction therapy	30–150 (20)
Multiple pregnancy	19–150 (12.7)

BMI: body mass index.

Table 2. Variables related to the severity of preeclampsia. Values are expressed as range (%) unless otherwise specified.

Variables	Values
Systolic BP > 160 or 110 mmHg	108–150 (72)
Thrombocytopenia under 100,000	63–150 (42)
High liver enzymes	38–150 (25.3)
Impaired renal function	8–150 (5.3)
HELLP	13–150 (8.7)
Eclampsia	8–150 (5.3)
IUGR	23–150 (15.3)
Fetal death	9–150 (6)
Prematurity under 34 weeks	32–150 (21.3)

BP: blood pressure; HELLP: hemolysis, elevated liver enzymes, and low platelet count; IUGR: intrauterine growth restriction.

No patient tested positive for anti-β_2-GPI. No aPL-positive patient showed any other clinical evidence of APS.

None of the 6 patients with aPL had risk factors for preeclampsia versus 71/144 patients without aPL (49.3%; p = 0.03). After excluding primiparity as a risk factor, we found similar results: 6/6 (100%) versus 66/144 patients (45.8%), respectively (p = 0.03).

Severe preeclampsia affected 116/144 aPL-negative women (80.6%) versus 5/6 aPL-positive women (83.3%; p = 1.00). In the subgroup of 79 women with no risk factors, the proportion of patients with aPL was 5/61 in women with severe preeclampsia (8.2%) versus 1/18 in patients with mild preeclampsia (5.6%; p = 1.00).

IUGR was diagnosed in 3/6 aPL-positive (50%) versus 20/144 aPL-negative patients (13.9%; p = 0.04). After adjustments, the final model identified current smoking (OR 6.3, 95% CI 1.7–23.2, p = 0.005) and aPL positivity (OR 7.9, 95% CI 1.1–54.1, p = 0.038) as the only independent predictors of IUGR. We did not identify any patients with aPL and fetal loss (Table 3). The frequency of prematurity below 34 weeks was similar in patients with and without aPL: 2/6 (33.3%) versus 30/144 (20.8%), respectively (p = 0.60). Preeclampsia started before 34 weeks in 2/6 patients with aPL (33.3%) versus 61/144 of patients without aPL (42.4%; p = 1.00). However, the estimated sample sizes per

Table 3. Relationship between aPL and pregnancy outcomes. Values are n (%) unless otherwise specified.

Pregnancy Outcomes	Negative aPL, n = 144	Positive aPL, n = 6	p
No risk factors for preeclampsia	73 (50.7)	6 (100)	0.03
Severe preeclampsia	116 (81)	5 (83.3)	1.00
IUGR*	20 (13.9)	3 (50)	0.04
Prematurity < 34 weeks	30 (20.8)	2 (33.3)	0.60
Late fetal loss	9 (6.3)	0 (0)	1.00
Early-onset preeclampsia	61 (42.4)	2 (33.3)	1.00

* OR 7.9, 95% CI 1.1–54.1, p = 0.038. aPL: antiphospholipid antibodies; IUGR: intrauterine growth restriction.

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group (1-sided α error = 0.05, power = 0.8) regarding these 2 latter comparisons were 313 and 267, respectively.

DISCUSSION

Women with APS have an increased risk of preeclampsia[2]. However, the role of aPL in individuals without APS is less clear. aPL are found in up to 5% of healthy subjects[10] and in 1–9% of low-risk obstetrical population[11]. The prevalence of aPL in high-risk obstetrical patients is 5–50%, heterogeneity partially explained by the different methods of testing and definitions of aPL positivity.

In our cohort of 150 unselected patients with preeclampsia, 4% were aPL-positive. This low prevalence could be attributable in part to the fact that only women testing repeatedly positive were considered[12]. Only a minority of previous studies has confirmed aPL positivity by repeated testing[11].

Although 2 case-control studies reported an increased rate of aPL among women with preeclampsia[13,14], a systematic review could not confirm this point[15]. Likewise, a metaanalysis of cohort studies found no association between aPL and preeclampsia[11]. Further, the PROMISSE study concluded that aCL and anti-β_2-GPI did not predict adverse pregnancy outcomes in the absence of LA[16]. In our series, we found a statistical association only between aPL and the lack of additional risk factors for preeclampsia.

The association between the severity of preeclampsia and aPL has been analyzed in case-control studies with conflicting results[14,17]. Our data could not confirm this link. The association of IUGR and fetal loss with aPL in women with preeclampsia without APS remains a matter of debate[10]. A positive association between aPL and IUGR has been shown in 1 case-control study[18]; however, 2 prospective studies found opposite results[19,20]. Our data support the association of aPL with IUGR in women with preeclampsia, with half of the children born to aPL-positive women being affected. On the contrary, a relationship between aPL and fetal loss was not found, probably because of the effect of preeclampsia itself on the placental function.

Our study has 3 main limitations. First, most of our patients had severe preeclampsia because most patients with mild forms were not admitted to the hospital. Thus, our study was underpowered to assess the association between aPL and severe preeclampsia. Second, the low prevalence of aPL decreased the potency to study their effect in specific subgroups of patients, particularly in women with prematurity and preeclampsia before the 34th week of gestation. Third, the cutoff values for aCL did not strictly fulfill the Sydney laboratory criteria[12]. However, titers of ≥ 20 GPL or MPL are proposed by the manufacturer as significant; in addition, we have validated the relationship with thrombosis of persistent aCL above these limits in our cohort of patients with SLE[6].

Our data point to a low prevalence of persistent aPL among unselected women admitted to a general university hospital because of (mostly severe) preeclampsia. However, 2 important associations were suggested by our results: (1) aPL can increase the risk for preeclampsia in those women without additional risk factors, and (2) the presence of aPL in women with preeclampsia can increase the risk for IUGR. Interestingly, such associations were not found for congenital thrombophilia (data not shown), which suggests a specific pathogenetic role for aPL.

Practical recommendations can be drawn from our study. Because of their low prevalence, it is probably not worth looking for aPL after an episode of preeclampsia if no other features of APS are present. The exception to this rule could be those women who present with severe preeclampsia and IUGR. The lack of associated risk factors could be an additional reason for testing. In such cases, aPL positivity would warrant further specific therapy given the potential thrombotic and obstetric complications associated with these antibodies.

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