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Angiogenic factors in pregnancies of women with antiphospholipid syndrome and systemic lupus erythematosus

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ABSTRACT

Objectives: An imbalance of angiogenic placental factors such as endoglin, soluble fms-like tyrosine kinase 1(sFlt-1) and placental growth factor (PlGF) has been implicated in the pathophysiology of preeclampsia. This study aimed to evaluate serum levels of sFlt-1, PlGF and endoglin in women with primary and secondary antiphospholipid Syndrome (APS) and systemic lupus erythematosus (SLE) longitudinally through pregnancy.
Material and Methods: Serum levels of sFlt-1, PlGF and endoglin were measured prospectively at 4-week intervals (from gestational weeks 12–36) in 17 women with primary APS (PAPS), 18 women with secondary APS (SAPS), and 23 women with SLE.
Results: 6/17 (35%) of women with PAPS, 3/18 (17%) of women with SAPS, and 2/23 (9%) of women with SLE developed early-onset preeclampsia. Women who developed preeclampsia had significantly higher mean sFlt-1 and endoglin levels, higher sFlt-1/PlGF ratios, and lower mean PlGF-levels than women who did not. These changes became statistically significant at 12 weeks for sFlt-1, PlGF and endoglin.
Discussion: Endoglin, sFlt-1 and PlGF are potential early screening parameters for the development of preeclampsia in pregnant women with autoimmune diseases like APS and SLE.

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies/aPl (anticardiolipin antibodies/ACLA, lupus anticoagulant/LA and anti-ß2-glycoprotein/anti-ß2-GPI) in the maternal circulation. These antibodies are associated with arterial and/or venous thromboses and with multiple adverse obstetric outcomes, such as early and recurrent fetal loss, preeclampsia (PE), intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) (Miyakis et al., 2006). APS occurs as primary APS (PAPS) or as secondary APS (SAPS) when combined with other autoimmune diseases such as systemic lupus erythematosus (SLE) (Miyakis et al., 2006; Lockwood et al., 1989; Pattison et al., 1993; Galarza-Maldonado et al., 2011; Asherson and Cervera, 2014; Gómez-Puerta and Cervera, 2014).

Systemic lupus erythematosus (SLE) is associated with an increased risk of adverse obstetric outcomes and increased lupus disease activity during pregnancy (Hochberg, 1997; Baer et al., 2011; Simard et al., 2017) Antiphospholipid antibodies are present in 20–40% of SLE patients (Levine et al., 2002). Pregnancy-associated complications include fetal loss, intrauterine fetal death (IUFD), intrauterine growth restriction (IUGR), preeclampsia (PE) and preterm delivery (Hochberg, 1997; Baer et al., 2011; Simard et al., 2017).

Preeclampsia complicates about 10–17% of pregnancies with APS and 8–35% of pregnancies with SLE, as compared with 3–5% of pregnancies without these conditions (Simard et al., 2017; Chakravarty et al., 2005; Chakravarty et al., 2006; Petri, 1997). Preeclampsia in patients with SLE and APS is often severe and occurs early in pregnancy (Smyth et al., 2010; Clark et al., 2007). The sFlt-1/PlGF ratio is used for the diagnosis of preeclampsia; additionally, it has been approved as a reliable predictor of preeclampsia in women with suspected preeclampsia (Zeisler et al., 2016).

In pregnant women with SLE, the sFlt-1/PlGF ratio is helpful to distinguish between preeclampsia and other conditions such as lupus nephritis (De Jesus et al., 2014).

The aim of the present study was the evaluation of serum levels of sFlt-1, PlGF and endoglin in women with primary and secondary APS and SLE longitudinally during pregnancy for potential early detection

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Table 1
Demographic characteristics of patients.

	PAPS (n = 17)	SAPS (n = 18)	SLE (n = 23)	P
Age of patients (years)	29 ± 6	29 ± 5	31 ± 6	0.544
Pregnancy BMI	25 (19- 30)	23 (20- 25)	22 (19- 26)	0.654
Average systolic blood pressure (mmHg)	130 ± 11	126 ± 12	126 ± 17	0.588
Average diastolic blood pressure (mmHg)	84 ± 8	83 ± 9	83 ± 13	0.930
Ethnicity				
Caucasian	15 (88.2%)	18 (100.0%)	18 (78.3%)	n.a.
Arabian	1 (5.9%)	0 (0.0%)	4 (17.4%)	
African	1 (5.9%)	0 (0.0%)	1 (4.3%)	
Smoking				
Yes	2 (11.8%)	0 (0.0%)	1 (4.5%)	0.292
No	15 (88.2%)	18 (100.0%)	21 (95.5%)	
Gestational diabetes				
Yes	2 (11.8%)	0 (0.0%)	0 (0.0%)	
No	15 (88.2%)	18 (100.0%)	23 (100.0%)	0.082
Antibodies				
LA	10 (58.8%)	6 (33.3%)		n.a.
ACLA	0 (0.0%)	1 (5.6%)		
ß2-Glycoprotein	0 (0.0%)	1 (5.6%)		
LA, ß2-Glycoprotein	0 (0.0%)	1 (5.6%)		
ACLA, ß2-Glycoprotein	1 (5.6%)	4 (22.2%)		
LA, ACLA, ß2-Glycoprotein	6 (35.3%)	5 (27.8%)		
Antibodies (categorised)				
Single positive	10 (58.8%)	8 (44.4%)		0.228
Double positive	1 (5.9%)	5 (27.8%)		
Triple positive	6 (35.3%)	5 (27.8%)		

Data are presented as total numbers (%) or as means ± standard deviation, or in case of a skewed distribution as medians and interquartile range. n.a. not applicable.
PAPS = primary antiphospholipid syndrome; SAPS = secondary antiphospholipid syndrome; SLE = systemic lupus erythematosus; LA = Lupus anticoagulant; ACLA = Anticardiolipin antibodies; SLE = systemic lupus erythematosus; ITP = autoimmune thrombocytopenia.

of preeclampsia. Additionally, profiles of sFlt-1, PlGF and endoglin levels in women with primary APS, secondary APS and SLE without antiphospholipid - antibodies (aPl) were compared.

2. Patients and methods

Seventeen pregnancies with primary APS (PAPS), 18 pregnancies with secondary APS (SAPS) and 24 pregnancies with SLE and lack of aPl antibodies were included in the study (Table 1). Women with APS fulfilled at least one of the Sydney clinical criteria (Miyakis et al., 2006) and women with SLE showed at least 4 of the 11 ACR (American College of Rheumatology) criteria (Gómez-Puerta and Cervera, 2014). Women were recruited at time of admission for prenatal care, starting at 12 weeks of gestation.

Adverse obstetric outcome was defined as recurrent early fetal loss late fetal loss/intrauterine fetal death, intrauterine growth restriction (IUGR) or preeclampsia/HELLP syndrome. Preeclampsia and HELLP syndrome were defined according to international criteria (ACOG Committee on et al., 2002; American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Obstetrics, 2011). Out of these criteria, recurrent early fetal loss was defined as three or more consecutive miscarriages before 10 weeks of gestation; late fetal loss/intrauterine fetal death (IUFD) was defined as fetal death after 10 weeks; IUGR was defined as fetal growth < 5th percentile of gestational age.

Blood samples were collected without anticoagulant every 4 weeks from early pregnancy until delivery. Samples were centrifuged at 800 rpm for 10 min; sera were portioned in 200 µl aliquots and stored at the Biobank Graz, Austria at −80 °C.

Endoglin was measured using a commercially available ELISA (R&D Systems, Inc. Minneapolis; USA) according to the manufacturer's protocol.

The intra-assay coefficients of variation were 2.8%–3.2%. The interassay coefficients of variation were 6.3–6.7%. The detection limit was 0.156 ng/ml.

sFlt-1 and PlGF were measured using an automated ELISA (Roche Diagnostics GmbH; Mannheim, Germany) according to the manufacturer's protocol. The detection limit was 6 pg/ml for sFlt-1 and < 2 pg/ml for PlGF. The intra-assay coefficients of variation were < 2% for sFlt-1 and PlGF, and the interassay coefficients of variation were 2.3%–4.3% for the sFlt-1 assay and 2.7%–4.1% for the PlGF assay.

3. Antibody detection

IgG/IgM aCl and anti-ß2-GPI antibodies were assessed using commercial kits (Orgentec Diagnostika, Mainz/Germany). Lupus anticoagulant was assessed by multiple coagulation tests using platelet-poor plasma samples following international guidelines (Brandt et al., 1995; Pengo et al., 2009). Both tests were repeated after 12 weeks.

The study protocol (23–523 ex 10/11) was approved by the Medical University Ethics Committee (IRB00002556) and informed consent was obtained from all patients.

4. Statistical methods

After data closure, all variables passed a plausibility check to detect outliers in the data set. No extreme values have been extracted from the full data set. Assumption of normal distribution was proved with Shapiro Wilk tests ($p > 0.05$ normally distributed data assumed) and Q−Q plots. If assumptions were met, a one-way ANOVA was used for group comparisons according to clinical characteristics, otherwise non-parametric Kruskal-Wallis tests have been applied using Bonferroni correction for multiple testing. Associations between categorical variables were analyzed with Chi^2 tests. Data are presented as total number, as mean ± standard deviation, or in case of a skewed distribution, as median and Interquartile range (25-percentile and 75-percentile).

Binary logistic regression analyses were performed to assess the influence of biomarkers (sFlt-1/PlGF and endoglin) on adverse obstetric outcome. Odds ratios (OR) estimated from logistic regression were reported with corresponding 95% confidence intervals (95% CI). Model performance was evaluated using the Hosmer-Lemeshow (HL) test for goodness-of-fit and area under the ROC curve (AUC) to assess discrimination. Improvements in prediction with the biomarkers (sFlt-1/PlGF and endoglin) were assessed using both the Nagelkerke R^2 and the change in AUC with the corresponding 95% confidence interval. Statistical tests were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL) and GraphPad Prism version 6.05 were used for visualizations. A two-tailed p-value of less than 0.05 was considered as statistically significant.

5. Results

5.1. Description of the cohort

Demographic characteristics are shown in Table 1. There were no significant differences in maternal age, pre-pregnancy BMI, average systolic and diastolic blood pressure at time of admission, ethnicity, smoking, as well as the pre-existence of gestational diabetes among the three groups (Table 1). The most frequent aPl antibodies were LA (59% in PAPS versus 33% in SAPS), as well as triple-positivity (LA, ACLA and anti-ß2-GPI positive) (35% in PAPS versus 28% in SAPS).

Pregnancy Outcomes are shown in Table 2. 35% of women with

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