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The role of angiogenic biomarkers and uterine artery Doppler in pregnant women with systemic lupus erythematosus or antiphospholipid syndrome

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ABSTRACT

Objective: To evaluate the usefulness of the uterine artery mean pulsatility index (mPI-UtA) and the sFlt-1/PlGF ratio in women with systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS) for the prediction of placental dysfunction-related adverse outcomes (AO), namely pre-eclampsia (PE) and intrauterine growth restriction (IUGR), and for differential diagnosis between PE and SLE flares.

Study design: Observational prospective cohort study of 57 pregnant women with SLE or APS.

Main outcome measures: mPI-UtA and sFlt-1/PlGF ratio in maternal serum were obtained at four gestational age periods (11–14, 19–22, 24–29 and 32–34 weeks). Comparisons among pregnancies with normal outcome, SLE flare and AO were performed.

Results: Overall, we had 44 ongoing pregnancies (36 with SLE and 8 with APS) of which most (n = 35, 80%) were uncomplicated. The overall rate of AO was 9% (n = 4), that was diagnosed at a mean (SD) gestational age of 34.1 (7.5) weeks. Five SLE patients (14%) suffered a SLE flare. No differences for these markers were found between normal pregnancies and those affected by SLE flare. mUtA-PI values were significantly higher in the AO group when compared with normal and SLE flare groups, at 19–22 weeks (1.52, 0.95 and 0.76) and 32–34 weeks (1.13, 0.68 and 0.65), respectively. The sFlt-1/PlGF ratio was significantly higher in the AO group at 24–29 weeks (191.1, 3.1 and 9.2), respectively.

Conclusion: Our preliminary results indicate that mPI-UtA and sFlt1/PlGF ratio may be useful to predict AO in women with SLE, and to make the differential diagnosis with a lupus flare.

1. Introduction

Systemic lupus erythematosus (SLE) disproportionately affects women during their childbearing ages. Pregnancy in patients with SLE, particularly in those with antiphospholipid syndrome (APS), but also with antiphospholipid antibodies (aPL) alone, is associated with an increased risk of adverse outcomes (AO) due to placental insufficiency and these patients have a much higher risk of preeclampsia (PE) (14–23%) [1–4], preterm delivery (20–31%) [1,3,5], intrauterine growth restriction (IUGR) (5–23%) and intrauterine fetal death [6,7].

PE is a specific pregnancy syndrome that usually manifests with high systemic blood pressure (SBP) and proteinuria, and resolves following delivery. Severe PE is characterized by very high SBP, as well as other multiorganic manifestations, including cerebral and visual symptoms, thrombocytopenia, hemolysis, renal insufficiency, and liver involvement [8]. In SLE patients, differentiating between disease activity, particularly lupus nephritis (LN), and PE can be challenging because they share symptoms such as hypertension or proteinuria.

Several angiogenic factors have been identified as biomarkers of placental dysfunction. Changes in the ratio between the pro-angiogenic placental growth factor (PlGF) and the anti-angiogenic factor soluble fms-like tyrosine kinase-1 (sFlt-1) has demonstrated to be useful for the prediction and diagnosis of PE, especially the early-onset forms [9], [10]. Moreover, detection of increased mean pulsatility index in the uterine arteries (mPI-UtA) has also a high sensitivity and specificity for predicting PE and IUGR [11]. Some combined algorithms using both predictive tools have been proposed for detecting patients at high risk of developing placental dysfunction-related diseases [12]. Moreover, previous results have pointed out that the sFlt-1/PlGF ratio as well as the mPI-UtA can be useful to differentiate between PE and SLE or APS

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nephropathies [12,13].

The aim of our study was to assess the value of the mPI-UtA and sFlt-1/PlGF ratio as early markers of placental dysfunction in pregnant patients with either SLE or APS, and to describe how these angiogenesis markers behave in SLE patients with disease activity.

2. Materials and methods

2.1. Study population

Pregnant patients with either SLE diagnosis, with or without aPL, or with APS referred to our high-risk pregnancy clinic from the first trimester of pregnancy were consecutively included from January 2011 to December 2015. SLE and APS diagnosis were established according to the American College of Rheumatology [14] and Sydney criteria [15], respectively. We excluded patients with poorly controlled arterial hypertension, those who were lost for follow-up during pregnancy or delivery, and when fetuses were affected by a chromosomal abnormality or major malformation. This study was consistent with the Helsinki Declaration and its amendments. All patients included should sign the informed consent approved by the Ethics Committee of our institution. The study itself did not interfere with usual clinical practice.

2.2. Schedule of follow-up

The clinical care of pregnant women with SLE or APS was carried out in coordination between maternal-fetal medicine specialists and rheumatologists, following the schedule described in Table 1. Additional visits and tests based on the clinical needs of each patient were added when necessary, as in women positive anti-SSA/Ro antibodies in which biweekly fetal echocardiograms from 16 to 26 weeks of gestation were scheduled to evaluate atrioventricular time intervals. In preconceptional or basal visit, we collected the medical history of patients, SLE/APS and obstetric history, previous and current treatments, toxic habits and allergies.

2.3. Description of variables

2.3.1. Main variables

PE and its severity were diagnosed according to the criteria of the International Society for the Study of Hypertension in pregnancy (ISSHP) [16]. Depending on the gestational age at onset, PE can be classified as early (< 34 weeks' gestation) and late (≥34 weeks' gestation) [17]. IUGR was defined as an estimated fetal weight by ultrasound [18] below the 3rd customized centile [19], or estimated fetal weight below the 10th centile plus abnormal fetal Doppler [20]. Preterm delivery was defined as babies being delivered before completed 37 weeks of pregnancy. Gestational age was calculated according to the recommendations of the American College of Obstetricians and Gynecologists, that is, accurate recall of the last menstrual period was respected unless there was a significant discrepancy with the first ultrasound estimation based on measurement of the crown-rump length before 14 + 0 weeks or biparietal diameter from 14 + 0 weeks onwards [21].

The disease activity was classified according to Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score adapted to pregnancy (SLEPDAI) [22]. We considered moderate activity (SLE flare) when SLEPDAI was ≥6.

2.3.2. Predictive variables

The mPI-UtA was calculated as the average PI of the right and left arteries, and was considered to be abnormal when it was > 95th centile [23].

The sFlt-1 and PlGF concentrations (picograms per milliliter) in maternal serum samples were performed using an automated assay system (Cobas® 6000 e701 module, Roche Diagnostics, Penzberg, Germany). The sFlt-1/PlGF ratio was calculated and expressed in absolute values. Previously described cut-off values of 38 (high suspicion of PE) [24] and 85 (aid in diagnosis of PE) [25] were used for interpretation of results.

2.4. Statistical analysis

The quantitative biochemical and ultrasound parameters were expressed in absolute values. Categorical variables were described as n (%) and continuous variables were described as mean and standard deviation (SD) unless otherwise stated. Three study groups were considered for analysis: pregnancies that were not complicated with PE/IUGR or SLE flare (normal outcome), SLE flare and pregnancies complicated with PE/IUGR (AO). Definitive outcome groups were assigned after a careful review of each case by an expert rheumatologist (E.R.) and fetal medicine specialist (I.H.). The values of mPI-UtA and the plasma levels of the sFlt-1/PlGF ratio, measured in each study period, were compared among the three groups by univariate analysis. For categorical variables, comparisons were performed across all columns using Fisher's exact test, and Kruskal-Wallis test for categorical variables, followed by post hoc Bonferroni's adjustment. Statistical analysis was performed with IBM SPSS Statistics 20.

3. Results

Fifty-seven patients were consecutively included, 46 (81%) with SLE and 11 (19%) with APS diagnosis. Fig. 1 shows the flow chart of the study population from enrollment to final outcome. Among SLE patients, 10 (22%) had spontaneous miscarriage and there were 36 ongoing pregnancies of whom 29 had normal pregnancy outcome (81%), 5 suffered a SLE flare (14%), and 2 (6%) had an AO (1 with early-onset IUGR and *abruption placentae* at 32 weeks of gestation resulting in severe hypoxic-ischemic encephalopathy, and 1 late-onset PE with IUGR and good postnatal outcome). Among the 11 patients with APS, 3 had spontaneous miscarriage (27%), and we had 8 ongoing pregnancies of which 6 had an uneventful outcome (75%), and 2 (25%) had an AO (1 early-onset PE with IUGR at 24 weeks with intrauterine fetal death, and 1 late-onset PE with IUGR and good postnatal outcome).

Demographic and baseline clinical characteristics of patients with uneventful pregnancy outcome, lupus flare and AO are detailed in

Table 1
Scheduled visits during pregnancy.

	Basal or Preconcepcional	10–14 w	19–22 w	24–29 w	32–34 w	Postpartum
Lab test	BC, LFT, Cr, complement, anti-DNA, Anti-Ro, Anti-la, aPL, urinalysis and P/C,	BC, LFT, Cr, urinalysis and P/C	BC, LFT, Cr, complement, anti-DNA, urinalysis and P/C	BC, LFT, Cr, urinalysis and P/C	BC, LFT, Cr, complement, anti-DNA, urinalysis and P/C	BC, LFT, Cr, complement, anti-DNA, urinalysis and P/C
Physical examination	Complete with BP	Complete with BP	Complete with BP	Complete with BP	Complete with BP	Complete with BP
sFlt-1/PlGF ratio	–	√	√	√	√	–
mUtA-PI	–	√	√	√	√	–

BC, blood count; BP, blood pressure; Cr, creatinine; LFT, liver function test; mPI-UtA, mean pulsatility index in the uterine arteries; P/C, urine protein/creatinine ratio.