Soluble Fms-like Tyrosine Kinase Associated with Preeclampsia in Pregnancy in Systemic Lupus Erythematosus

UMAIR QAZI, CHUN LAM, S. ANANTH KARUMANCHI, and MICHELLE PETRI

ABSTRACT. ***Objective.*** Placental synthesis of soluble Fms-like tyrosine kinase (sFlt-1) is responsible for the increased level of serum sFlt-1 in preeclampsia. sFlt-1 binds to the receptor-binding domain of placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), acting as an endogenous inhibitor of VEGF and PlGF signaling in endothelial cells. It has been hypothesized that increased circulating sFlt-1 contributes to the endothelial dysfunction, hypertension, and proteinuria of preeclampsia. We examined the association of sFlt-1 and preeclampsia in pregnancies in patients with systemic lupus erythematosus (SLE).

Methods. A case-control study was performed using stored serum samples. Cases were SLE pregnancies with later preeclampsia and controls were SLE pregnancies without later preeclampsia.

Results. The 52 SLE pregnancies occurred from 1998 to 2001. Nine (17%) pregnancies met the definition of preeclampsia and an additional 9 (17%) met the definition of superimposed preeclampsia. sFlt-1 concentration was significantly higher in SLE pregnancies with preeclampsia (1768 ± 196 pg/ml) than in those without (1177 ± 143 pg/ml) (p = 0.0185).

Conclusion. Our study shows for the first time that sFlt-1 is associated with preeclampsia in patients with SLE, as previously shown in the general pregnancy population. This suggests that SLE pregnancies at risk for preeclampsia can be identified early in the pregnancy by sFlt-1, thus identifying them for high-risk obstetric referral and appropriate monitoring. (First Release Feb 15 2008; J Rheumatol 2008;35:631–4)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS PREGNANCY PREECLAMPSIA

Although the rate of fetal loss has decreased over the last 40 years[1], pregnancy in patients with systemic lupus erythematosus (SLE) still leads to an increased risk of fetal loss[2], prematurity[2-6], fetal growth restriction[3], stillbirth[5], pregnancy loss[6], spontaneous abortions[5], neonatal deaths[3], low birth weight[7], intrauterine growth retardation[8], and preeclampsia[8], compared to normal pregnancies.

Preeclampsia is a pregnancy-related disease characterized by high blood pressure and increased urine protein. It is a major cause of obstetrically-induced preterm birth[2-6]. Delivery is the definitive known cure of preeclampsia[9]. Preeclampsia occurs in 22%[10] to 30%[8] of SLE pregnancies, compared to 5%[11-13] to 7%[8] of non-SLE pregnancies. Despite advances in obstetric care, neither dietary nor pharmacologic therapy is effective in the prevention of preeclampsia[14].

Some predictors of preeclampsia in SLE have been suggested in previous studies. In one study of 63 pregnancies in 48 women with SLE, thrombocytopenia was associated with an increased risk of preeclampsia[10]. Other potential predictors in SLE include preexisting renal disease[10,15] and antiphospholipid antibodies[16], although the latter were not confirmed in a recent study[10].

In non-SLE pregnancies, no reliable test to predict the development of preeclampsia has been identified[17]. In the general female population, some demographic and clinical features may identify a subset of women at greater risk of preeclampsia, including prior renal disease[10], systolic blood pressure[18], chronic hypertension[19], family history of preeclampsia[20], and second trimester amniotic fluid endothelin concentration[21]. Multiple studies have identified obesity as a risk factor[18,19,22,23]. Interestingly, some researchers have found smoking as a protective factor against developing preeclampsia[18,19,24].

Placental synthesis of soluble Fms-like tyrosine kinase

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Supported by the Kirkland Scholar Program. The Hopkins Lupus Cohort is supported by NIAMS R01 AR43737 and the Johns Hopkins University General Clinical Research Center M01-RR00052.

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Accepted for publication November 3, 2007.

(sFlt-1) is responsible for the increased serum levels of sFlt-1 in preeclampsia[13]. sFlt-1 adheres to the receptor-binding domain of placental growth factor (PlGF) and vascular endothelial growth factor (VEGF). This antagonizes VEGF and PlGF signaling on cell surfaces, leading to the endothelial dysfunction, hypertension, and proteinuria that are characteristic of preeclampsia. In pregnant mice, administration of exogenous sFlt-1 leads to hypertension, proteinuria, and glomerular endotheliosis[13,25-28]. In clinical cancer trials, administration of VEGF-neutralizing antibody has resulted in hypertension and proteinuria[29]. Alterations in sFlt-1 are present several weeks before the onset of any preeclamptic symptoms[30]. These data suggest that sFlt-1 is not just a marker of preeclampsia, but is involved in its pathogenesis.

We designed a nested case-control study of lupus pregnancies, followed prospectively as part of the Hopkins Lupus Cohort. Stored sera from lupus pregnancies with and without later preeclampsia were used to measure serum sFlt-1. All samples were obtained in mid-pregnancy prior to the development of any clinical signs and symptoms of preeclampsia. We also used demographic, clinical, laboratory, and treatment data from the prospective Hopkins Lupus Cohort to determine risk factors for preeclampsia in SLE.

MATERIALS AND METHODS

Patients. All patients had consented to participate in the Hopkins Lupus Cohort, approved by the Johns Hopkins University School of Medicine institutional review board. Stored serum samples from gestational age 22–32 weeks were available in 52 SLE pregnancies. Demographic, clinical, and laboratory data were collected every 3 months (when not pregnant) and every 4 to 6 weeks during pregnancy, as part of the Hopkins Lupus Cohort protocol.

Diagnosis of preeclampsia. All medical records were thoroughly reviewed to document the blood pressure and urine protein during the pregnancies. The American College of Gynecology (ACOG) clinical management guidelines were used to define preeclampsia[31]. The 2 criteria were (1) blood pressure 140 mm Hg systolic or 90 mm diastolic in a woman with previously normal blood pressure; and (2) proteinuria, defined as urinary excretion of ≥ 0.3 g protein in a 24-hour urine sample. The diagnosis of superimposed preeclampsia was defined using the "working group" definition[32] as follows:

1. In women with hypertension and no proteinuria early in pregnancy (< 20 wks' gestation), new onset proteinuria, defined as urinary excretion of ≥ 0.3 g in a 24-hour specimen, is present.
2. In women with hypertension and proteinuria before 20 weeks' gestation, if any of the following are noted: (1) sudden increase in proteinuria; (2) sudden increase in blood pressure in women whose hypertension was previously well controlled; (3) thrombocytopenia (platelet count < 100,000/mm^3); (4) increase in alanine-aminotransferase (ALT) or aspartate-aminotransferase (AST) to abnormal levels.

Diagnosis of SLE. All SLE patients met 4 of the revised American College of Rheumatology criteria for classification of SLE[33,34].

Assays. Samples were obtained from visits at gestational age between 22 and 32 weeks. One non-preeclamptic patient, at 33.14 weeks' gestation, was included, but this did not affect the statistical significance. ELISA for human sFlt-1 and free PlGF were performed in duplicate at Beth Israel Deaconess Medical Center, using commercial kits (R&D Systems, Minneapolis, MN, USA). The minimal detectable level in the assays for sFlt-1 and free PlGF was 5 pg/ml. Assays were done blinded to the preeclampsia/eclampsia status.

Statistical analysis. The relevant demographic, clinical, and laboratory variables were extracted from the Hopkins Lupus Cohort Access database using the Cohort ID as the unique identifier. Statistical analysis was performed using Fisher's exact test for categorical variables and the Student t-test for continuous variables. A p value of 0.05 was taken as statistically significant.

RESULTS

Serum samples from 52 pregnancies in 52 patients with SLE were analyzed; the pregnancies occurred from 1998 to 2001. The average age at pregnancy was 30.24 years. The patients were 40% African American, 58% Caucasian, and 1% Asian. Eighty-one percent had at least a high school education. Seventeen percent were taking hydroxychloroquine and 33% prednisone at the time of the pregnancy visit.

Nine (17%) cases met the definition of preeclampsia. An additional 9 (17%) of the total 52 pregnancies met the definition of superimposed preeclampsia (based on sudden increase in blood pressure, sudden increase in urine protein, low platelet count of < 100,000/ml^3, and increased liver function tests). We combined the 2 categories, for a total of 18 with preeclampsia (35%). Among those diagnosed later with superimposed preeclampsia, 5 of the total of 9 (55.6%) developed a sudden increase in blood pressure, while 33% had a sudden increase in proteinuria, and 22% had a sudden increase in liver function tests or decrease in platelet count. sFlt findings are shown in Figure 1.

Demographic variables and obstetric results are shown in Table 1. sFlt concentration was significantly higher in SLE pregnancies with preeclampsia (1768 ± 196 pg/ml) than in those without (1177 ± 143 pg/ml) (p = 0.0185). There was no difference in mean level of PlGF (587 ± 128 pg/ml vs 522 ± 93 pg/ml; p = 0.684; Table 2). There was no association with disease activity measured as either the physician's global assessment or SLE Disease Activity Index (SLEDAI) score (Figure 2).

DISCUSSION

Our nested case-control study shows, for the first time, that

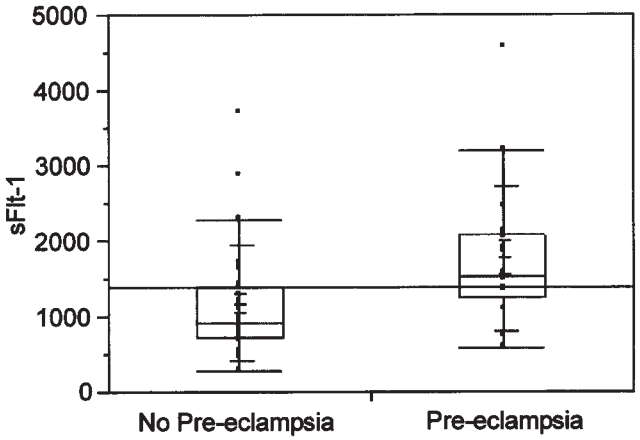

Figure 1. sFlt-1 in SLE patients with preeclampsia and no preeclampsia.

Table 1. Demographic variables and obstetric results in preeclampsia and no-preeclampsia groups.

Demographic Variable	No Preeclampsia n = 34 (65%)	Preeclampsia n = 18 (35%)	p
Age, yrs	29.78 ± 5.38	31.12 ± 4.89	0.381
Caucasian, n	22 (64.7%)	8 (44.4%)	0.230
High school education, n	30 (88.2%)	13 (76.5%)	0.416
Gestational age at delivery, wks	38.14 ± 2.51	35.97 ± 3.12	0.009
Birth weight, g	3131.97 ± 678.64	2624.22 ± 563.29	0.009

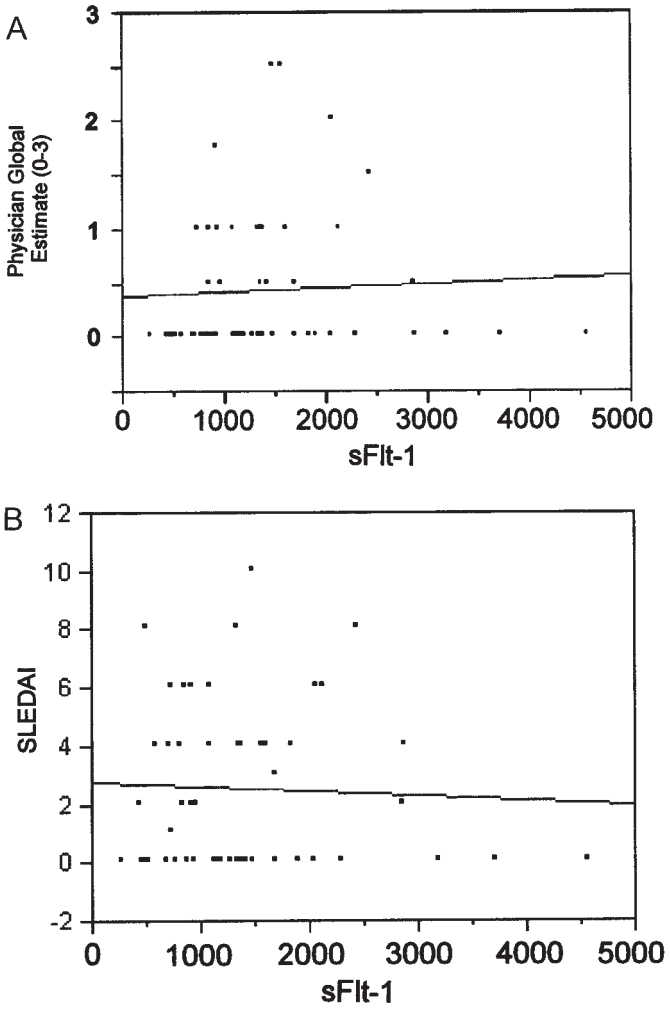

Figure 2. Lack of correlation between sFlt-1 and lupus disease activity measures. A. Linear correlation of sFlt-1 with physician global estimate. B. Linear correlation of sFlt-1 with SLEDAI.

sFlt-1 is associated with preeclampsia in SLE, as previously shown in the general pregnancy population[13,30,35]. Although sFlt-1 has been shown to be increased in non-pregnant patients with lupus during a flare[36], we found no association with disease activity. Unlike in the general pregnant population, in which the ratio of sFlt-1 to PlGF is most predictive, sFlt-1 alone functions well as a predictor in SLE pregnancy. It is unclear why PlGF was not decreased in our cohort of SLE patients who developed subsequent preeclampsia, as observed in pregnant patients without SLE[30].

The mechanism of preeclampsia in SLE is likely similar to that in preeclampsia in non-SLE women, with sFlt-1 potentially leading to placental and systemic vasoconstriction. SLE pregnancies at risk for preeclampsia might be identified at the 22nd to 32nd week of pregnancy by sFlt-1, thus identifying them for high-risk obstetric referral and appropriate monitoring and followup. Finally, the role of sFlt-1 in diagnosis of preeclampsia in lupus pregnancies, including at the time of symptoms of clinical SLE, remains to be determined in large prospective studies[37].

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Table 2. Soluble Fms-like tyrosine kinase (sFlt) and placental growth factor (PlGF) in SLE pregnancies.

Laboratory Variable	No Preeclampsia n = 34 (65%)	Preeclamptic n = 18 (35%)	p
sFlt-1 ± SD, pg/ml	1177 ± 143	1768 ± 196	0.0185
PlGF ± SD, pg/ml	522 ± 93	587 ± 128	0.6837
Gestational age at date of sampling, wks	24.37 ± 3.47	25.25 ± 3.40	0.385

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