OBSTETRICS

Identification of patients at risk for early onset and/or severe preeclampsia with the use of uterine artery Doppler velocimetry and placental growth factor

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OBJECTIVE: Preeclampsia has been proposed to be an antiangiogenic state that may be detected by the determination of the concentrations of the soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) and placental growth factor (PIGF) in maternal blood even before the clinical development of the disease. The purpose of this study was to determine the role of the combined use of uterine artery Doppler velocimetry (UADV) and maternal plasma PIGF and sVEGFR-1 concentrations in the second trimester for the identification of patients at risk for severe and/or early onset preeclampsia.

STUDY DESIGN: A prospective cohort study was designed to examine the relationship between abnormal UADV and plasma concentrations of PIGF and sVEGFR-1 in 3348 pregnant women. Plasma samples were obtained between 22 and 26 weeks of gestation at the time of ultrasound examination. *Abnormal UADV* was defined as the presence of bilateral uterine artery notches and/or a mean pulsatility index above the 95th percentile for the gestational age. Maternal plasma PIGF and sVEGFR-1 concentrations were determined with the use of sensitive and specific immunoassays. The primary outcome was the development of early onset preeclampsia (≤34 weeks of gestation) and/or severe preeclampsia. Secondary outcomes included preeclampsia, the delivery of a small for gestational age (SGA) neonate without preeclampsia, spontaneous preterm birth at ≤32 and ≤35 weeks of gestation, and a composite of severe neonatal morbidity. Contingency tables, chi-square test, receiver operating characteristic curve, and multivariate logistic regression were used for statistical analyses. A probability value of $<.05$ was considered significant.

RESULTS: (1) The prevalence of preeclampsia, severe preeclampsia, and early onset preeclampsia were 3.4% (113/3296), 1.0% (33/3296), and 0.8% (25/3208), respectively. UADV was performed in 95.4% (3146/3296) and maternal plasma PIGF concentrations were determined in 93.5% (3081/3296) of the study population. (2) Abnormal UADV and a maternal plasma PIGF of <280 pg/mL were independent risk factors for the occurrence of preeclampsia, severe preeclampsia, early onset preeclampsia, and SGA without preeclampsia. (3) Among patients with abnormal UADV, maternal plasma PIGF concentration contributed significantly in the identification of patients destined to develop early onset preeclampsia (area under the curve, 0.80; $P < .001$) and severe preeclampsia (area under the curve, 0.77; $P < .001$). (4) In contrast, maternal plasma sVEGFR-1 concentration was of limited use in the prediction of early onset and/or severe preeclampsia. (5) The combination of abnormal UADV and maternal plasma PIGF of <280 pg/mL was associated with an odds ratio (OR) of 43.8 (95% CI, 18.48-103.89) for the development of early onset preeclampsia, an OR of 37.4 (95% CI, 17.64-79.07) for the development of severe preeclampsia, an OR of 8.6 (95% CI, 5.35-13.74) for the development of preeclampsia, and an OR of 2.7 (95% CI, 1.73-4.26) for the delivery of a SGA neonate in the absence of preeclampsia.

CONCLUSION: The combination of abnormal UADV and maternal plasma PIGF concentration of <280 pg/mL in the second trimester is associated with a high risk for preeclampsia and early onset and/or severe preeclampsia in a low-risk population. Among those with abnormal UADV, a maternal plasma concentration of PIGF of <280 pg/mL identifies most patients who will experience early onset and/or severe preeclampsia.

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Preeclampsia is a leading cause of pregnancy-related maternal death.[1-3] The earlier the gestational age at diagnosis, the higher the risk of maternal death exists.[1] For example, the risk of maternal death is 4 times higher if preeclampsia develops between 32 weeks of gestation than after this gestational age. Thus, the identification of patients at risk for severe and/or early onset preeclampsia followed by prophylactic interventions may prevent or delay the clinical presentation of the disease and/or reduce its severity.

Abnormal uterine artery Doppler velocimetry (UADV)[4-8] as well as abnormal maternal plasma concentration of proangiogenic and antiangiogenic factors are risk factors for the subsequent development of preeclampsia.[9-14] Recently, it has been reported that UADV between 22 and 25 weeks of gestation is the "best test" for the identification of patients destined to develop preeclampsia, compared with biochemical indicators in the maternal plasma, such as markers for (1) lipid peroxidation (F2-isoprostane), (2) total antioxidant capacity of plasma (ferric reducing ability of plasma and uric acid concentrations), (3) antioxidant enzymes in erythrocytes (catalase, superoxide dismutase, and glutathione peroxidase), (4) putative markers for endothelial cell dysfunction (von Willebrand factor, plasminogen activator inhibitor types 1 and 2, and thrombomodulin), and (5) pro- and antiangiogenic factors (placental growth factor [PlGF], vascular endothelial growth factor [VEGF], and soluble vascular endothelial growth factor receptor-1 [sVEGFR-1]).[15] The purpose of this study was to determine whether the maternal plasma concentration of the angiogenic factor PlGF and the antiangiogenic factor sVEGFR-1 in the mid trimester of pregnancy can improve the risk assessment determined by UADV for severe and/or early onset preeclampsia.

MATERIAL AND METHODS

Study design

A prospective cohort study was conducted between January 1998 and April 2004 to examine the relationship between UADV and plasma concentrations of PlGF and sVEGFR-1 in pregnant women. Plasma samples were obtained at the time of ultrasound examination between 22 and 26 weeks of gestation. Preeclampsia was diagnosed in the presence of gestational hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on at least 2 occasions, 6 hours to 1 week apart) and proteinuria (≥300 mg in a 24-hour urine collection or 1 dipstick measurement of ≥2+). Patients with preeclampsia were subclassified as either early-onset (≤34 weeks of gestation) or late-onset (>34 weeks of gestation) disease according to the gestational age at which preeclampsia was diagnosed. *Severe preeclampsia* was defined as severe gestational hypertension (diastolic blood pressure ≥110 mm Hg) and mild proteinuria or mild gestational hypertension and severe proteinuria (a 24-hour urine sample that contained ≥3.5 g protein or a urine specimen of ≥3+ protein by dipstick measurement). Patients with an abnormal liver function test (aspartate aminotransferase >70 IU/L) and thrombocytopenia (platelet count <100,000/cm^3) were also classified as having severe preeclampsia. *Small for gestational age* (SGA) neonate was defined as a birthweight of <10th percentile for the gestational age at birth, according to the national birthweight distribution of a Hispanic population.[16] Patients with chronic hypertension, multiple pregnancies, fetal anomalies, or chronic renal disease were excluded from the study. All women provided written informed consent before the collection of plasma samples. The collection and use of samples was approved by the Human Investigation Committee of the Sotero del Rio Hospital, Santiago, Chile (an affiliate of the Pontificia Catholic University of Santiago), and the Institutional Review Board of the National Institute of Child Health and Human Development of the National Institutes of Health.

UADV

Five experienced sonographers performed Doppler ultrasound of the uterine arteries at the time of blood sampling using real-time ultrasound equipment (ACUSON 128-XP; Acuson Corporation, Mountain View, CA) with a 3.5-MHz or a 5-MHz curvilinear probe. The right and left uterine arteries were identified in an oblique plane of the pelvis at the crossover with the external iliac arteries, and the Doppler signals were sampled. When 3 similar consecutive waveforms were obtained, the pulsatility index of the right and left uterine arteries were measured, and the mean pulsatility index of the 2 vessels was calculated. The presence of an early diastolic notch in the uterine arteries was determined according to the criteria proposed by Bower et al.[17] An *abnormal UADV* was defined as the presence of bilateral uterine artery notches and/or a mean pulsatility index of >95th percentile for the gestational age.

Sample collection and human sVEGFR-1 immunoassay

Venipuncture was performed, and the blood was collected into tubes that contained EDTA. The samples were centrifuged for 10 minutes at 4°C and stored at −70°C until assayed. The concentrations of sVEGFR-1 were measured with an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). The details of the method have been described previously.[18] The inter- and intraassay coefficients of variation for human sVEGFR-1 immunoassay in our