OBSTETRICS

First-trimester maternal serum PP13 in the risk assessment for preeclampsia

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OBJECTIVE: The objective of the study was to determine whether first-trimester maternal serum placental protein 13 (PP13) concentrations can be used in the risk assessment for preeclampsia.

STUDY DESIGN: This case-control study included 50 patients with preeclampsia and 250 patients with normal pregnancies. Samples were collected between 8 and 13 weeks of gestation. Serum PP13 concentrations were measured by immunoassay and expressed as medians and multiples of the median (MoM) for gestational age. Sensitivity and specificity were derived from receiver-operating characteristic curve analysis.

RESULTS: (1) Serum PP13 concentration in the first trimester was significantly lower in patients who developed preterm and early-onset preeclampsia than in those with normal pregnancies; and (2) at 80% specificity, a cutoff of 0.39 MoM had a sensitivity of 100% for early-onset preeclampsia and 85% for preterm preeclampsia.

CONCLUSION: Maternal serum first-trimester PP13 appears to be a reasonable marker for risk assessment for preterm preeclampsia but a weak marker for severe preeclampsia at term, and ineffective for identifying mild preeclampsia at term.

Key words: high-risk pregnancy, maternal serum biochemistry, prenatal care, risk assessment, screening

Cite this article as: Romero R, Kusanovic JP, Than NG, et al. First-trimester maternal serum PP13 in the risk assessment for preeclampsia. Am J Obstet Gynecol 2008;199:122.e1-122.e11.

Preeclampsia complicates approximately 5% of all pregnancies and remains a leading cause of maternal and perinatal morbidity and mortality.[1-6] It is increasingly recognized that patients presenting with preeclampsia at early gestational ages have a more severe form of the disease with a higher frequency of multisystemic involvement and small for gestational age (SGA) fetuses than those presenting at term.[4,7-16] Early-onset preeclampsia (less than 34 weeks of gestation) is characterized by uteroplacental vascular insufficiency and damage to the placental villous tree.[2,13,17-22] Indeed, patients with early-onset disease are more likely to have abnormal uterine and umbilical artery Doppler velocimetry studies[23-31] and lesions recognized by placental histological examination.[20,32-44] Moreover, the perinatal morbidity and mortality is higher in early-onset disease,[4,8,15] as are the frequencies of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome[10,45-48] and placental abruption.[49-52]

Risk assessment for preeclampsia remains a major challenge in prenatal care. A wide range of markers have been the subject of investigation, ranging from uterine artery Doppler velocimetry[23-31] to analytes

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Presented at the 27th Annual Meeting of the Society for Maternal-Fetal Medicine, San Francisco, CA, Feb. 5-10, 2007.

Received July 9, 2007; revised Oct. 17, 2007; accepted Jan. 11, 2008.

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This research was supported, in part, by the Intramural Research Program of the National Institute of Child Health and Human Development, *Eunice Kennedy Shriver* National Institutes of Health, Department of Health and Human Services, and Grants 31851 and 42872 from Israel Chief Scientist (to H.M.).

0002-9378/$34.00 • © 2008 Published by Mosby, Inc. • doi: 10.1016/j.ajog.2008.01.013

such as soluble vascular endothelial growth factor receptor-1,[16,53-76] placental growth factor,[16,53,61,70,72-83] soluble endoglin,[70,74,84-87] and others.[88]

Placental Protein 13 (PP13)[89-92] is a member of the galectin family,[93,94] predominantly expressed by the placenta, specifically by the syncytiotrophoblast, in which it is localized on the brush-border membrane at the maternal-fetal interface.[94,95] Recently, maternal serum PP13 concentrations were found to be significantly reduced during the first trimester among women who subsequently developed preeclampsia.[96,97]

The purpose of this study was to determine whether PP13 serum concentrations in the first trimester of pregnancy can be used in the risk assessment for preeclampsia. We have conducted a nested case-control study in a Hispanic population, which has been reported to have an increased relative risk for preeclampsia than that of non-Hispanic Caucasian women.[98]

MATERIALS AND METHODS

A nested case-control study was designed using data from a prospective, longitudinal study conducted by the Perinatology Research Branch of the National Institute of Child Health and Human Development (NICHD). This cohort included pregnant patients seeking care at the prenatal clinics of the Sótero del Río Hospital in Santiago, Chile. First-trimester blood samples were obtained on enrollment, beginning at 7 weeks of gestation.[54] All women provided written informed consent prior to the collection of samples. The collection and utilization of the samples was approved by the Institutional Review Boards of both the Sótero del Río Hospital, Santiago, Chile, and the National Institute of Child Health and Human Development (NICHD/National Institutes of Health/Department of Health and Human Services (Bethesda, MD).

Women aged 18-45 years with a singleton gestation who delivered after 26 weeks were eligible for inclusion. Patients were classified into the following study groups: preeclampsia (n = 50) and normal pregnancy (n = 250). Women in the preeclampsia group were further classified as: (1) preterm preeclampsia (n = 13); (2) severe preeclampsia at term (n = 21); and (3) mild preeclampsia at term (n = 16). From the group of patients with preterm preeclampsia, 6 women with early-onset preeclampsia (preeclampsia requiring delivery before 34 weeks of gestation) were examined as a separate group. Each patient with preeclampsia was matched to 5 women with normal pregnancies. The cases were matched by gestational age at venipuncture (± 1 week) and duration of storage of the specimen (± 2 weeks).

Baseline demographics, blood pressure measurements, and urinalyses from the first prenatal visit through the postpartum period as well as subsequent outcome of pregnancy were collected prospectively by practitioners throughout prenatal care. Serum samples were collected at the time of the first prenatal visit and at regular intervals thereafter.

Definitions

Gestational age (GA) was determined by the last menstrual period and verified by fetal biometry in the first or second trimester of pregnancy in all patients. Preeclampsia was defined as hypertension (systolic blood pressure 140 mm Hg or greater or diastolic blood pressure 90 mm Hg or greater on at least 2 occasions, 4 hours to 1 week apart) associated with proteinuria (greater than 300 mg in a 24 hour urine collection or 1 dipstick measurement of 2+ or greater).[99] Severe preeclampsia was defined as systolic blood pressure of 160 mm Hg or greater or diastolic blood pressure of 110 mm Hg or greater and/or proteinuria greater than 5 g in a 24 hour collection or 3+ or greater on dipstick.[6]

Patients with preeclampsia were subclassified as either early-onset (less than 34 weeks) or preterm (less than 37 weeks) preeclampsia according to the gestational age at which delivery was required. SGA was defined as a birthweight below the 10th percentile for the gestational age at birth, according to the national birthweight distribution of a Hispanic population.[100] Normal pregnancy was defined as one that resulted in the delivery of an appropriate-for-gestational age neonate at term without complications.

PP13 immunoassay

Samples of peripheral blood from pregnant women were obtained by venipuncture, centrifuged, and stored at −80°C. Maternal serum concentration of PP13 was measured using a solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) with a pair of PP13-specific monoclonal antibodies, marked with amplified biotin-extravidin-horseradish-peroxidase complex, and developed with tetramethylbenzidine substrate, as previously described.[92] The optical density was measured at 450 nm against a 650 nm background. Concentrations were determined by extrapolation from a standard curve constructed using recombinant PP13 standards (0-500 pg/mL). The sensitivity of the assay was 5 pg/ml. The intra- and interassay coefficients of variation for this study were 7.3% and 19.5%, respectively. The laboratory staff performing the assays was blinded to pregnancy outcome.

Statistical analysis

Baseline demographics, clinical and delivery characteristics were compared using Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. The first-trimester concentration of PP13 for each subject was converted into a multiple of the gestational age-specific median (MoM) following the method described by Cuckle and Wald.[101] In brief, this was done by computing the median PP13 concentration of pregnancies with normal outcomes. Medians were calculated for each completed week of gestation at venipuncture, and adjustment was then made using weighted (by number of patients) regression to model the relationship between PP13 concentration and gestational age. Because of the wide window range of gestational age, the cubic weighted regression model showed superior fit over the linear weighted regression model for this population.