OBSTETRICS

First-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume

Jiri Sonek, MD, RDMS; David Krantz, MA; Jon Carmichael, PhD; Cathy Downing, RDMS; Karen Jessup, MD; Ziad Haidar, MD; Shannon Ho, MD; Terrence Hallahan, PhD; Harvey J. Kliman, MD; David McKenna, MD, RDMS

BACKGROUND: Preeclampsia is a major cause of perinatal morbidity and mortality. First-trimester screening has been shown to be effective in selecting patients at an increased risk for preeclampsia in some studies.

OBJECTIVE: We sought to evaluate the feasibility of screening for preeclampsia in the first trimester based on maternal characteristics, medical history, biomarkers, and placental volume.

STUDY DESIGN: This is a prospective observational nonintervention cohort study in an unselected US population. Patients who presented for an ultrasound examination between 11-13+6 weeks' gestation were included. The following parameters were assessed and were used to calculate the risk of preeclampsia: maternal characteristics (demographic, anthropometric, and medical history), maternal biomarkers (mean arterial pressure, uterine artery pulsatility index, placental growth factor, pregnancy-associated plasma protein A, and maternal serum alpha-fetoprotein), and estimated placental volume. After delivery, medical records were searched for the diagnosis of preeclampsia. Detection rates for early-onset preeclampsia (<34 weeks' gestation) and later-onset preeclampsia (≥34 weeks' gestation) for 5% and 10% false-positive rates using various combinations of markers were calculated.

RESULTS: We screened 1288 patients of whom 1068 (82.99%) were available for analysis. In all, 46 (4.3%) developed preeclampsia, with 13 (1.22%) having early-onset preeclampsia and 33 (3.09%) having late-onset preeclampsia. Using maternal characteristics, serum biomarkers, and uterine artery pulsatility index, the detection rate of early-onset preeclampsia for either 5% or 10% false-positive rate was 85%. With the same protocol, the detection rates for preeclampsia with delivery <37 weeks were 52% and 60% for 5% and 10% false-positive rates, respectively. Based on maternal characteristics, the detection rates for late-onset preeclampsia were 15% and 48% for 5% and 10%, while for preeclampsia at ≥37 weeks' gestation the detection rates were 24% and 43%, respectively. The detection rates for late-onset preeclampsia and preeclampsia with delivery at >37 weeks' gestation were not improved by the addition of biomarkers.

CONCLUSION: Screening for preeclampsia at 11-13+6 weeks' gestation using maternal characteristics and biomarkers is associated with a high detection rate for a low false-positive rate. Screening for late-onset preeclampsia yields a much poorer performance. In this study the utility of estimated placental volume and mean arterial pressure was limited but larger studies are needed to ultimately determine the effectiveness of these markers.

Key words: first-trimester screening, mean arterial pressure, placental growth factor, placental volume, preeclampsia, pregnancy-associated plasma protein-A, uterine artery

Introduction

Preeclampsia (PE) affects 2-8% of all pregnancies worldwide and is a leading cause of maternal and perinatal death.[1-3] A recent study indicates that short-term cost of PE to the US health care system is $2.18 billion annually, and members of the Preeclampsia Foundation and the Centers for Disease Control and Prevention state that there is not time for complacency.[4,5] Recent evidence suggests that the short-term costs of PE only represent the tip of the iceberg, because women affected by this disorder are more likely to develop major cardiovascular risk factors later in life, more commonly have calcifications in the coronary arteries 3 decades later, are more likely to develop type 2 diabetes mellitus, and have a higher risk for cognitive impairment in later life.[6-10]

PE predominantly affects primigravidas but in some patients, it may recur in subsequent pregnancies, particularly if the father is a different one from that of the previous gestations.[11-13] Obesity is a risk factor, as are gestational diabetes, pregestational diabetes, and other medical complications such as antiphospholipid antibodies and systemic lupus erythematosus.[14-17]

Multiple biomarkers have been proposed for the identification of PE.[18-20] It has been recognized that PE can be early (≤34 weeks) or late (>34 weeks) onset.[21] There is a wealth of evidence that the hemodynamic characteristics, frequency of placental lesions, and biomarkers that identify early-onset PE (EOPE) and late-onset PE (LOPE) are different.[22-24] A major effort in modern research is to develop predictive models of PE, for both EOPE and LOPE.[24-26]

Moreover, there is now great interest in the use of aspirin for the prevention of PE after the publication of the ASPRE trial and several meta-analyses.[27-30] However, there is controversy as to the dose of aspirin, the gestational age at which the medication should be started, and in which patients it should be administered.[31-36] There are even differences among the recommendations of professional societies and the US Preventive Services Task Force.[37-40]

Evidence suggests that aspirin administered in early pregnancy (started at

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13-14 weeks of gestation) reduces the rate of EOPE by 80%, that the response is dependent upon compliance of patients, and that some patients do not respond to aspirin (eg, those with chronic hypertension or aspirin resistance).[27,41,42] Therefore, it is necessary to determine if the models developed in Europe and elsewhere are applicable to the US population.[25,43,44] The current study was undertaken to assess this question.

Materials and Methods

This is a prospective observational nonintervention cohort study performed from 2013 through 2016 at a single institution. An approval from the Wright State University Institutional Review Board was obtained prior to initiating this study.

Patients who were referred to the Maternal-Fetal Medicine, Ultrasound, and Genetics Center at Miami Valley Hospital in Dayton, OH, for first-trimester combined screening at 11+0 to 13+6 weeks' gestation were offered participation in this study. Upon agreeing to participate, the patients signed an informed consent. Patients with multiple gestations, with fetal congenital anomalies, and who delivered <20 weeks' gestation were excluded from the study.

The gestational age was confirmed by measuring the crown-rump length. Only those patients with crown-rump length measurements of 45-84 mm were enrolled. The ultrasound portion of the study protocol included transabdominal Doppler measurement of the uterine artery (UtA) pulsatility index (PI) and estimated placental volume (EPV). The UtA-PI Doppler measurement was done in accordance with the Fetal Medicine Foundation (FMF) protocol. Briefly, UtA was identified using color Doppler. Pulsed Doppler was used to obtain a waveform to measure the PI using the following specifications: Doppler gate was set at 2 mm, the angle of insonation was <30 degrees, and the peak systolic velocity was ≥60 cm/s. After 3 similar consecutive waveforms were obtained, the UtA-PI was measured in both the left and right UtA. All sonographers obtaining this measurement had a current FMF accreditation for this procedure. Each Doppler measurement was reviewed for compliance with the FMF criteria by one of the authors (C.D.) after the completion of the study. Doppler was performed using curvilinear transducers on either E8 (GE) or S2000 (Siemens) ultrasound equipment.

The EPV measurement using 2-dimensional ultrasound was obtained using an approach described previously.[45] Briefly, the placental edges were identified and the distance between them was measured. Then, a measurement between this line and the placental-uterine interface was obtained. This measurement was obtained approximately midway between the placental edges and at right angle to the direction of the first measurement irrespective of the placental cord insertion location. The placental thickness was measured at this point as well. A formula that includes these values was then used to calculate the EPV (Supplementary Figure).[45,46] Each placental volume measurement was reviewed for compliance with established criteria by one of the authors (C.D.), who was unaware of the pregnancy outcome, after the completion of the study.

Maternal blood pressure was obtained using an automated device (premium blood pressure monitor, model BP3NQ1-4X; Microlife) with the patient in a seated position.[47] After a short period of rest, blood pressure was measured in both arms twice and the average of these measurements was used in risk assessment.

Serum specimens were shipped at ambient temperature overnight to NTD Labs (Melville, NY). Upon receipt, specimens were centrifuged and stored at −20°C until analysis. Specimens were analyzed for pregnancy-associated plasma protein (PAPP)-A, placental growth factor (PlGF), and maternal serum alpha-fetoprotein (MSAFP) (serum biomarkers). Details on assay methodology are provided elsewhere.[48] The patient was weighed and historical data were obtained and recorded. Outcome data were gathered using either electronic medical records (Epic) or through birth certificates. The primary

FIGURE 1
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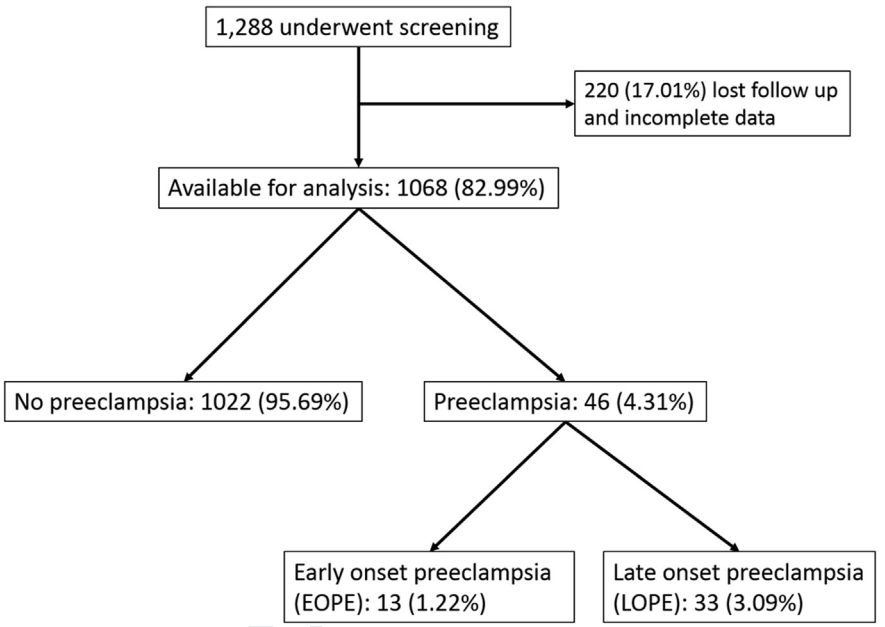

Study flow chart.

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