First-Trimester Prediction of Hypertensive Disorders in Pregnancy

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Abstract—This study aimed to establish a method of screening for pregnancy hypertension by a combination of maternal variables, including mean arterial pressure, uterine artery pulsatility index, pregnancy-associated plasma protein-A, and placental growth factor in early pregnancy. The base-cohort population constituted of 7797 singleton pregnancies, including 34 case subjects who developed preeclampsia (PE) requiring delivery before 34 weeks (early PE) and 123 with late PE, 136 with gestational hypertension, and 7504 cases subjects (96.3%) who were unaffected by PE or gestational hypertension. Maternal history, uterine artery pulsatility index, mean arterial pressure, and pregnancy-associated plasma protein-A were recorded in all of the cases in the base cohort, but placental growth factor was measured only in the case-control population of 209 cases who developed hypertensive disorders and 418 controls. In each case the measured mean arterial pressure, uterine artery pulsatility index, pregnancy-associated plasma protein-A, and placental growth factor were converted to a multiple of the expected median (MoM) after correction for maternal characteristics found to affect the measurements in the unaffected group. Early PE and late PE were associated with increased mean arterial pressure (1.15 MoM and 1.08 MoM) and uterine artery pulsatility index (1.53 MoM and 1.23 MoM) and decreased pregnancy-associated plasma protein-A (0.53 MoM and 0.93 MoM) and placental growth factor (0.61 MoM and 0.83 MoM). Logistic regression analysis was used to derive algorithms for the prediction of hypertensive disorders. It was estimated that, with the algorithm for early PE, 93.1%, 35.7%, and 18.3% of early PE, late PE, and gestational hypertension, respectively, could be detected with a 5% false-positive rate and that 1 in 5 pregnancies classified as being screen positive would develop pregnancy hypertension. This method of screening is far superior to the traditional approach, which relies entirely on maternal history. (Hypertension. 2009;53:812-818.)

Key Words: first-trimester screening ■ mean arterial pressure ■ uterine artery Doppler ■ PAPP-A ■ placental growth factor ■ preeclampsia

Preeclampsia (PE), which affects ≈2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality.1-4 In the United Kingdom, the National Institute for Clinical Excellence has issued guidelines on routine prenatal care recommending that at the first prenatal visit a woman’s level of risk for PE should be evaluated so that a plan for her schedule of prenatal visits can be formulated.5 There is no proven effective method for the prevention of PE. Nevertheless, routine prenatal care in the last 50 years has evolved with the aim of early identification of women at high-risk for PE, which could potentially improve pregnancy outcome. Intensive maternal and fetal monitoring in such patients would lead to an earlier diagnosis of the clinical signs of the disease and the associated fetal growth restriction and avoid the development of serious complications through such interventions as the administration of antihypertensive medication and early delivery. Early identification of the high-risk group for the development of PE is also important for future studies investigating the potential role of pharmacological interventions starting from the first trimester to improve placentation and reduce the prevalence of the disease.

The traditional method of screening for PE is maternal history. The likelihood of developing PE is increased in black compared with white women, in nulliparous compared with parous women, in those with a high body mass index (BMI), and in those with a previous or family history of PE.6 However, screening on the basis of such history would identify ≈30% of cases destined to develop early PE, requiring delivery before 34 weeks of gestation, and 20% of late PE, for a false-positive rate of 5%.7 There is evidence that, in a high proportion of pregnancies destined to develop PE at 11 to 13 weeks of gestation, the maternal mean arterial pressure (MAP) and uterine artery pulsatility index (PI) are increased, and the maternal serum concentration of the placental factors pregnancy-associated protein-A (PAPP-A) and placental growth factor (PlGF) are reduced.8-11

The aims of this study are to derive specific algorithms for the calculation of patient-specific risks for early PE, late PE,
and gestational hypertension (GH), based on a combination of factors in the maternal history, the measurements of MAP and uterine artery PI, and maternal serum levels of PAPP-A and PlGF at 11 to 13 weeks of gestation, as well as to examine the performance of each of the 3 algorithms in the early detection of pregnancy hypertension.

**Methods**

### Study Population

This was a prospective screening study for hypertensive complications of pregnancy in women attending for their routine first hospital visit in pregnancy. In this visit, which is held at 11 to 13 weeks of gestation, all of the women have an ultrasound scan for the following reasons: (1) to confirm gestational age from the measurement of the fetal crown-rump length (CRL); (2) to diagnose any major fetal abnormalities; and (3) to measure fetal nuchal translucency thickness as part of the screening for chromosomal abnormalities. In addition, the maternal serum PAPP-A and free β-human chorionic gonadotropin are determined, and the results are combined with the fetal nuchal translucency to calculate the patient-specific risk for trisomy 21. We recorded maternal characteristics and medical history, measured MAP by automated devices, and stored serum at −80°C for subsequent biochemical analysis. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by King’s College Hospital Ethics Committee.

We prospectively examined 8481 singleton pregnancies between March 2006 and August 2007. We excluded 684 (8.1%) because they had missing outcome data (n = 43), or fetal aneuploidy (n = 50), the pregnancies resulted in the delivery before 24 weeks of gestation (n = 130), the pregnancies were terminated for social reasons (n = 17), or when there was ≥1 episode of hypertension, but on the basis of the available data, it was not possible to determine whether the diagnosis was PE (n = 27). In the remaining 7797 cases (base-cohort population), there were 157 (2.0%) who developed PE, including 34 who required delivery before 34 weeks (early PE) and 123 with late PE, 136 with GH, and 7504 (96.3%) cases who were unaffected by PE or GH.

In this study, maternal history, uterine artery PI, MAP, and PAPP-A were recorded in all of the cases in the base-cohort population (n = 7797). In addition, maternal serum PlGF was measured in a case-control population of 29 cases with early PE, 98 with late PE, 82 with GH, and 418 controls from pregnancies that did not develop any complications and resulted in the live birth of phenotype usually normal neonates. The selection of the specific samples from each group of hypertensive disorders was simply based on availability. For each case of hypertensive disorders, we selected 2 cases of controls matched for length of storage of their samples. The analyses were performed in October 2007 and February 2008. None of the samples were previously thawed and refrozen. This study is part of a research program on the early prediction of pregnancy complications, and the data from some of the patients on individual components of the present study were published previously.4-11

### Maternal History

Patients were asked to complete a questionnaire on maternal age, racial origin (white, black, Indian or Pakistani, Chinese or Japanese, and Mixed), cigarette smoking during pregnancy (yes or no), method of conception (spontaneous or assisted), medical history (including chronic hypertension, diabetes mellitus, antiphospholipid syndrome, thrombophilia, and sickle cell disease), medication (including anti-hypertensive, antidepressant, antiepileptic, aspirin, steroids, beta-metric, insulin, and thyroxin), parity (parous or nulliparous if no delivery beyond 23 weeks), obstetric history (including previous pregnancy with PE), and family history of PE (mother). The questionnaire was then reviewed by a doctor together with the patient. The maternal weight and height were measured, and the BMI was calculated in kilograms per meter squared.

### Outcome Measures

The definitions of PE and GH were those of the International Society for the Study of Hypertension in Pregnancy. In GH, the diastolic blood pressure should be ≥90 mm Hg on ≥2 occasions 4 hours apart developing after 20 weeks of gestation in previously normotensive women in the absence of significant proteinuria, and in PE there should be GH with proteinuria of ≥300 mg in 24 hours or 2 readings of ≥2 pluses on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In PE superimposed on chronic hypertension, significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks of gestation in the absence of throblastic disease).

### Sample Analysis

A duplicate serum sample of 100 μL was used to measure PlGF concentration by a quantitative ELISA technique using Quantikine human PlGF immunoassay (R&D Systems Europe Ltd). The assays were performed on an automated ELISA processor (Dade-Behring BEP 2000). Absorbance readings were taken on a VICTOR3 plate reader (PerkinElmer Life and Analytic Sciences), and PlGF concentrations were determined using MultiCalc software (PerkinElmer Life and Analytic Sciences). The lower limit of detection of the assay was 7 pg/mL, and the between-batch imprecision was 8.3% at a PlGF concentration of 48 pg/mL, 5.6% at 342 pg/mL, and 5.1% at 722 pg/mL. All of the samples were analyzed in duplicate, and those with a coefficient of variation >15% were reanalyzed.

Maternal serum PAPP-A was measured using the DELFIA XPRESS analyzer (PerkinElmer Life and Analytic Sciences). The variation of the DELFIA XPRESS PAPP-A assay was determined in 20 runs with 2 replicates using this DELFIA XPRESS system. The calibration curve of the first run was used as a reference curve during the 14-day period. The intra-assay and interassay variations were 1.2% and 2.1%, respectively, at a PAPP-A concentration of 462 mU/L, 1.4% and 2.3% at 2124 mU/L, and 1.3% and 2.5% at 5543 mU/L.

### Statistical Analysis

Maternal history, uterine artery PI, MAP, and PAPP-A were recorded in all of the cases in the base cohort, but PlGF was measured only in the case-control population.

Comparisons between base-cohort and case-control populations was by χ² or Fisher’s exact test for categorical variables and by Mann–Whitney test for continuous variables. Comparisons between outcome groups in the case-control study were by χ² or Fisher’s exact test for categorical variables and by Kruskal-Wallis test and Dunn’s procedure for continuous variables.

The following steps were taken to develop a specific algorithm for the calculation of patient-specific risk of early PE, late PE, and GH.

First, the distributions of uterine artery PI, MAP, PAPP-A, and PlGF were made Gaussian after logit transformation. Second, multiple regression analysis was used to determine which of the factors among the maternal characteristics, medical and obstetric history, and gestation were significant predictors of log uterine artery PI and log MAP in the unaffected group of the base-cohort population and of log PlGF in the unaffected group of the case-control population. Then, the distribution of log uterine artery PI, log MAP, and log PlGF expressed as multiples of the median (MoM) of the unaffected group, were determined in the PE and GH groups of the case-control population. Fourth, the measured PAPP-A was converted into MoM after adjustment for gestation, maternal age, racial origin, weight, parity, cigarette smoking status, and method of conception, as described previously. Fifth, logistic regression analysis was used to determine which of the factors among the maternal characteristics, log uterine artery PI MoM, log MAP MoM, log PlGF MoM, and log PAPP-A MoM, had a significant contribution in predicting early PE, late PE, and GH. Sixth, the detection and false-positive rates were calculated as the respective proportions of PE or GH (detection rate) and unaffected pregnancies (false-positive rate) with MoM values...
above the given cutoffs. The statistical software package SPSS 15.0 (SPSS Inc) was used for all of the data analyses.

Results
The maternal characteristics of each of the outcome groups in the base-cohort and case-control populations are compared in Table 1. There were no significant differences in any of the maternal characteristics between each of the outcome groups in these populations. In the case-control population, in the early PE and late-PE groups compared with controls, the BMI was significantly higher, there were more black women, more women had PE in their previous pregnancies, and more women were chronic hypertensives on antihypertensive medication. In addition, in the early PE group compared with controls, more women conceived with assisted conception; in the GH group compared with controls, the BMI was significantly higher, there were fewer Indian or Pakistani women, and more women had PE in their previous pregnancies.

Unaffected Group
Multiple regression analysis in the unaffected group of the base-cohort population demonstrated that, for log uterine artery PI, significant independent contributions were provided by fetal CRL, maternal BMI, age, and racial origin (Table 2; \( R^2 = 0.030; P < 0.0001 \)). In the case of log MAP, significant independent contributions were provided by fetal CRL, maternal BMI, age, smoking, parity, and racial origin (Table 2; \( R^2 = 0.116; P < 0.0001 \)). Multiple regression analysis in the unaffected group of the case-control population demonstrated that, for log PI GF, significant independent contributions were provided by fetal CRL, maternal weight, smoking, and racial origin (Table 2; \( R^2 = 0.254; P < 0.0001 \)).

In each patient, we used these formulas to derive the expected log uterine artery PI, log MAP, and log PI GF and then expressed the observed value as an MoM (Table 3).
Logistic regression analysis demonstrated that, in the prediction of early PE, there were significant contributions from maternal factors, uterine artery PI, MAP, PAPP-A, and PlGF: $Y = -8.776 + 14.177 \log \text{uterine artery PI} + 42.960 \log \text{MAP} + 2.233 \log \text{PAPP-A} + 5.329 \log \text{PIGF}$. Logistic regression analysis demonstrated that, in the detection of late PE, there were significant contributions from maternal factors, uterine artery PI, MAP, and PIGF but not PAPP-A ($P = 0.814$): $Y = -5.324 + 2.233 \log \text{uterine artery PI} + 23.134 \log \text{MAP} + 2.408 \log \text{PIGF}$. Logistic regression analysis demonstrated that, in the prediction of GH, there were significant contributions from maternal factors and MAP but not PAPP-A ($P = 0.693$), PIGF ($P = 0.274$), and PI GF. Logistic regression analysis demonstrated that, in the detection of GH, there were significant contributions from maternal factors and MAP but not PAPP-A ($P = 0.693$), PIGF ($P = 0.274$), and PI GF.

<p>| Table 3. MAP, Uterine Artery PI, PAPP-A, and PIGF in the 4 Outcome Groups of the Cohort and Case Control |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Maternal Variable</th>
<th>MAP (Median, IQR) mm Hg</th>
<th>Uterine Artery PI (Median, IQR)</th>
<th>Serum PAPP-A (Median, IQR) mU/L</th>
<th>Serum PIGF (Median, IQR) pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>1.00 (0.95 to 1.05)</td>
<td>84.3 (79.5 to 89.5)</td>
<td>1.00 (0.84 to 1.22)</td>
<td>1.63 (1.35 to 1.98)</td>
</tr>
<tr>
<td>Case control</td>
<td>1.00 (0.96 to 1.06)</td>
<td>84.5 (80.7 to 89.7)</td>
<td>1.05 (0.84 to 1.28)</td>
<td>1.70 (1.37 to 2.02)</td>
</tr>
<tr>
<td>Early PE</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cohort</td>
<td>1.13 (1.05 to 1.19)</td>
<td>94.5 (88.4 to 102.0)</td>
<td>1.51 (1.29 to 1.67)</td>
<td>2.45 (2.22 to 2.64)</td>
</tr>
<tr>
<td>Case control</td>
<td>1.15 (1.06 to 1.22)</td>
<td>98.0 (90.2 to 105.3)</td>
<td>1.53 (1.26 to 1.68)</td>
<td>2.50 (2.16 to 2.65)</td>
</tr>
<tr>
<td>Late PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>1.08 (1.02 to 1.14)</td>
<td>93.5 (87.7 to 98.8)</td>
<td>1.19 (0.90 to 1.44)</td>
<td>1.92 (1.53 to 2.36)</td>
</tr>
<tr>
<td>Case control</td>
<td>1.08 (1.01 to 1.13)</td>
<td>93.8 (87.0 to 98.8)</td>
<td>1.23 (0.93 to 1.45)</td>
<td>2.02 (1.54 to 2.40)</td>
</tr>
<tr>
<td>GH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>1.07 (1.00 to 1.13)</td>
<td>92.4 (86.0 to 98.1)</td>
<td>1.06 (0.87 to 1.29)</td>
<td>1.71 (1.39 to 2.06)</td>
</tr>
<tr>
<td>Case control</td>
<td>1.09 (1.01 to 1.32)</td>
<td>93.7 (86.0 to 98.1)</td>
<td>1.11 (0.90 to 1.32)</td>
<td>1.78 (1.43 to 2.10)</td>
</tr>
</tbody>
</table>

Comparisons are between outcome groups in the case-control study (Dunn’s procedure for continuous variables).
or uterine artery PI ($P=0.133$); $Y=-4.506+19.852\times \log {\text{MAP MoM}}+0.105\times {\text{BMI}}$ in kg/m$^2$ + (1.446 if family history of PE) + (−0.795 if parous no previous PE or 0 if parous with previous PE or nulliparous; $R^2=0.209$; $P<0.0001$).

**Performance of Screening**

The Figure showed the performance of screening for early PE, late PE, and GH using each of the algorithms for early PE, late PE, and GH. At a 5% false-positive rate, the estimated respective detection rates of early PE, late PE, and GH were 93.1%, 82.8%, 44.9%, and 23.2% using the algorithm for late PE; 41.4%, 40.8%, and 34.1% using the algorithm for GH.

Screening for hypertensive disorders using the algorithm for early PE in our base-cohort population of 7797 cases would have potentially classified as screen-positive a total of 476 pregnancies including 375 (5% of the 7504) with no hypertensive disorders, 32 (93.1% of the 34) with early PE; 44 (35.7% of the 123) with late PE, and 25 (18.3% of the 136) with GH. Therefore, 21.2% of the pregnancies classified as screen-positive would develop hypertensive disorders.

**Discussion**

The findings of this study confirm, in women who develop hypertensive disorders during pregnancy, the MAP and uterine artery PI are increased, and the serum concentrations of PAPP-A and PlGF are decreased at 11 to 13 weeks of gestation.8–11 Furthermore, the patient-specific risk for both chromosomal defects and hypertensive disorders can be derived by algorithms combining maternal racial origin, BMI, and personal or family history of PE with the measurements of MAP, uterine artery PI, PAPP-A, and PlGF.

We chose 11 to 13 weeks as the gestation for screening, because this is emerging as the first hospital visit of pregnant women at which combined sonographic and biochemical testing for chromosomal and other major defects is carried out.12,13 At this visit, first, a record is made of maternal characteristics; second, an ultrasound scan is carried out to determine the number of fetuses, confirm the gestation from the fetal CRL, exclude major defects, and measure the nuchal translucency thickness and other first-trimester markers of chromosomal defects; and, third, maternal blood is taken for measurement of free β-human chorionic gonadotropin and PAPP-A.13 Recent evidence suggests that improved first-trimester screening for chromosomal defects may be provided by the inclusion of serum PlGF.16 There is also evidence that, because low PAPP-A is observed in both chromosomal abnormalities and early PE, but uterine artery PI is normal in the former and high in the latter, inclusion of uterine artery PI could also improve first-trimester screening for chromosomal defects.17 Consequently, women attending their first hospital visit could have a series of biophysical and biochemical measurements that will then be used to estimate their patient-specific risk for both chromosomal defects and hypertensive disorders.

In the unaffected group, which did not develop PE or GH, the measured values of MAP, uterine artery PI, serum PAPP-A, and serum PlGF changed with fetal CRL and, therefore, gestational age, maternal BMI, and racial origin, and, in addition, some of the variables were affected by maternal age, smoking, and parity. Consequently, the measured values were adjusted for these variables before comparing results with pathological pregnancies.

PlGF is a member of the vascular endothelial growth factor subfamily, it is expressed by trophoblast cells, and has both vasculogenetic and angiogenetic functions. Its angiogenetic abilities have been speculated to play a role in normal pregnancy, and changes in the levels of PlGF or its inhibitory receptor have been implicated in the development of PE.18–21 PAPP-A is a syncytiotrophoblast-derived metalloproteinase that enhances the mitogenic function of the insulin-like growth factors by cleaving the complex formed between such growth factors and their binding proteins.22,23 Because the insulin-like growth factor system is believed to play a significant role in trophoblast invasion, it is not surprising that low-serum PAPP-A is associated with a higher incidence of PE.24

In both early PE and late PE, but not in GH, there were significant differences from the unaffected group in uterine
artery PI and serum PAPP-A and PI GF, and the values in early PE were substantially different from those developing late PE. In contrast, MAP was increased in all types of hypertensive disorders, with the values being higher in those developing early PE and similar between late PE and GH. Early screening for hypertensive disorders by a combination of maternal factors, MAP, uterine artery PI, PAPP-A, and PI GF is particularly effective in identifying severe early onset PE than late PE or GH with respective detection rates of \( \approx 90\% \), \( 35\% \), and \( 20\% \). The detection rate of \( \approx 90\% \) for early PE, at a false-positive rate of 5\%, by the suggested combination of biophysical and biochemical parameters in this study, is substantially higher than the 60\% in screening by history, uterine artery PI, and PAPP-A or the 40\% in screening by history and MAP.8,10

The high detection rate for early PE is important because it is this rather than late PE or GH that is associated with increased risk of perinatal mortality and morbidity and both short-term and long-term maternal complications.25–28 The underlying mechanism for PE is thought to be impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide nonmuscular channels.29,30 It is, therefore, possible that the difference in the performance of screening between early and late PE may simply reflect that there is a wide spectrum in such impaired placentation and consequent clinical presentation of the disease. Alternatively, this difference may support emerging evidence that PE may be a common clinical expression of distinct pathophysiologic processes. Recent studies on placental pathology have suggested that early onset disease is more likely to be associated with abnormal villous and vascular morphology, whereas in late onset disease, the placental morphology and histology are not dissimilar to those in controls.30,31 On the contrary, there is evidence that late onset compared with early onset disease is more likely to be related to impaired glucose metabolism32 and a hyperdynamic-low peripheral resistance (as opposed to a low-cardiac output-vasoconstricted) maternal cardiovascular profile,33,34 a profile that resembles the one found in nonpregnant obese patients with subclinical glucose intolerance.35–37

Our model includes variables that are either reflective of placental function (PAPP-A and PI GF) or depict increased resistance in the uteroplacental circulation (uterine artery PI). If, therefore, late PE is a disease not associated with impaired placentation, it is not surprising that PAPP-A and PI GF do not perform as well as in early disease. In addition, our previous work that showed a positive correlation between maternal peripheral resistance and uterine artery PI explains why uterine artery PI would not perform as well in a group of patients who are more likely to have a low-peripheral resistance hemodynamic profile.33,34,39

First-trimester screening can identify a high proportion of pregnancies destined to develop hypertensive disorders, and it was estimated that 1 in 5 pregnancies classified as being screen-positive would develop such disorders. Such high detection rates and positive predictive values cannot be achieved by the traditional approach of screening, which relies entirely on maternal history. Consequently, if our results are confirmed by further prospective studies, the proposed combined approach to screening could be incorporated into routine care for early assessment of patient-specific risk for hypertensive disorders.5 Such an approach would rationalize the frequency and type of prenatal visits for pregnant women according to estimated risk, as recommended by the National Institute of Clinical Excellence in the United Kingdom.5 It is aimed that the care of low-risk pregnancies is decentralized to local, 1-stop settings or at home, whereas high-risk pregnancies are cared for in specialized centers.40 In the academic setting, centralized care of pregnancies at high risk for PE would lead to a more effective concentration of research activity in an attempt to improve the understanding of the pathophysiology and treatment of the condition.

Perspectives

The traditional approach to screening for PE, which is based on maternal demographic characteristics and medical history, identifies \( \approx 30\% \) of cases destined to develop early PE for a false-positive rate of 5\%. This study proposes a new screening method by a combination of factors in the maternal history, MAP, uterine artery PI, and serum PAPP-A and PI GF at 11 to 13 weeks of gestation, which, for the same false-positive rate of 5\%, could identify \( >90\% \) of cases of early PE.

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Disclosures

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References


