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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 plasma 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,

DOI: 10.1161/HYPERTENSIONAHA.108.127977

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.[12,13] We recorded maternal characteristics and medical history, measured the uterine artery PI by transabdominal color Doppler,[9] measured MAP by automated devices,[8] 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=417), there was a fetal major defect (n=43) or fetal aneuploidy (n=50), the pregnancies resulted in fetal death or miscarriage 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 phenotypically 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.[8–11]

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 antihypertensive, antidepressant, antiepileptic, aspirin, steroids, betamimetic, 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.[14] 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 trophoblastic 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 χ^2 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 χ^2 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 logarithmic 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.[15] 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

Table 1. Maternal Characteristics in the 4 Outcome Groups of the Cohort and Case Controls

Maternal Variable	Control Cohort (n=7504)	Control Case Control (n=418)	Early PE Cohort (n=34)	Early PE Case Control (n=29)	Late PE Cohort (n=123)	Late PE Case Control (n=98)	GH Cohort (n=136)	GH Case Control (n=82)
Maternal age, median (IQR), y	32.3 (28.2 to 35.9)	32.2 (28.7 to 36.0)	31.6 (25.5 to 36.2)	31.7 (26.3 to 37.4)	32.2 (27.2 to 36.8)	31.5 (26.6 to 36.3)	33.0 (28.8 to 35.7)	32.9 (30.0 to 35.6)
BMI, median (IQR), kg/m^2	24.4 (22.1 to 27.6)	24.7 (22.4 to 27.8)	27.6 (23.3 to 31.9)	27.9 (23.9 to 32.0)‡	27.3 (23.8 to 32.0)	27.0 (23.7 to 33.2)‡	26.5 (23.9 to 31.0)	26.6 (24.4 to 31.2)‡
Racial origin								
White, n (%)	5345 (71.2)	306 (73.2)	13 (38.2)	11 (37.9)‡	53 (43.1)	41 (41.8)‡	103 (75.7)	62 (75.6)
Black, n (%)	1425 (19.0)	73 (17.5)	17 (50.0)	14 (48.3)‡	51 (41.5)	41 (41.8)‡	25 (18.4)	15 (18.3)
Indian or Pakistani, n (%)	365 (4.9)	25 (6.0)	2 (5.9)	2 (6.9)	8 (6.5)	7 (7.1)	1 (0.7)	0*
Chinese or Japanese, n (%)	106 (1.4)	7 (1.7)	0	0	3 (2.4)	2 (2.0)	1 (0.7)	1 (1.2)
Mixed, n (%)	263 (3.5)	7 (1.7)	2 (5.9)	2 (6.9)	8 (6.5)	7 (7.1)	6 (4.4)	4 (4.9)
Parity								
Nulliparous, n (%)	3536 (47.1)	197 (47.1)	18 (52.9)	15 (51.7)	75 (61.0)	64 (65.3)†	86 (63.2)	46 (56.1)
Parous, no previous PE, n (%)	3784 (50.4)	212 (50.7)	8 (23.5)	7 (24.1)†	30 (24.4)	23 (23.5)‡	38 (27.9)	29 (35.4)*
Parous, previous PE, n (%)	184 (2.5)	9 (2.2)	8 (23.5)	7 (24.1)‡	18 (14.6)	11 (11.2)‡	12 (8.8)	7 (8.5)*
Cigarette smoker, n (%)	641 (8.5)	25 (5.5)	0	0	7 (5.7)	6 (6.1)	11 (8.1)	7 (8.5)
Family history of PE, mother, n (%)	286 (3.8)	11 (2.6)	3 (8.8)	3 (10.3)	15 (12.2)	12 (12.2)†	15 (11.0)	8 (9.8)†
Conception								
Spontaneous, n (%)	7233 (96.4)	406 (97.1)	29 (85.3)	25 (86.2)§	117 (95.1)	94 (95.9)	127 (93.4)	80 (97.6)
Assisted, n (%)	271 (3.6)	12 (2.9)	4 (14.7)	4 (13.8)§	8 (4.9)	4 (4.1)	9 (6.6)	2 (2.4)
Medical history								
None, n (%)	7340 (97.8)	408 (97.6)	29 (85.3)	24 (82.8)†	116 (94.3)	93 (94.9)	134 (98.5)	80 (97.6)
Chronic hypertension, n (%)	53 (0.7)	2 (0.5)	4 (11.8)	4 (13.8)†	4 (3.3)	4 (4.1)*	0§	0§
Diabetes mellitus, n (%)	60 (0.8)	5 (1.2)	0	0	2 (1.6)	0	2 (1.5)	2 (2.4)
APS/thrombophilia, n (%)	36 (0.4)	2 (0.5)	1 (2.9)	1 (3.4)	1 (0.8)	1 (1.0)	0	0
Other, n (%)	15 (0.2)	1 (0.2)	0	0	0	0	0	0
Medication during pregnancy								
None, n (%)	6905 (92.0)	390 (93.3)	29 (85.3)	25 (86.2)	112 (91.1)	90 (91.8)	119 (87.5)	72 (87.8)
Antihypertensives, n (%)	44 (0.6)	0	2 (5.9)	2 (6.9)‖	2 (1.6)	2 (2.0)§	0	0
Insulin, n (%)	54 (0.7)	4 (1.0)	0	0	2 (1.6)	0	2 (1.5)	2 (2.4)
Antiasthmatics, n (%)	226 (3.1)	8 (1.9)	1 (2.9)	0	0	0	0	0
Thyroxin, n (%)	96 (1.3)	5 (1.2)	1 (2.9)	1 (3.4)	1 (0.8)	1 (1.0)	2 (1.5)	2 (2.4)
Aspirin, n (%)	77 (1.0)	4 (1.0)	1 (2.9)	1 (3.4)	0	0	2 (1.5)	1 (1.2)
Antidepressant, n (%)	44 (0.6)	4 (1.0)	0	0	1 (0.8)	1 (1.0)	2 (1.5)	1 (1.2)
Antiepileptic, n (%)	38 (0.5)	2 (0.5)	0	0	0	0	2 (1.5)	1 (1.2)
Others, n (%)	20 (0.3)	1 (0.2)	0	0	0	0	0	0

APS indicates antiphospholipid syndrome.

Comparisons between base-cohort and case-control populations showed no significant difference.

Comparisons between outcome groups in the case-control study (χ^2 or Fisher's exact test for categorical variables and Kruskal-Wallis test and Dunn's procedure for continuous variables): *$P<0.05$, †$P<0.01$, ‡$P<0.0001$.

§By definition, there were no cases of chronic hypertension in women who developed GH.

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 PlGF, 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 PlGF and then expressed the observed value as an MoM (Table 3).

Table 2. Multiple Regression Analysis in the Unaffected Group in Predicting Log Uterine Artery PI, Log MAP, and Log PlGF by Maternal Characteristics and Gestation

Independent Variable	Log Uterine Artery PI		Log MAP		Log PlGF	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Intercept	0.411 (0.381 to 0.441)	<0.0001	1.859 (1.850 to 1.868)	<0.0001	1.098 (0.920 to 1.276)	<0.0001
Fetal crown rump length, mm	−0.002 (−0.003 to −0.002)	<0.0001	−0.0002 (−0.0003 to −0.0001)	0.001	0.008 (0.006 to 0.010)	<0.0001
Maternal age, y	−0.001 (−0.001 to −0.0002)	0.003	0.001 (0.0004 to 0.0007)	<0.0001	. . .	. . .
BMI, kg/m^2	−0.002 (−0.002 to −0.001)	<0.0001	0.003 (0.002 to 0.003)	<0.0001	−0.002 (−0.003 to −0.0004)*	0.012
Smoking	. . .	. . .	−0.007 (−0.010 to −0.004)	<0.0001	0.194 (0.117 to 0.271)	<0.0001
Parous	. . .	. . .	−0.006 (−0.007 to −0.004)	<0.0001	. . .	. . .
Racial origin						
Black	0.023 (0.016 to 0.030)	<0.0001	−0.004 (−0.006 to −0.001)	0.002	0.187 (0.140 to 0.234)	<0.0001
Indian or Pakistani	. . .	. . .	−0.004 (−0.008 to −0.001)	0.022	0.117 (0.042 to 0.192)	0.002
Chinese or Japanese	. . .	. . .	−0.010 (−0.017 to −0.003)	0.006	. . .	. . .
Mixed	0.019 (0.004 to 0.034)	0.011	−0.005 (−0.010 to −0.001)	0.025	. . .	. . .

*Weight is in kilograms.

Similarly, we used a previously derived formula for PAPP-A[15] to calculate the respective MoM value for this metabolite.

Hypertensive Disorders

As shown in Table 3, the MAP was significantly higher in early PE, late PE, and GH than in the controls ($P<0.0001$); in early PE than in late PE ($P=0.02$); and in early PE than in GH ($P=0.01$). Uterine artery PI was higher in early PE than in controls ($P<0.0001$), in late PE than in controls ($P=0.0002$), in early PE than in late PE ($P=0.001$), and in early PE than in GH ($P<0.0001$). Serum PAPP-A was lower in early PE than in controls ($P<0.0001$), in late PE than in controls ($P=0.03$), in early PE than in late PE ($P=0.005$), and in early PE than in GH ($P=0.001$). Serum PlGF was lower in early PE and late PE than in controls ($P<0.0001$), in early PE than in GH ($P<0.0001$), and in late PE than in GH ($P=0.02$).

Patient-Specific Risks for PE and GH

The patient-specific risks for PE and GH (%) were calculated from the formula: odds/(1+odds), where odds=e^Y. Y was derived from logistic regression analysis.

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=$-8.776+14.177\times$log uterine artery PI MoM+$42.960\times$log MAP MoM$-2.249\times$log PAPP-A MoM$-3.529\times$log PlGF MoM+$0.120\times$BMI in kg/m^2+(-1.472 if parous with no previous PE or 0 if nulliparous or parous with previous PE; $R^2=0.636$; $P<0.0001$).

Logistic regression analysis demonstrated that, in the detection of late PE, there were significant contributions from maternal factors, uterine artery PI, MAP, and PlGF but not PAPP-A ($P=0.814$): Y=$-5.324+2.233\times$log uterine artery PI+$23.134\times$log MAP MoM$-2.408\times$log PlGF MoM+$0.123\times$BMI in kg/m^2+(1.019 if black, 2.028 if mixed race, or 0 if other racial origins)+(1.298 if family history of PE)+(-1.443 if parous no previous PE or 0 if parous with previous PE or nulliparous; $R^2=0.412$; $P<0.0001$).

Logistic regression analysis demonstrated that, in the prediction of GH, there were significant contributions from maternal factors and MAP but not PAPP-A ($P=0.693$), PlGF ($P=0.274$),

Table 3. MAP, Uterine Artery PI, PAPP-A, and PlGF in the 4 Outcome Groups of the Cohort and Case Control

Maternal Variable	MAP (Median, IQR)		Uterine Artery PI (Median, IQR)		Serum PAPP-A (Median, IQR)		Serum PlGF (Median, IQR)	
	MoM	mm Hg	MoM	Unit	MoM	mU/L	MoM	pg/mL
Unaffected								
Cohort	1.00 (0.95 to 1.05)	84.3 (79.5 to 89.5)	1.00 (0.84 to 1.22)	1.63 (1.35 to 1.98)	1.00 (0.69 to 1.41)	2.80 (1.79 to 4.33)	. . .	. . .
Case control	1.00 (0.96 to 1.06)	84.5 (80.7 to 89.7)	1.05 (0.84 to 1.28)	1.70 (1.37 to 2.02)	1.03 (0.72 to 1.42)	2.95 (1.83 to 4.68)	0.98 (0.80 to 1.29)	33.7 (26.0 to 46.2)
Early PE								
Cohort	1.13 (1.05 to 1.19)	94.5 (88.4 to 102.0)	1.51 (1.29 to 1.67)	2.45 (2.22 to 2.64)	0.56 (0.47 to 0.98)	2.35 (1.09 to 3.36)	. . .	. . .
Case control	1.15 (1.06 to 1.22)	98.0 (90.2 to 105.3)	1.53 (1.26 to 1.68)	2.50 (2.16 to 2.65)	0.53 (0.39 to 0.96)	2.44 (0.89 to 3.18)	0.61 (0.47 to 0.82)	25.8 (14.7 to 33.9)
Late PE								
Cohort	1.08 (1.02 to 1.14)	93.5 (87.7 to 98.8)	1.19 (0.90 to 1.44)	1.92 (1.53 to 2.36)	0.92 (0.60 to 1.25)	2.64 (1.49 to 4.09)	. . .	. . .
Case control	1.08 (1.01 to 1.13)	93.8 (87.0 to 98.8)	1.23 (0.93 to 1.45)	2.02 (1.54 to 2.40)	0.93 (0.57 to 1.31)	2.66 (1.49 to 4.32)	0.83 (0.54 to 1.07)	29.8 (21.3 to 35.7)
GH								
Cohort	1.07 (1.00 to 1.13)	92.4 (86.0 to 98.1)	1.06 (0.87 to 1.29)	1.71 (1.39 to 2.06)	0.94 (0.62 to 1.33)	2.16 (1.54 to 3.52)	. . .	. . .
Case control	1.09 (1.01 to 1.32)	93.7 (86.0 to 98.1)	1.11 (0.90 to 1.32)	1.78 (1.43 to 2.10)	0.94 (0.64 to 1.45)	2.05 (1.56 to 3.52)	0.95 (0.69 to 1.24)	29.2 (23.2 to 42.3)

Comparisons are between outcome groups in the case-control study (Dunn's procedure for continuous variables).

A

B

C
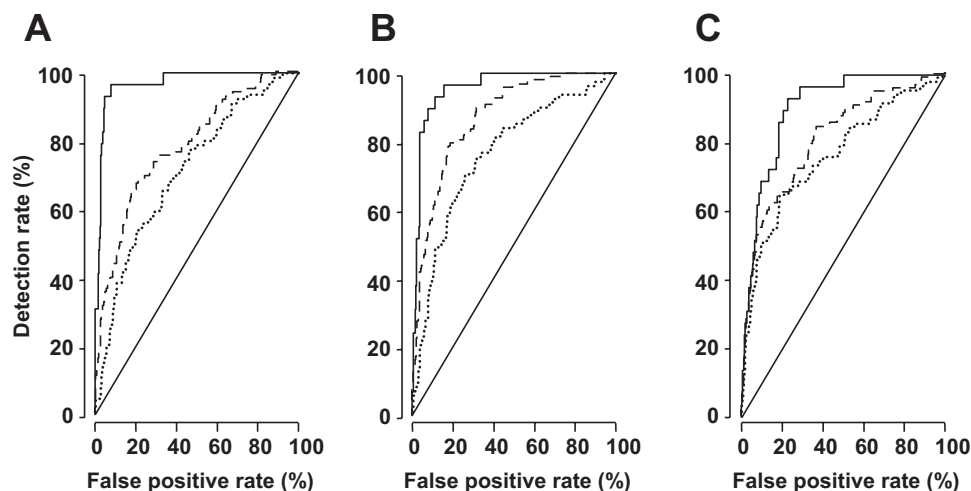
Figure. Detection rates of early PE (solid line), late PE (long-dashed line), and GH (dotted line) for fixed false-positive rates using the algorithms for early PE (A), late PE (B), and GH (C), based on a combination of maternal characteristics, uterine artery Doppler, MAP, and serum PAPP-A and PlGF.

or uterine artery PI ($P=0.133$): $Y=-4.506+19.852\times\log$ MAP MoM$+0.105\times$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%, 35.7%, and 18.3% using the algorithm for early PE; 82.8%, 44.9%, and 23.2% using the algorithm for late PE; and 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 that, 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 the development of these complications 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 PlGF, 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 PlGF is particularly effective in identifying severe early onset PE than late PE or GH with respective detection rates of ≈90%, 35%, and 20%. The detection rate of ≈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 pathophysiological 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 metabolism[32] 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 PlGF) 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 PlGF 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[38] 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 ≈30% of cases destined to develop early PE for a false-positive rate of 5%.[7] 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 PlGF at 11 to 13 weeks of gestation, which, for the same false-positive rate of 5%, could identify >90% of cases of early PE.

Disclosures
None.

References
1. World Health Organization. *Make Every Mother and Child Count.* World Health Report, 2005. Geneva, Switzerland: World Health Organization; 2005.
2. Lewis G, ed. The Confidential Enquiry into Maternal and Child Health (CEMACH). *Saving Mothers' Lives: Reviewing Maternal Deaths to Make Motherhood Safer—2003–2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom.* London, United Kingdom: Confidential Enquiry into Maternal and Child Health; 2007.
3. Confidential Enquiry into Maternal and Child Health (CEMACH). *Perinatal Mortality 2006: England, Wales and Northern Ireland.* London, United Kingdom: Confidential Enquiry into Maternal and Child Health; 2008.
4. American College of Obstetricians and Gynecologists Committee on Practice Bulletins–Obstetrics. ACOG practice bulletin: diagnosis and management of pre-eclampsia and eclampsia: number 33, January 2002. *Obstet Gynecol.* 2002;99:159–167.
5. National Collaborating Centre for Women's and Children's Health. *Antenatal Care: Routine Care for the Healthy Pregnant Woman. Clinical Guideline*. Commissioned by the National Institute for Clinical Excellence. London, United Kingdom: RCOG Press; 2008.
6. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ.* 2005;330: 565–572.

7. Yu CK, Smith GC, Papageorghiou AT, Cacho AM, Nicolaides KH. An integrated model for the prediction of preeclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. *Am J Obstet Gynecol*. 2005;193:429–436.

8. Poon LC, Kametas NA, Pandeva I, Valencia C, Nicolaides KH. Mean arterial pressure at 11(+0) to 13(+6) weeks in the prediction of pre-eclampsia. *Hypertension*. 2008;51:1027–1033.

9. Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. Uterine artery Doppler at 11+0 to 13+6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol*. 2007;30:742–749.

10. Poon LCY, Maiz N, Valencia C, Plasencia W, Nicolaides KH. First-trimester maternal serum PAPP-A and preeclampsia. *Ultrasound Obstet Gynecol*. 2008;33:23–33.

11. Akolekar R, Zaragoza E, Poon LCY, Pepes S, Nicolaides KH. Maternal serum placental growth factor (PlGF) at 11+0 to 13+6 weeks of gestation in the prediction of preeclampsia. *Ultrasound Obstet Gynecol*. 2008;32:732–739.

12. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10–14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. Lancet. 1998;352:343–346.

13. Kagan KO, Wright D, Baker A, Sahota D, Nicolaides KH. Screening for trisomy 21 by maternal age, fetal NT, free β hCG and PAPP-A. *Ultrasound Obstet Gynecol*. 2008;31:618–624.

14. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol*. 1988;158:892–898.

15. Kagan KO, Wright D, Spencer K, Molina FS, Nicolaides KH. First-trimester screening for trisomy 21 by free beta-human chorionic gonad-otropin and pregnancy-associated plasma protein-A: impact of maternal and pregnancy characteristics. *Ultrasound Obstet Gynecol*. 2008;31:493–502.

16. Zaragoza E, Akolekar R, Poon LCY, Pepes S, Nicolaides KH. Maternal serum placental growth factor (PlGF) at 11+0–13+6 weeks in chromosomally abnormal pregnancies. *Ultrasound Obstet Gynecol*. 2009;33:382–386.

17. Bindra R, Curcio P, Cicero S, Martin A, Nicolaides KH. Uterine artery Doppler at 11–14 weeks of gestation in chromosomally abnormal fetuses. *Ultrasound Obstet Gynecol*. 2001;18:587–589.

18. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest*. 2003;111:649–658.

19. Ahmad S, Ahmed A. Elevated placental soluble vascular endothelial growth factor receptor-1 inhibits angiogenesis in preeclampsia. *Circ Res*. 2004;95:884–891.

20. Stepan H, Unversucht A, Wessel N, Faber R. Predictive value of maternal angiogenic factors in second trimester pregnancies with abnormal uterine perfusion. *Hypertension*. 2007;49:818–824.

21. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, Schisterman EF, Thadhani R, Sachs BP, Epstein FH, Sibai BM, Sukhatme VP, Karumanchi SA. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med*. 2004;350:672–683.

22. Lawrence JB, Oxvig C, Overgaard MT, Sottrup-Jensen L, Gleich GJ, Hays LG, Yates JR III, Conover CA. The insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease secreted by human fibroblasts is pregnancy-associated plasma protein-A. *Proc Natl Acad Sci U S A*. 1999;96:3149–3153.

23. Bonno M, Oxvig C, Kephart GM, Wagner JM, Kristensen T, Sottrup-Jensen L, Gleich GJ. Localization of pregnancy-associated plasma protein-A and colocalization of pregnancy-associated plasma protein-A messenger ribonucleic acid and eosinophil granule major basic protein messenger ribonucleic acid in placenta. *Lab Invest*. 1994;71:560–566.

24. Irwin JC, Suen LF, Martina NA, Mark SP, Giudice LC. Role of the IGF system in trophoblast invasion and pre-eclampsia. *Hum Reprod*. 1999;14(suppl 2):90–96.

25. von Dadelszen P, Magee LA, Roberts JM. Subclassification of pre-eclampsia. *Hypertens Pregnancy*. 2003;22:143–148.

26. Witlin GA, Saade GR, Mattar FM, Sibai BM. Predictors of neonatal outcome in women with severe pre-eclampsia or eclampsia between 24 and 33 weeks' gestation. *Am J Obstet Gynecol*. 2000;182:607–611.

27. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ*. 2001;323:1213–1217.

28. Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. *BJOG*. 1986;93:1049–1059.

29. Pijnenborg R, Anthony J, Davey DA, Rees A, Tiltman A, Vercruysse L, van Assche A. Placental bed spiral arteries in the hypertensive disorders of pregnancy. *BJOG*. 1991;98:648–655.

30. Moldenhauer JS, Stanek J, Warshak C, Khoury J, Sibai B. The frequency and severity of placental findings in women with pre-eclampsia are gestational age dependent. *Am J Obstet Gynecol*. 2003;189:1173–1177.

31. Egbor M, Ansari T, Morris N, Green CJ, Sibbons PD. Morphometric placental villous and vascular abnormalities in early- and late-onset pre-eclampsia with and without fetal growth restriction. *BJOG*. 2006;113:580–589.

32. D'Anna R, Baviera G, Corrado F, Giordano D, De Vivo A, Nicocia G, Di Benedetto A. Adiponectin and insulin resistance in early- and late-onset pre-eclampsia. *BJOG*. 2006;113:1264–1269.

33. Bosio PM, McKenna PJ, Conroy R, O'Herlihy C. Maternal central hemodynamics in hypertensive disorders or pregnancy. *Obstet Gynecol*. 1999;94:978–984.

34. Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. *Obstet Gynecol*. 1990;76:1061–1069.

35. Collis T, Devereux RB, Roman MJ, de Simone G, Yeh J, Howard BV, Fabsitz RR, Welty TK. Relations of stroke volume and cardiac output to body composition: the strong heart study. *Circulation*. 2001;103:820–825.

36. Messerli FH, Ventura HO, Reisin E, Dreslinski GR, Dunn FG, MacPhee AA, Frohlich ED. Borderline hypertension and obesity: two prehypertensive states with elevated cardiac output. *Circulation*. 1982;66:55–60.

37. Sharma AM. Mediastinal fat, insulin resistance, and hypertension. *Hypertension*. 2004;44:117–118.

38. Khaw A, Kametas NA, Turan OM, Bamfo JE, Nicolaides KH. Maternal cardiac function and uterine artery Doppler at 11–14 weeks in the prediction of pre-eclampsia in nulliparous women. *BJOG*. 2008;115:369–376.

39. De Paco C, Kametas N, Rencoret G, Strobl I, Nicolaides KH. Maternal cardiac output between 11 and 13 weeks of gestation in the prediction of preeclampsia and small for gestational age. *Obstet Gynecol*. 2008;111:292–300.

40. Darzi A. *A Framework for Action*. London, United Kingdom: NHS London; 2007. Available at: http://www.healthcareforlondon.nhs.uk. Accessed September 20, 2008.