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Hypertensive disorders in pregnancy: screening by uterine artery Doppler imaging and blood pressure at 11–13 weeks

L. C. Y. POON, G. KARAGIANNIS, A. LEAL, X. C. ROMERO and K. H. NICOLAIDES

Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK

KEYWORDS: gestational hypertension; mean arterial pressure; pre-eclampsia; screening; uterine artery Doppler

ABSTRACT

Objectives *To examine the performance of screening for hypertensive disorders in pregnancy at 11–13 weeks by a combination of the maternal history, uterine artery Doppler imaging and blood pressure.*

Methods *This was a prospective screening study for pre-eclampsia (PE) requiring delivery before 34 weeks (early PE), late PE and gestational hypertension (GH) in women attending for their routine first hospital visit in pregnancy at 11 + 0 to 13 + 6 weeks of gestation. Maternal history was recorded, color flow Doppler imaging was used to identify the uterine artery with the lowest pulsatility index (L-PI) and automated devices were used to measure the mean arterial pressure (MAP). The performance of screening for PE and GH by a combination of the maternal factor-derived a-priori risk, the uterine artery L-PI and MAP was determined.*

Results *There were 8061 (96.4%) cases unaffected by PE or GH, 165 (2.0%) that developed PE including 37 that required delivery before 34 weeks (early PE) and 128 with late PE, and 140 (1.7%) that developed GH. The MAP was higher in early PE, late PE and GH than in the unaffected group ($P < 0.0001$), and in early PE than in GH ($P = 0.002$). The uterine artery L-PI was significantly higher in early PE and late PE than in the unaffected group ($P < 0.0001$), in early PE than late PE or GH ($P < 0.0001$), and in GH than in the unaffected group ($P = 0.014$). In screening by a combination of the maternal factor-derived a-priori risk, uterine artery L-PI and MAP, the estimated detection rate at a 10% false-positive rate was 89.2% (95% CI, 74.6–96.9%) for early PE, 57.0% (95% CI, 48.0–65.7%) for late PE and 50.0% (95% CI, 41.4–58.6%) for GH.*

Conclusions *Effective screening for hypertensive disorders in pregnancy is provided by a combination of maternal history, uterine artery Doppler imaging and blood pressure at 11–13 weeks.* Copyright © 2009 ISUOG. *Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Pre-eclampsia (PE), which affects about 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality[1–3]. Hypertension developing in the second half of pregnancy is subdivided according to the presence or absence of coexisting significant proteinuria into PE and gestational hypertension (GH). Recent evidence suggests that PE can be further subdivided into early PE and late PE, the former being associated with a higher incidence of fetal growth restriction and both short-term and long-term maternal mortality and morbidity[4–6].

In the UK, the National Institute for Health and Clinical Excellence (NICE) has issued guidelines on routine antenatal care, recommending that at the booking visit a woman's level of risk for PE, based on factors in her history, should be determined and the subsequent intensity of antenatal care should be based on this risk[7]. We have recently demonstrated that the NICE recommendations of screening for PE by maternal characteristics and previous history is potentially useful only when the various factors are incorporated into a combined algorithm derived by multivariate analysis[8]. Such an approach made it possible to derive the maternal factor-derived *a-priori* risk for early PE requiring delivery before 34 weeks, late PE and GH based on maternal age, body mass index (BMI), racial origin, history of PE, chronic hypertension and method of conception. The estimated detection rates for early PE, late PE and GH are about 47%, 41% and 31%, respectively, at a 10% false-positive rate[8].

Correspondence to: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK (e-mail: fmf@fetalmedicine.com)

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The underlying mechanism for the development of PE is thought to be impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide non-muscular channels independent of maternal vasomotor control[9–12]. Doppler studies of the uterine arteries at 11–13 weeks have demonstrated that impedance to flow is increased in pregnancies that subsequently develop hypertensive disorders and that the increase is particularly marked for early PE[13–15]. The best performance of screening is provided by assessing the uterine artery with the lowest pulsatility index (L-PI)[15]. The estimated detection rate, at a 10% false-positive rate, in screening by a combination of the maternal factor-derived *a-priori* risk with uterine artery L-PI was 81% for early PE, 45% for late PE and 35% for GH[15]. Early prediction of hypertensive disorders can also be provided by measurement of the mean arterial pressure (MAP) at 11–13 weeks[16,17]. The estimated detection rate, at a 10% false-positive rate, in screening by a combination of the maternal factor-derived *a-priori* risk with MAP was 79% for early PE, 52% for late PE and 48% for GH[17].

The aim of this study was to examine the performance of screening for hypertensive disorders in pregnancy by a combination of the maternal factor-derived *a-priori* risk with the uterine artery L-PI and MAP at 11–13 weeks.

METHODS

This was a prospective screening study for hypertensive disorders in women attending for their routine first hospital visit in pregnancy. In this visit, which is held at 11 + 0 to 13 + 6 weeks of gestation, all women have an ultrasound scan to confirm gestational age from the measurement of the fetal crown–rump length (CRL), to diagnose any major fetal abnormalities and to measure fetal nuchal translucency thickness as part of screening for chromosomal abnormalities[18,19]. We recorded maternal characteristics and medical history, and measured the MAP and uterine artery L-PI[8,15,17]. 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 9149 singleton pregnancies between March 2006 and November 2007. We excluded 783 (8.6%) because they had missing outcome data ($n = 443$), there was a major fetal defect or aneuploidy ($n = 153$), the pregnancies resulted in fetal death or miscarriage before 24 weeks of gestation ($n = 139$), the pregnancies were terminated for social reasons ($n = 15$), or when there was at least one episode of hypertension but on the basis of the available data it was not possible to determine whether the diagnosis was PE ($n = 33$). Of the remaining 8366 cases, 165 (2.0%) developed PE including 37 that required delivery before 34 weeks (early PE) and 128 with late PE, 140 with GH and 8061 (96.4%) cases that were unaffected by PE or GH. This was the same population described in the individual papers on maternal factor-derived *a-priori* risk[8], uterine artery L-PI[15], and MAP[17].

The blood pressure was taken by automated devices (3BTO-A2, Microlife, Taipei, Taiwan) which were calibrated before and at regular intervals during the study[20]. Recordings were made with the women in the seated position and the MAP was measured as described previously[17]. The pulsatility index (PI) from both uterine arteries was measured by transabdominal ultrasound imaging as described previously and the lower of the two (L-PI) was used for analysis[14,15]. In total 34 sonographers participated in the study and they had all obtained the Fetal Medicine Foundation Certificate of competence in obstetric Doppler imaging (http://www.fetalmedicine.com). The results of the MAP and uterine artery PI were not given to the women or their doctors and did not influence the subsequent management of the pregnancies.

This study is part of a research program on the early prediction of pregnancy complications. The data on uterine artery PI and MAP were the subject of previous publications[15,17]. In this study we present the combined data.

Outcome measures

The definitions of PE and GH were those of the International Society for the Study of Hypertension in Pregnancy[21]. In GH the diastolic blood pressure should be 90 mmHg or more on at least two occasions 4 h apart, developing after 20 weeks of gestation in previously normotensive women in the absence of significant proteinuria. In PE there should be GH with proteinuria of 300 mg or more in 24 h, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h 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).

Statistical analysis

The measured MAP and uterine artery L-PI were converted to multiples of the expected normal median (MoM) corrected for fetal CRL, maternal age, BMI, smoking and racial origin[15,17]. Comparison of MAP MoM and uterine artery L-PI MoM between each hypertensive disorder group and the unaffected group was by Mann–Whitney *U*-test, with *post-hoc* Bonferroni correction (critical statistical significance $P < 0.0167$). Linear regression analysis was used to determine the significance of association between log MAP MoM with log uterine artery L-PI MoM in each outcome group. The maternal factor-derived *a-priori* risks for early PE, late PE and GH were determined as decribed previously

and were then logarithmically transformed[8]. Logistic regression analysis was used to determine whether the log transformed maternal factor-derived *a-priori* risks, log MAP MoM and log uterine artery L-PI MoM had a significant contribution in predicting early PE, late PE and GH. The performance of screening was determined by receiver–operating characteristics (ROC) curves.

The statistical software package SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analyses.

RESULTS

The MAP MoM was higher in early PE, late PE and GH than in the unaffected group ($P < 0.0001$) and in early PE than in GH ($P = 0.002$). The uterine artery L-PI MoM was significantly higher in early PE and late PE than in the unaffected group ($P < 0.0001$), in early PE than in late PE ($P < 0.0001$), in early PE than in GH ($P < 0.0001$), and in GH than in the unaffected group ($P = 0.014$) (Table 1).

In the unaffected group, there was a significant association between log MAP MoM and log uterine artery L-PI MoM ($r = 0.065$, $P < 0.0001$). However, there was no significant association between log MAP MoM and log uterine artery L-PI MoM in the early PE ($r = 0.303$, $P = 0.068$), late PE ($r = 0.013$, $P = 0.885$) and GH ($r = 0.010$, $P = 0.911$) groups.

Patient-specific risks for pre-eclampsia and gestational hypertension

The patient-specific risk for each hypertensive disorder is calculated from the formula: odds/(1 + odds), where odds $= e^Y$ and Y is derived from multivariate logistic regression analysis of the disease-specific maternal factor-derived *a-priori* risk, MAP MoM and uterine artery L-PI MoM:

Patient-specific risk for early PE

$$\begin{aligned} Y = {} & -3.657 + 1.592 \times \log \text{maternal factor-derived} \\ & \textit{a-priori} \text{ risk for early PE} \\ & + 31.396 \times \log \text{MAP MoM} \\ & + 13.322 \times \log \text{uterine artery L-PI MoM} \\ & R^2 = 0.371, P < 0.0001. \end{aligned}$$

Patient-specific risk for late PE

$$\begin{aligned} Y = {} & -0.468 + 2.272 \times \log \text{maternal factor-derived} \\ & \textit{a-priori} \text{ risk for late PE} \\ & + 21.147 \times \log \text{MAP MoM} \\ & + 3.537 \times \log \text{uterine artery L-PI MoM} \\ & R^2 = 0.212, P < 0.0001. \end{aligned}$$

Patient-specific risk for GH

$$\begin{aligned} Y = {} & -0.357 + 2.253 \times \log \text{maternal factor-derived} \\ & \textit{a-priori} \text{ risk for GH} \\ & + 18.953 \times \log \text{MAP MoM} \\ & + 1.869 \times \log \text{uterine artery L-PI MoM} \\ & R^2 = 0.130, P < 0.0001. \end{aligned}$$

Areas under the ROC curves (AUCs) and detection rates of early PE, late PE and GH for different false-positive rates in screening by the combination of the

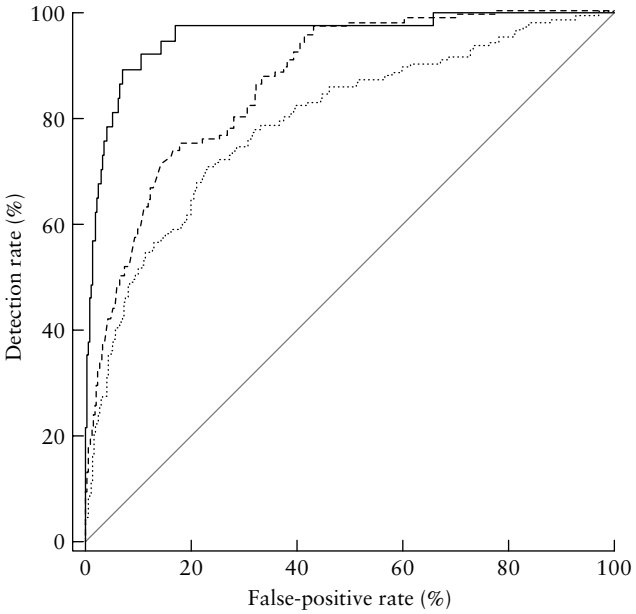

Figure 1 Receiver–operating characteristics curves of maternal risk factors, mean arterial pressure and lowest uterine artery pulsatility index in the prediction of early pre-eclampsia (———), late pre-eclampsia (- - - -) and gestational hypertension (· · · · ·).

Table 1 Mean arterial pressure and lowest uterine artery pulsatility index (L-PI) in the four outcome groups

	Mean arterial pressure (median (IQR))		*Uterine artery L-PI (median (IQR))*	
Group	*MoM*	*mmHg*	*MoM*	*Value*
Unaffected	1.00 (0.94–1.06)	84.3 (79.3–89.3)	1.01 (0.83–1.23)	1.40 (1.14–1.72)
Early pre-eclampsia	1.14 (1.06–1.19)	94.5 (88.3–101.8)	1.60 (1.31–1.77)	2.26 (1.82–2.41)
Late pre-eclampsia	1.09 (1.02–1.14)	93.8 (87.7–98.8)	1.23 (0.88–1.54)	1.68 (1.24–2.16)
Gestational hypertension	1.07 (1.01–1.14)	92.4 (86.0–98.0)	1.10 (0.85–1.38)	1.51 (1.18–1.86)

MoM, multiples of the median.

Table 2 Comparison of the performance of screening for pre-eclampsia and gestational hypertension by maternal risk factor, lowest uterine artery pulsatility index (L-PI) and mean arterial pressure (MAP): area under receiver–operating characteristics curve

	Area under receiver–operating characteristics curve (95% CI)		
Screening test	*Early pre-eclampsia*	*Late pre-eclampsia*	*Gestational hypertension*
Maternal risk factor	0.794 (0.720–0.869)	0.796 (0.761–0.830)	0.721 (0.677–0.765)
Maternal risk factor and L-PI	0.912 (0.863–0.962)	0.812 (0.777–0.847)	0.729 (0.686–0.771)
Maternal risk factor and MAP	0.898 (0.845–0.952)	0.854 (0.826–0.882)	0.782 (0.740–0.823)
Maternal risk factor, L-PI and MAP	0.954 (0.919–0.989)	0.863 (0.855–0.870)	0.788 (0.779–0.797)

Table 3 Detection rates for pre-eclampsia and gestational hypertension by maternal risk factor, lowest uterine artery pulsatility index (L-PI) and mean arterial pressure (MAP)

	Detection rate (% (95% CI)) for fixed false-positive rate (FPR)					
	Early pre-eclampsia		*Late pre-eclampsia*		*Gestational hypertension*	
Group	*FPR 5%*	*FPR 10%*	*FPR 5%*	*FPR 10%*	*FPR 5%*	*FPR 10%*
Maternal risk factor	37.0 (12.5–50.0)	47.0 (22.5–65.0)	28.9 (21.2–37.6)	41.4 (32.8–50.4)	20.7 (14.3–28.4)	30.7 (23.2–39.1)
Maternal risk factor and L-PI	64.9 (47.5–79.8)	81.1 (64.8–92.0)	32.0 (24.1–40.9)	45.3 (36.5–54.3)	17.9 (11.9–25.2)	35.0 (27.1–43.5)
Maternal risk factor and MAP	48.6 (31.9–65.6)	75.7 (58.8–88.2)	39.8 (31.3–48.9)	52.3 (43.3–61.2)	36.4 (28.5–45.0)	47.9 (39.4–56.5)
Maternal risk factor, L-PI and MAP	78.4 (61.8–90.1)	89.2 (74.6–96.9)	42.2 (33.5–51.2)	57.0 (48.0–65.7)	35.7 (27.8–44.2)	50.0 (41.4–58.6)

disease-specific maternal factor-derived *a-priori* risk, MAP and uterine artery L-PI are given in Figure 1. The AUC for the detection of early PE was 0.954 (95% CI, 0.919–0.989) and, at a 10% false-positive rate, the estimated detection rate of early PE was 89.2% (95% CI, 74.6–96.9%) (Tables 2 and 3). The respective AUCs and detection rates for late PE and GH were 0.863 (95% CI, 0.855–0.870) and 57.0% (95% CI, 48.0–65.7%) and 0.788 (95% CI, 0.779–0.797) and 50.0% (95% CI, 41.4–58.6%).

Example

In a black woman in her first pregnancy, with no family history of PE, who is 30 years old, has a BMI of 25 kg/m^2, does not smoke, and with a uterine artery L-PI of 1.6 and MAP of 85 mmHg at 12 weeks of gestation (CRL 65 mm), the estimated risks of developing early PE, late PE and GH are 0.24%, 2.86% and 1.86%, respectively.

Log expected uterine artery L-PI =

$0.348 - 0.002 \times 65$ (CRL in mm)

$+ 0.035$ (black race)

$- 0.002 \times 25$ (BMI in kg/m^2)

$- 0.001 \times 30$ (age in years)

$= 0.204$

Log uterine artery L-PI MoM = 0.036

Log expected MAP =

$1.861 - 0.0002 \times 65$ (CRL in mm)

$+ 0.003 \times 25$ (BMI in kg/m^2)

$+ 0.0004 \times 30$ (age in years)

$+ 0$ (no smoking)

$- 0.005$ (black race)

$= 1.929$

Log MAP MoM = 0.007

Maternal factor-derived a-priori *risk for early PE*

$Y = -5.674 + 1.267$(black race)

$+ 0$ (no history of chronic hypertension)

$+ 0$ (spontaneous conception)

$+ 0$ (nulliparous)

$= -4.406$

Odds: $e^y = 0.012202$

A-priori risk: odds/(1 + odds) = 0.012055

Maternal factor-derived a-priori *risk for late PE*

$Y = -7.860 + 0.034 \times 30$(age in years)

$+ 0.096 \times 25$ (BMI in kg/m^2)

$+ 1.089$ (black race)

$+ 0$ (woman's mother had no history of PE)

$+ 0$ (nulliparous)

$= -3.344$

Odds: $e^y = 0.035278$

A-priori risk: odds/(1 + odds) = 0.034076

Maternal factor-derived a-priori *risk for GH*

$$Y = -7.532 + 0.040 \times 30(\text{age in years}) + 0.098 \times 25\ (\text{BMI in kg/m}^2) + 0\ (\text{woman's mother had no history of PE}) + 0\ (\text{nulliparous}) = -3.875$$

Odds: $e^y = 0.020747$

A-priori risk: odds/(1 + odds) = 0.020325

A-posteriori *risk for early PE*

$$Y = -3.657 + 1.592 \times -1.919\ (\text{log maternal factor-derived } \textit{a-priori} \text{ risk for early PE}) + 31.396 \times 0.007\ (\text{log MAP MoM}) + 13.322 \times 0.036\ (\text{log uterine artery L-PI MoM}) = -6.010$$

Odds: $e^y = 0.0024534$

Risk for early PE = 0.0024474 = 0.24%

A-posteriori *risk for late PE*

$$Y = -0.468 + 2.272 \times -1.468\ (\text{log maternal factor-derived } \textit{a-priori} \text{ risk for late PE}) + 21.147 \times 0.007\ (\text{log MAP MoM}) + 3.537 \times 0.036\ (\text{log uterine artery L-PI MoM}) = -3.524$$

Odds: $e^y = 0.02949$

Risk for late PE = 0.028645 = 2.86%

A-posteriori *risk for GH*

$$Y = -0.357 + 2.253 \times -1.692\ (\text{log maternal factor-derived } \textit{a-priori} \text{ risk for GH}) + 18.953 \times 0.007\ (\text{log MAP MoM}) + 1.869 \times 0.036\ (\text{log uterine artery L-PI MoM}) = -3.966$$

Odds: $e^y = 0.0189502$

Risk for late PE = 0.0185977 = 1.86%

If the same woman had a BMI of 35 kg/m^2, with an L-PI of 2.4 and MAP of 100 mmHg, her risks for early PE, late PE and GH would be 12.57%, 27.37% and 13.99%, respectively.

DISCUSSION

This study has demonstrated that in screening for hypertensive disorders in pregnancy the patient-specific risk for early PE, late PE and GH can be derived by combining the disease-specific maternal factor-derived *a-priori* risk with the measurements of the uterine artery L-PI and MAP. The estimated detection rate of early PE, for a 10% false-positive rate, is increased from 47% in screening by maternal factors alone to 89% with combined screening by maternal factors, uterine artery L-PI and MAP. The respective detection rates for late PE increased from 41% to 57% and for GH increased from 31% to 50%.

This screening study for hypertensive disorders examined more than 8000 pregnancies, including more than 300 cases that developed PE or GH. We used multiple regression analysis to define the contribution of maternal factors, MAP and uterine artery L-PI, and the interaction between these covariates. The algorithms we derived can be used to calculate the combined *a-priori* risk in future smaller case–control studies investigating the potential value of additional biophysical or biochemical measurements. Since the population we examined in this study is large it is likely that the data on maternal factors, MAP and uterine artery L-PI would be more universally applicable than those derived from small case–control studies.

We chose 11–13 weeks as the gestational age for screening because this is emerging as the time of the first hospital visit of pregnant women at which combined sonographic and biochemical testing for chromosomal and other major defects is carried out[18,19]. At this visit, first, a record is made of maternal characteristics, such as age, ethnic origin, BMI, smoking status, and medical and obstetric history; second, an ultrasound scan is carried out to determine the number of fetuses, confirm the gestational age from the fetal CRL, exclude major defects, 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 pregnancy-associated plasma protein-A (PAPP-A). It would be easy to measure the MAP and uterine artery PI of women in this same visit, and utilize the same methodology to calculate the patient-specific risk for both chromosomal defects and hypertensive disorders. This methodology could be applied for improved screening in the future with the use of additional biochemical markers, such as maternal serum PAPP-A and placental growth factor[22].

PE is the most common pregnancy complication associated with serious maternal–fetal morbidity and mortality, and at present the only effective treatment is delivery of the placenta. The ability to predict those women at risk for PE in very early pregnancy might decrease maternal and fetal morbidity through closer surveillance by physicians experienced or specialized in

high-risk obstetrics, as well as delivery at tertiary care centers[23]. Centralized care of pregnancies at high-risk for PE would also lead to a more effective concentration of research activity in an attempt to improve understanding of the pathophysiology and treatment of the condition.

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