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Maternal cardiac function at 35–37 weeks' gestation: prediction of pre-eclampsia and gestational hypertension

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KEYWORDS: cardiac output; gestational hypertension; maternal cardiovascular function; pre-eclampsia; third-trimester screening; total peripheral resistance

ABSTRACT

Objective *To investigate the potential value of combining maternal factors with multiples of the normal median values of maternal cardiovascular parameters at 35–37 weeks' gestation in the prediction of pre-eclampsia (PE) and gestational hypertension (GH).*

Methods *In 2764 singleton pregnancies maternal characteristics and medical history were recorded; uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP) and maternal cardiovascular parameters were measured. Multivariable logistic regression analysis was then used to determine if the maternal factors and maternal cardiovascular parameters made a significant contribution to predicting PE and GH. The performance of screening was determined by the area under receiver–operating characteristics curves.*

Results *In pregnancies that subsequently delivered with PE or GH, total peripheral resistance and MAP were higher and maternal cardiac output was lower, mainly owing to a decrease in heart rate in PE and a decrease in stroke volume in GH. The increases in total peripheral resistance and MAP were inversely related to gestational age at delivery. The performance of screening for PE and GH achieved by maternal characteristics and medical history was improved by the inclusion of MAP, but not by UtA-PI or maternal cardiovascular parameters.*

Conclusions *In women developing term PE total peripheral resistance and MAP are increased and maternal cardiac output is reduced. However, assessment of maternal cardiac function at 35–37 weeks' gestation is unlikely to improve the performance of screening for PE provided by maternal factors and MAP alone. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Preterm pre-eclampsia (PE) is thought to be a consequence of impaired placentation reflected in increased uterine artery pulsatility index (UtA-PI) and this biomarker, either on its own or in combination with mean arterial pressure (MAP) and serum placental growth factor (PlGF), provides a useful method for the prediction of preterm PE[1–6]. In contrast, UtA-PI measured in the first, second or third trimester shows little or no discriminatory power for term PE[3,7]. There is some evidence from first- and second-trimester studies that preterm PE and term PE are characterized by different hemodynamic profiles; preterm PE, which is often associated with the birth of small-for-gestational-age (SGA) neonates, is preceded by low cardiac output and high peripheral resistance, whereas term PE, which is usually accompanied by normal fetal growth, is preceded by high cardiac output and low peripheral resistance[8–11].

Our approach to screening is to use Bayes' theorem to combine the prior risk from maternal factors, derived by a multivariable logistic regression model, with the results of various combinations of biophysical and biochemical measurements made at different times during pregnancy[4–7,12]. However, in such combined screening for PE, it is essential to standardize the measured values of biomarkers for any variables included in the prior model by converting the measurements into multiples of the normal median (MoM) values. A recent screening study of 3013 singleton pregnancies at 35–37 weeks' gestation assessed maternal cardiovascular function using a non-invasive, bioreactance method and reported MoM values for cardiac output, total peripheral resistance, stroke volume, heart rate, cardiac power, thoracic fluid capacity and ventricular ejection time[13].

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The objective of this screening study at 35–37 weeks' gestation was to investigate the potential value of combining maternal factors with MoM values of maternal cardiovascular parameters in the prediction of PE and gestational hypertension (GH).

METHODS

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at King's College Hospital, London, UK and Medway Maritime Hospital, Kent, UK, between March 2015 and December 2015. This visit, which is held at 35 + 0 to 37 + 6 weeks' gestation, included the recording of maternal characteristics and medical history, ultrasonographic estimation of fetal weight and measurement of UtA-PI, MAP and maternal cardiovascular parameters. Gestational age was determined by measurement of the fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[14,15].

Written informed consent was obtained from the women agreeing to participate in this study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. In this paper we present the results on combined screening with maternal factors, UtA-PI and maternal cardiovascular parameters in the prediction of PE and GH. The patients included in the study all had pregnancies resulting in the live birth of a phenotypically normal baby and were part of our previous study population on the relationship of maternal cardiovascular function and maternal characteristics[13].

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The definitions of GH and PE were those of the International Society for the Study of Hypertension in Pregnancy[16]. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to confirm that the condition was chronic hypertension, PE or GH. The newborn was considered to be SGA if the birth weight was less than the 10th percentile after correction for gestational age at delivery[17].

Maternal cardiovascular function

Cardiovascular function was assessed using a non-invasive, bioreactance method (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK)[18]. Four dual-surface electrodes were applied across the maternal thorax and, after 15 min of rest in a sitting position, recordings were made for 5 min. The signal processing unit of the system determines the relative phase shift of electrical current between the input signal and the output signal; the phase shift occurs owing to instantaneous changes in blood flow in the aorta. Cardiac output is subsequently estimated as the product of stroke volume and heart rate, with total peripheral resistance calculated as the product of cardiac output and MAP. This operator-independent technology has been validated in both non-pregnant and pregnant populations[19,20].

Statistical analysis

The observed measurements of UtA-PI and the maternal cardiovascular parameters were expressed as MoM values after adjustment for those characteristics found to provide a substantial contribution to their measurements[13,21]. The Mann–Whitney *U*-test was used to compare the observed values and the normalized values of these maternal parameters between the outcome groups. Regression analysis was used to determine the significance of association between the normalized values of the maternal cardiovascular parameters and gestational age at birth. The *a-priori* risks for PE and GH were determined using the algorithm derived from the multivariable logistic regression analysis of maternal characteristics and history, as previously described[12]. Multivariable logistic regression analysis was then used to determine if the maternal factor-derived logit (*a-priori* risk) and maternal cardiovascular parameters had a significant contribution to predicting PE and GH. The performance of screening was determined by receiver–operating characteristics (ROC) curves.

The statistical software packages SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analysis.

RESULTS

Maternal characteristics of the study population have been reported in a previous paper[13]. Our study population consisted of 66 and 112 women who subsequently developed PE and GH, respectively, and 2856 women who remained normotensive (unaffected). Cardiac output was significantly lower in PE and GH than in unaffected pregnancies; this decrease was due to a lower heart rate and a non-significant lower stroke volume in PE and a lower stroke volume in GH (Table 1; Figure 1). Compared with values in unaffected pregnancies, total peripheral resistance and MAP were higher in PE and GH (Table 1; Figure 1), ventricular ejection time was decreased in PE but not in GH, and UtA-PI, cardiac power and thoracic fluid capacity were not significantly different in PE and GH (Table 1).

Pearson correlation between $\log_{10}$MoM values of cardiac output, stroke volume, total peripheral resistance, MAP, ventricular ejection time and MoM values of heart rate in the unaffected, PE and GH groups are shown in Table S1. Correlations between $\log_{10}$MoM values of cardiac output, stroke volume, total peripheral resistance, MAP, ventricular ejection time, and MoM values of heart rate with gestational age at birth in the unaffected, PE and GH groups are shown in Table S2.

Patient-specific risks for pre-eclampsia and gestational hypertension

The patient-specific risk for each hypertensive disorder was calculated from the formula: risk = odds/(1 + odds),

Table 1 Maternal cardiovascular parameters and uterine artery pulsatility index (UtA-PI) in 66 women with pre-eclampsia (PE), 112 with gestational hypertension (GH) and 2586 unaffected women

	Unaffected (n = *2586)*		*PE* (n = *66)*		*GH* (n = *112)*	
Parameter	*Observed value*	*Log_{10}MoM*	*Observed value*	*Log_{10}MoM*	*Observed value*	*Log_{10}MoM*
CO (L/min)	6.880 (5.870 to 8.065)	0.004 (−0.058 to 0.065)	6.321 (5.398 to 7.317)*	−0.030 (−0.105 to 0.022)*	6.261 (5.327 to 7.190)*	−0.026 (−0.091 to 0.017)*
SV (mL/beat)	76.556 (64.648 to 89.809)	0.004 (−0.063 to 0.068)	70.212 (58.756 to 82.003)*	−0.020 (−0.086 to 0.050)	70.505 (60.788 to 82.153)*	−0.025 (−0.101 to 0.028)*
HR (bpm)	90 (83 to 97)	0.001 (−0.031 to 0.029)	88 (81 to 101)	−0.025 (−0.060 to 0.014)*	89 (82 to 97)	−0.005 (−0.038 to 0.031)
TPR (dynes × s/cm^5)	1057.8 (888.7 to 1252.5)	−0.005 (−0.070 to 0.064)	1342.7 (1146.0 to 1590.3)*	0.085 (0.010 to 0.164)*	1325.2 (1129.9 to 1503.9)*	0.074 (0.019 to 0.140)*
MAP (mmHg)	89.7 (84.0 to 95.5)	0.000 (−0.027 to 0.026)	103.9 (95.8 to 107.1)*	0.049 (0.025 to 0.077)*	101.2 (93.5 to 107.3)*	0.051 (0.016 to 0.074)*
CP (L/min)	1.350 (1.150 to 1.600)	0.006 (−0.067 to 0.070)	1.400 (1.200 to 1.650)	0.017 (−0.034 to 0.068)	1.342 (1.175 to 1.633)	0.016 (−0.070 to 0.074)
TFC	64.300 (54.612 to 78.490)	−0.007 (−0.075 to 0.075)	63.241 (54.896 to 74.197)	−0.002 (−0.055 to 0.056)	58.756 (51.328 to 69.672)*	−0.043 (−0.084 to 0.043)
VET (ms)	248.646 (224.667 to 270.042)	0.005 (−0.031 to 0.037)	225.538 (209.832 to 244.750)*	−0.020 (−0.052 to 0.014)*	236.477 (216.167 to 259.417)*	0.0002 (−0.035 to 0.023)
UtA-PI	0.665 (0.565 to 0.775)	−0.032 (−0.098 to 0.035)	0.728 (0.583 to 0.860)	0.012 (−0.093 to 0.068)	0.660 (0.560 to 0.804)	−0.030 (−0.115 to 0.060)

Comparisons between outcome groups were by Mann–Whitney *U*-test, with *post-hoc* Bonferroni correction (*$P < 0.025$). CO, cardiac output; CP, cardiac power; HR, heart rate; MAP, mean arterial pressure; MoM, multiples of the median; SV, stroke volume; TFC, thoracic fluid capacity; TPR, total peripheral resistance; VET, ventricular ejection time.

where odds = e^Y. The Y for each hypertensive disorder was derived from backward stepwise multivariate regression analysis of the maternal factor-derived logit (*a-priori* risk) and the normalized values of each of the maternal cardiovascular parameters. Multivariable logistic regression analysis for the prediction of PE and GH with maternal factors and various maternal cardiovascular parameters are shown in Tables S3 and S4.

The performance of screening for PE and GH is shown in Table 2 and Figure 2. The performance of screening for PE and GH achieved by maternal characteristics and medical history was improved by the measurement of MAP (area under the ROC curve (AUC) for PE, 0.799 (95% CI, 0.751–0.846) *vs* 0.884 (95% CI, 0.848–0.919) and AUC for GH, 0.669 (95% CI, 0.623–0.715) *vs* 0.835 (95% CI 0.798–0.871)), but not by UtA-PI or maternal cardiovascular parameters.

DISCUSSION

Principal findings of the study

This screening study at 35–37 weeks' gestation has demonstrated that, in pregnancies that subsequently delivered with PE or GH, total peripheral resistance and MAP were increased and maternal cardiac output was reduced, mainly owing to a decrease in heart rate and a non-significant decrease in stroke volume in PE and to a decrease in stroke volume in GH. The increases in total peripheral resistance and MAP were inversely related to gestational age at delivery; the values were higher in those with a shorter interval between assessment and delivery with PE or GH. UtA-PI was not increased in either the PE or the GH group.

The performance of screening for PE and GH achieved by maternal characteristics and medical history was improved by the inclusion of MAP. A further small improvement in the detection rate of PE was achieved with the addition of heart rate, and for GH the detection rate improved with the addition of cardiac output; however, the study was not powered to demonstrate that such improvements in performance were significant.

Strengths and limitations of the study

The strengths of this late third-trimester screening study for PE are first, examination of pregnant women attending routine assessment of fetal growth and wellbeing; second, recording of data on maternal characteristics and medical history to define the prior risk; third, use of an automated non-invasive cardiac monitor to provide accurate measurement of cardiovascular function and expression of values as MoMs after adjustment for factors that affect the measurements; and fourth, use of multivariable logistic regression to combine the prior risk with biomarkers to estimate patient-specific posterior risks and the performance of screening for PE.

A limitation of the study is that the development of a prediction model and performance of screening were carried out in the same population, which introduces 'optimistic bias'. This was a cross-sectional study and it is not possible to determine whether the observed decrease in cardiac output in the few weeks before delivery with PE or GH was preceded by high or low cardiac output; this can only be answered by longitudinal studies.

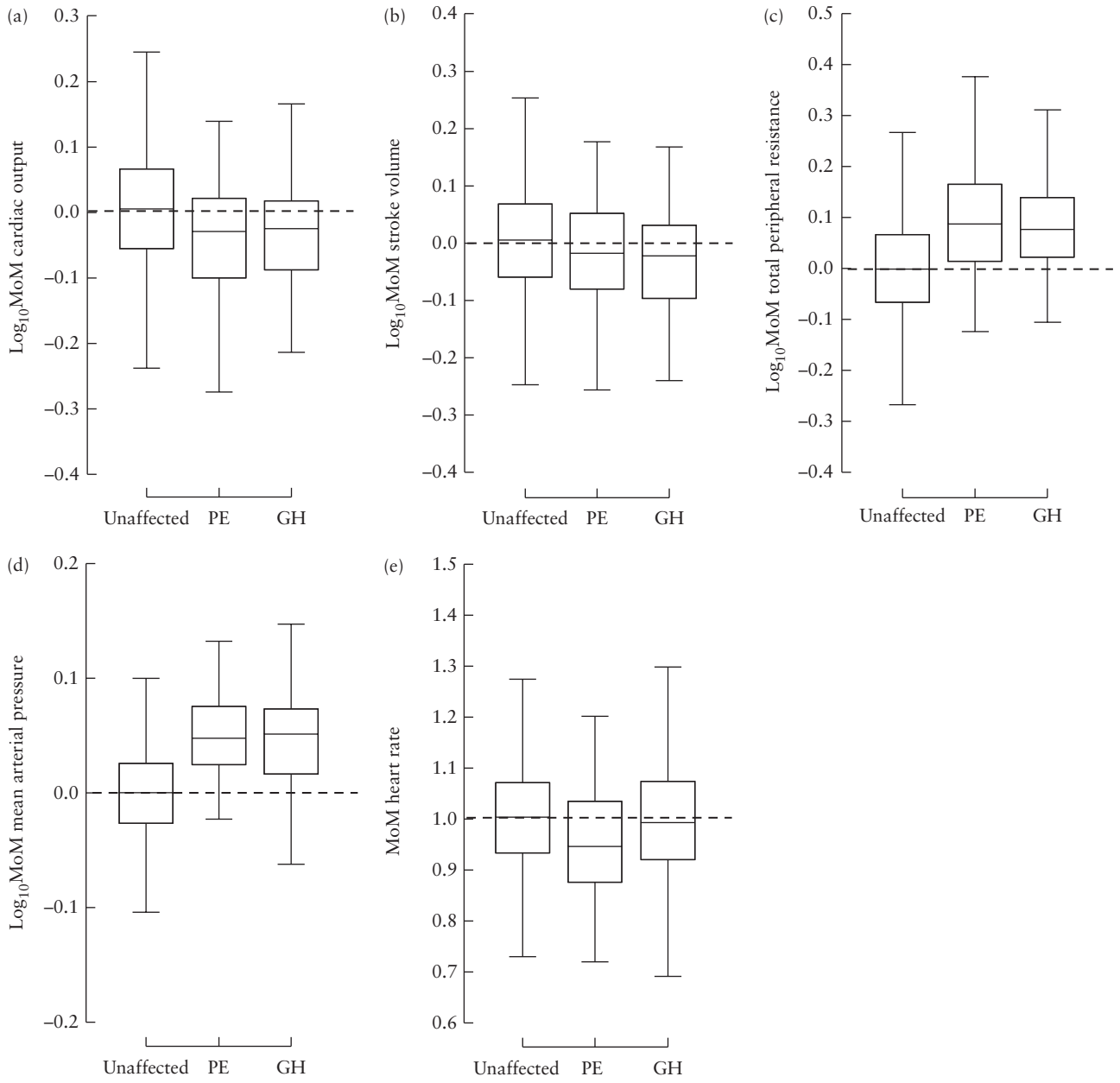

Figure 1 Box-and-whisker plots of $\log_{10}$ multiples of the median (MoM) values of cardiac output (a), stroke volume (b), total peripheral resistance (c) and mean arterial pressure (d) and MoM values of heart rate (e) in pregnancies affected by pre-eclampsia (PE) or gestational hypertension (GH) and unaffected pregnancies. Boxes with internal lines represent median and interquartile range and whiskers are range.

Comparison with previous studies

Our finding that term PE is preceded by low cardiac output and high peripheral resistance contradicts the results of previous small studies during the first and second trimesters of pregnancy that suggest that, in contrast to preterm PE, which is preceded by low cardiac output and high peripheral resistance, term PE may be preceded by high cardiac output and normal or decreased peripheral resistance[8–11]. Our screening study was carried out on an unselected population, whereas previous ones reported on high-risk pregnancies or compared normal pregnancies with those with PE. Additionally, our study was the only one that adjusted the measured cardiovascular parameters for the influence of maternal characteristics and medical history by converting the values into MoMs; failure to do so could lead to the erroneous conclusion that a biomarker may improve the prediction provided by a maternal factor purely because the given biomarker is altered by that maternal factor.

Bosio *et al.*[10] supported the concept of a hyperdynamic disease model for PE, with a subsequent hemodynamic crossover to low cardiac output and high resistance circulation coinciding with the onset of the clinical syndrome; in women with GH there is no such hemodynamic crossover and a hyperdynamic circulation is maintained throughout pregnancy. The authors hypothesized that elevated cardiac output during the latent phase of PE could result in compensatory vasodilatation to maintain near-normal blood pressure;

Table 2 Performance of screening for pre-eclampsia and gestational hypertension with maternal factors and various combinations of maternal cardiovascular parameters at 35–37 weeks' gestation

	Pre-eclampsia			*Gestational hypertension*		
		Detection rate (%)			*Detection rate (%)*	
Parameter	*AUC*	*5% FPR*	*10% FPR*	*AUC*	*5% FPR*	*10% FPR*
History	0.799 (0.751–0.846)	24.2 (14.5–36.4)	40.9 (29.0–53.7)	0.669 (0.623–0.715)	14.3 (8.4–22.2)	20.5 (13.5–29.2)
History plus:						
CO	0.805 (0.758–0.852)	30.3 (19.6–42.9)	39.4 (27.6–52.2)	0.714 (0.668–0.759)	14.3 (8.4–22.2)	27.7 (19.6–36.9)
SV	—	—	—	0.699 (0.653–0.744)	12.5 (7.0–20.1)	18.8 (12.0–27.2)
HR	0.811 (0.761–0.861)	27.3 (17.0–39.6)	45.5 (33.1–58.2)	—	—	—
TPR	0.835 (0.791–0.879)	37.9 (26.2–50.7)	50.0 (37.4–62.6)	0.786 (0.748–0.823)	21.4 (14.2–30.2)	37.5 (28.5–47.1)
MAP	0.884 (0.848–0.919)	47.0 (34.6–59.7)	68.2 (55.6–79.1)	0.835 (0.798–0.871)	34.8 (26.1–44.4)	53.6 (43.9–63.0)
VET	0.799 (0.752–0.847)	28.8 (18.3–41.3)	39.4 (27.6–52.2)	—	—	—
CO, MAP	0.886 (0.849–0.922)	51.5 (38.9–64.0)	65.2 (52.4–76.5)	0.849 (0.815–0.883)	39.3 (30.2–49.0)	56.3 (46.6–65.6)
SV, TPR	—	—	—	0.826 (0.791–0.860)	36.6 (27.7–46.2)	45.5 (36.1–55.2)
SV, MAP	—	—	—	0.838 (0.802–0.873)	39.3 (30.2–49.0)	53.6 (43.9–63.0)
SV, VET	—	—	—	—	—	—
HR, TPR	0.839 (0.791–0.887)	40.9 (29.0–53.7)	57.6 (44.8–69.7)	—	—	—
HR, MAP	0.893 (0.855–0.930)	53.0 (40.3–65.4)	68.2 (55.6–79.1)	—	—	—
HR, VET	0.811 (0.760–0.862)	31.8 (20.9–44.4)	45.5 (33.1–58.2)	—	—	—
TPR, VET	0.841 (0.795–0.886)	39.4 (27.6–52.2)	54.6 (41.8–66.9)	—	—	—

Data in parentheses are 95% CI. AUC, area under receiver–operating characteristics curve; CO, cardiac output; FPR, false-positive rate; HR, heart rate; MAP, mean arterial pressure; SV, stroke volume; TPR, total peripheral resistance; VET, ventricular ejection time.

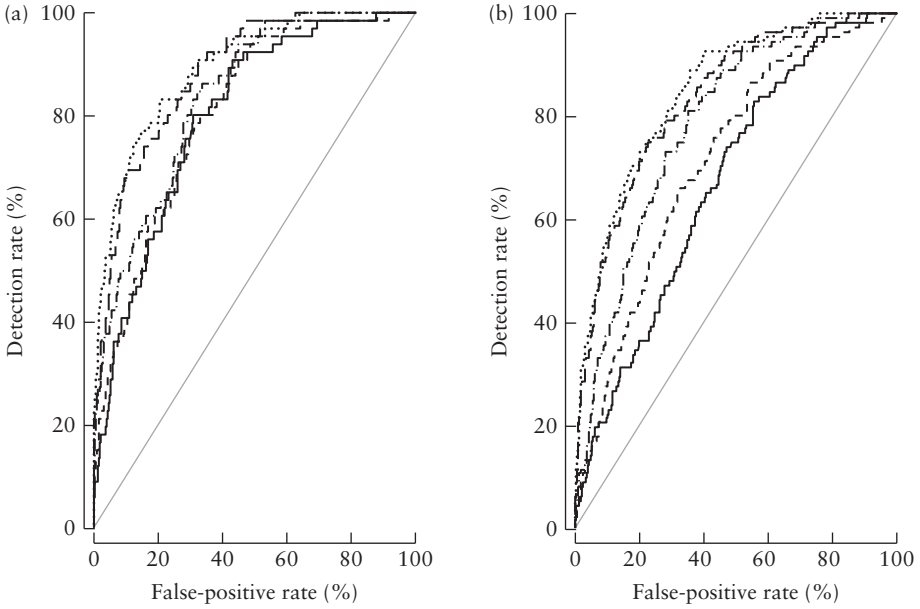

Figure 2 Receiver–operating characteristics curves of maternal factors (——) and maternal factors with cardiac output (- - -), total peripheral resistance (–·–·-), mean arterial pressure (— —) and mean arterial pressure and heart rate (·····) at 35–37 weeks' gestation, in the prediction of: (a) pre-eclampsia and (b) gestational hypertension.

the excessively dilated terminal arterioles would then expose the delicate endothelium of the capillary beds to high systemic pressures and flow, which could in turn exacerbate the endothelial damage already present in latent PE[22–24]. Our data do not support the hyperdynamic disease model for PE and GH; we found that even before the clinical presentation of the conditions there is low cardiac output and high peripheral resistance, as seen in clinical PE and GH.

In a previous screening study involving more than 5000 singleton pregnancies at 35–37 weeks' gestation we reported that the best prediction of PE was by a combination of maternal factors, MAP and serum PlGF and serum soluble fms-like tyrosine kinase-1 (sFlt-1), with a detection rate of about 70% at a false-positive rate of 5%[7]. The study also showed that in most cases of PE, UtA-PI was normal, suggesting that late PE, unlike preterm PE, is not caused by impaired placentation.

Clinical implications of the study

This study demonstrates that, in women developing term PE, total peripheral resistance and MAP are increased and maternal cardiac output is reduced, whereas UtA-PI is not significantly altered. However, assessment of maternal cardiac function at 35–37 weeks' gestation is unlikely to improve the performance of screening for PE provided by maternal factors and MAP alone; the best performance of screening for PE at this gestation is provided by a combination of maternal factors, MAP, sFlt-1 and PlGF[7].

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Pearson correlation between $\log_{10}$ MoM values of cardiac output, stroke volume, total peripheral resistance, mean arterial pressure, ventricular ejection time and heart rate MoM in the unaffected, pre-eclampsia (PE) and gestational hypertension (GH) groups

Table S2 Pearson correlation between $\log_{10}$ MoM values of cardiac output, stroke volume, total peripheral resistance, mean arterial pressure, ventricular ejection time and heart rate MoM with gestational age at birth in the unaffected, pre-eclampsia (PE) and gestational hypertension (GH) groups

Table S3 Fitted regression models with maternal characteristics and history (maternal factors) and maternal cardiovascular parameters at 35–37 weeks' gestation for the prediction of pre-eclampsia

Table S4 Fitted regression models with maternal characteristics and history (maternal factors) and maternal cardiovascular parameters at 35–37 weeks' gestation for the prediction of gestational hypertension