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Maternal Cardiac Function at Midgestation and Development of Preeclampsia

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ABSTRACT

BACKGROUND Preeclampsia (PE) is an independent risk factor for adverse maternal cardiovascular outcomes. The role of maternal cardiac function in the pathophysiology of PE remains unclear.

OBJECTIVES This study sought to describe differences in cardiac function at midgestation between women who develop PE and those with uncomplicated pregnancy and to establish whether routine cardiac assessment at midgestation can improve performance of screening for PE achieved by established biomarkers.

METHODS Mean arterial pressure was measured, medical history was obtained, and left ventricular (LV) systolic and diastolic functions were assessed using standard echocardiography and speckle tracking imaging. Uterine artery pulsatility index and serum placental growth factor and soluble fms-like tyrosine kinase-1 were measured.

RESULTS In 4,795 pregnancies, 126 (2.6%) developed PE. Following multivariable analysis, peripheral vascular resistance was significantly higher and LV global longitudinal systolic strain, ejection fraction, cardiac output, and left atrial area were mildly lower in women who developed PE compared to those who did not. There was a weak association between maternal cardiovascular indices and biomarkers of placental perfusion and function. Cardiac indices did not improve the performance of screening for PE on top of maternal risk factors, mean arterial pressure, and biomarkers of placental perfusion and function.

CONCLUSION Women who develop PE have an increase in peripheral vascular resistance and a mild reduction in LV functional cardiac indices long before PE development. However, cardiac indices do not improve the performance of screening for PE; thus, their routine clinical use is not advocated. (J Am Coll Cardiol 2022;79:52-62)

Preeclampsia (PE) is a pregnancy-related complication with short- and long-term adverse effects for the mother and her fetus (1). Development of PE is thought to be the consequence of impaired placental perfusion leading to placental hypoxia/ischemia, which, in turn, results in oxidative stress; intravascular inflammation; and consequent endothelial cell dysfunction, vasospasm, and platelet activation (2-5). Supporting evidence for impaired placental perfusion and function has been provided by the finding that in pregnancies that develop PE, there is increased impedance to flow in the uterine arteries reflected in a high pulsatility index (UtA-PI), increased circulating maternal concentration of the antiangiogenic soluble fms-like tyrosine kinase-1 (sFLT-1), and reduced serum concentration of the proangiogenic placental growth factor (PlGF) (6-8).

There is also some evidence implicating maternal cardiac maladaptation during pregnancy as a risk

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factor for the development of PE (9). In a screening study in late gestation, we reported that women who are at imminent risk for the development of PE have distinct cardiac changes, with an increase in left ventricular (LV) mass and an increase in LV filling pressure (10). Other researchers investigated more selected groups, such as those with abnormal UtA-PI (11), in midgestation and reported mild LV diastolic dysfunction and increased LV mass, mostly in women who subsequently developed preterm (<37 weeks) rather than term (≥37 weeks) PE (12,13). The contribution of midgestational structural and functional cardiovascular indices to PE risk prediction is unknown.

The objectives of this prospective study were: 1) to describe the cardiovascular profile of a large unselected population of women who attended a clinic for their routine fetal ultrasonography scan at midgestation and identify differences between those who develop PE (preterm or term) and those with uncomplicated pregnancy; 2) to determine the relationship between cardiovascular indices and biomarkers of placental perfusion and function; and 3) to establish whether routine cardiac assessment at midgestation can contribute to the prediction of PE over and above the established biomarkers of mean arterial pressure (MAP), UtA-PI, PlGF, and sFLT-1.

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METHODS

STUDY DESIGN AND PARTICIPANTS. This was a prospective observational study in women attending for a routine hospital visit at 19^{+1} to 23^{+3} weeks' gestation at King's College Hospital, London, United Kingdom between August 2019 and April 2020. This visit included recording of maternal demographic characteristics and medical history; ultrasonographic examination for fetal anatomy and growth; maternal cardiovascular assessment; measurement of MAP by validated automated devices (Microlife BPA2-B, Microlife AG Swiss Corporation); and a standardized protocol with 2 blood pressure recordings taken in the right and left arms (14), transvaginal color Doppler ultrasonography of the left and right uterine arteries and calculation of the mean UtA-PI (15), and measurement of the serum concentrations of PlGF and sFLT-1 by an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific). Gestational age was determined from the measurement of fetal crown-rump length at 11 to 13 weeks' gestation or the fetal head circumference at 19 to 24 weeks (16,17). The women gave written informed consent to participate in the Advanced Cardiovascular Imaging Study (Research Ethics Committees no. 18/NI/0013, Integrated Research Approval System ID: 237936), which was approved by the National Health Service Research Ethics Committee.

The inclusion criteria for this study were a singleton pregnancy and delivery of a nonmalformed liveborn or stillborn neonate. Exclusion criteria for the study were the presence of major fetal abnormalities and inability to consent for the study. Women were excluded if they had breast implants because these obscure the echocardiographic windows.

ABBREVIATIONS AND ACRONYMS

GH = gestational hypertension
LV = left ventricle
MAP = mean arterial pressure
MoM = multiples of median
PE = preeclampsia
PlGF = placental growth factor
sFLT-1 = soluble fms-like tyrosine kinase-1
UtA-PI = uterine artery pulsatility index

MATERNAL CARDIOVASCULAR ASSESSMENT. All participants were studied by 2-dimensional and conventional and tissue Doppler transthoracic echocardiography at rest in the left lateral decubitus position, and data were acquired during unforced expiration (Canon Aplio i900 scanner, Canon Medical Systems Europe BV). Speckle tracking was used to assess global longitudinal systolic strain of the LV.

The protocol included standard parasternal and apical views, and systolic and diastolic LV functional indices were obtained as per the American Society of Echocardiography and European Cardiovascular Imaging guidelines (18,19). Echocardiography was performed by fetal medicine fellows who were trained in the acquisition and analysis of echocardiograms. All fellows were blinded to patients' medical histories when obtaining and analyzing echocardiographic data. In a previous study, we reported excellent interobserver reproducibility of various cardiac indices (10).

Hemodynamic parameters that were measured included cardiac output and peripheral vascular resistance, as previously reported (10,20). LV systolic function was assessed by ejection fraction, myocardial performance index, and global longitudinal strain. LV diastolic function was evaluated by the mitral peak early (E) and late (A) diastolic flow velocities, and E/A ratio was calculated. LV filling pressure was assessed by E/e′ ratio from pulsed tissue Doppler recordings obtained at the septal and lateral aspects of basal LV at the junction with the mitral valve annulus in the apical 4-chamber view. Timing intervals (isovolumic contraction and relaxation time) were measured as previously described (10). The left atrial area was measured in the 4-chamber apical view at end systole on the frame just before mitral valve opening by tracing the left atrial border, excluding the area under the mitral valve annulus and the inlet of the pulmonary veins. Measurements

were indexed to body surface area. LV mass was calculated with the Devereux formula using measurements of the anatomic M-mode applied in the parasternal long axis (10).

OUTCOME MEASURE. Outcome measure was delivery with PE. Data on pregnancy outcomes were collected from the hospital maternity records or the general medical practitioners of the women. Diagnosis of PE was determined based on the finding of new-onset hypertension (systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mmHg on at least 2 occasions 4 hours apart developing after 20 weeks' gestation in previously normotensive women) or chronic hypertension and at least 1 of the following: proteinuria (≥300 mg/24 h or protein-to-creatinine ratio of ≥30 mg/mmoL or ≥2+ on dipstick testing), renal insufficiency with serum creatinine of >97 μmol/L in the absence of underlying renal disease, hepatic dysfunction with blood concentration of transaminases more than twice the upper limit of normal (≥65 IU/L for our laboratory), thrombocytopenia (platelet count of <100,000/μL), neurologic complications (eg, cerebral or visual symptoms), or pulmonary edema (21).

CURRENT METHOD FOR CALCULATION OF RISK FOR PREECLAMPSIA. Our approach for calculation of the risk for PE is based on a survival time model for the gestational age at delivery with PE (22). Every pregnant woman has a personalized distribution of gestational age at delivery with PE, which comes from the application of the Bayes theorem to combine a prior distribution, determined from maternal demographic characteristics and medical history, with likelihoods from biomarkers. In the prior model, the risk of development of PE is increased with advancing maternal age; increasing weight; Black and South Asian racial origin; medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus, or antiphospholipid syndrome; conception by in vitro fertilization; and family or personal history of PE. The risk for PE is decreased with increasing maternal height and in parous women with no previous PE. At 19 to 24 weeks' gestation, useful biomarkers for the subsequent development of PE are MAP, UtA-PI, PlGF, and sFlt-1 (6,23). The measured values for these biomarkers are expressed as multiples of the median (MoM) after adjustment for gestational age, weight, race, method of conception, medical conditions, elements from the obstetric history associated with the individual on whom they are measured, and the instrument used for measurement. In pregnancies that develop PE, MoM values of MAP, UtA-PI, and sFLT-1 tend to be higher, and PlGF tends to be lower than in normal pregnancies (6). The effect sizes increase with increasing severity of the disease, quantified by the gestational age at delivery. The posterior distribution of gestational age at delivery with PE is obtained using the Bayes theorem by multiplying the prior probability density from maternal risk factors by the likelihood function from biomarker MoM values.

STATISTICAL ANALYSIS. Data are expressed as median (interquartile range) for continuous variables and n (percentage) for categorical variables. Student's *t*-test and chi-square test or the Fisher exact test were used for comparing outcome groups for continuous and categorical data, respectively. Bonferroni corrections were made to take account of multiple testing.

The following 15 cardiovascular indices were examined: E, A, E/A, E/e′, isovolumic relaxation time, left atrial area, myocardial performance index, global longitudinal systolic strain, LV ejection fraction, mitral valve s′, isovolumic contraction time, peripheral vascular resistance, LV cardiac output, LV stroke volume, and LV mass indexed for body surface area. Distributional properties of each index were investigated using histograms and boxplots and by plotting marker measurements against gestational age and maternal weight in PE and unaffected pregnancies. On the basis of these exploratory analyses, we determined the relevancy or need for transformation, for example, $\log_{10}$, of any of the 15 indices to achieve homogeneity of variance and approximate Gaussian distributional form. Multivariable linear regression models were then fitted between the various cardiac indices and the following maternal characteristics and elements from the medical history: heart rate, systolic blood pressure, maternal age, maternal weight, maternal height, self-reported racial origin (White, Black, South Asian, East Asian, and mixed), method of conception (natural, in vitro fertilization, use of ovulation drugs), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), history of preexisting diabetes mellitus (yes or no), history of systemic lupus erythematosus or antiphospholipid syndrome (yes or no), family history of PE in the mother of the patient (yes or no), and obstetric history including parity (parous or nulliparous if no previous pregnancies at ≥24 weeks' gestation), previous pregnancy with PE (yes or no), gestational age at delivery and birth weight of the neonate in the last pregnancy, and interval in years between the birth of the last child and estimated date of conception of the current pregnancy.

To determine whether the cardiovascular indices would be useful in predicting PE, both PE as a binary

TABLE 1 Maternal and Pregnancy Characteristics of the Study Population

	No PE or GH (n = 4,557)	GH (n = 112)	*P* Value	PE (n = 126)	*P* Value
Maternal age, y	33.0 (30.0-36.0)	33.0 (30.0-37.0)	0.684	34.0 (30.25-38.0)	0.101
Maternal weight, kg	70.6 (63.5-79.9)	77.0 (69.3-87.0)	<0.0001	76.0 (68.0-88.7)	<0.0001
Maternal height, cm	166 (161-170)	168 (163-171)	0.219	166 (162-171)	0.960
Body mass index, kg/m^2	25.5 (23.1-28.7)	28.0 (24.5-31.6)	<0.0001	27.5 (24.3-31.8)	<0.0001
Gestational age, weeks	21.3 (20.9-21.6)	21.3 (20.9-21.6)	0.978	21.3 (20.9-21.5)	0.926
Racial origin			0.031		0.018
White	3,326 (73.0)	75 (67.0)		81 (64.3)	
Black	661 (14.5)	27 (24.1)		32 (25.4)	
South Asian	269 (5.9)	6 (5.4)		7 (5.6)	
East Asian	130 (2.9)	0 (0.0)		2 (1.6)	
Mixed	171 (3.8)	4 (3.6)		4 (3.2)	
Medical history					
Chronic hypertension	58 (1.3)	0 (0.0)	0.442	14 (11.1)	<0.0001
Diabetes mellitus type 1	9 (0.2)	1 (0.9)	0.290	2 (1.6)	0.005
Diabetes mellitus type 2	43 (0.9)	1 (0.9)	0.290	2 (1.6)	0.005
SLE/APS	9 (0.2)	2 (1.8)	0.015	0 (0.0)	1
Smoker	55 (1.2)	2 (1.8)	0.908	3 (2.4)	0.443
Family history of PE	128 (2.8)	4 (3.6)	0.736	13 (10.3)	<0.0001
Method of conception			0.297		<0.0001
Natural	4,284 (94.0)	103 (92.0)		106 (84.1)	
In vitro fertilization	240 (5.3)	9 (8.0)		19 (15.1)	
Ovulation drugs	33 (0.7)	0 (0.0)		1 (0.8)	
Parity			0.011		<0.0001
Nulliparous	2,456 (53.9)	73 (65.2)		80 (63.5)	
Parous—no PE	2,023 (44.4)	35 (31.3)		26 (20.6)	
Parous—PE	78 (1.7)	4 (3.6)		20 (15.9)	
Birth weight of last neonate, g	3,377 (3,012-3,700)	3,403 (3,023-3,703)	0.659	3,300 (2,724-3,632)	0.059
Interpregnancy interval, y	2.5 (1.5-4.2)	3.5 (2.0-5.1)	0.152	3.2 (1.7-5.9)	0.170
Placental growth factor, pg/mL	259.6 (191.8-360.4)	214.4 (140.8-332.1)	0.028	228.5 (155.9-313.9)	0.014
Soluble fms-like tyrosine kinase-1, pg/mL	1,212.6 (816.6-1,767.7)	1,248.1 (794.4-1,866.4)	0.060	931.3 (739.9-1,440.1)	0.104
Uterine artery pulsatility index	0.98 (0.8-1.20)	1.02 (0.81-1.37)	<0.001	1.10 (0.88-1.34)	<0.0001
Systolic blood pressure, mm Hg	117 (110-123)	128 (121-132)	<0.0001	126 (119-131)	<0.0001
Diastolic blood pressure, mm Hg	69 (64-73)	78 (73-82)	<0.0001	76 (71-82)	<0.0001
Mean arterial pressure, mm Hg	84.4 (79.7-89.5)	93.9 (90.4-98.3)	<0.0001	92.6 (87.0-97.3)	<0.0001

Values are median (interquartile range) or n (%). Comparisons were made between no PE or GH and GH and between no PE or GH and PE. Comparisons between outcome groups were by the chi-square or Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables. In view of multiple testing, the significant difference between the 2 groups is indicated by $P < 0.002$.

APS = antiphospholipid syndrome; GH = gestational hypertension; PE = preeclampsia; SLE = systemic lupus erythematosus.

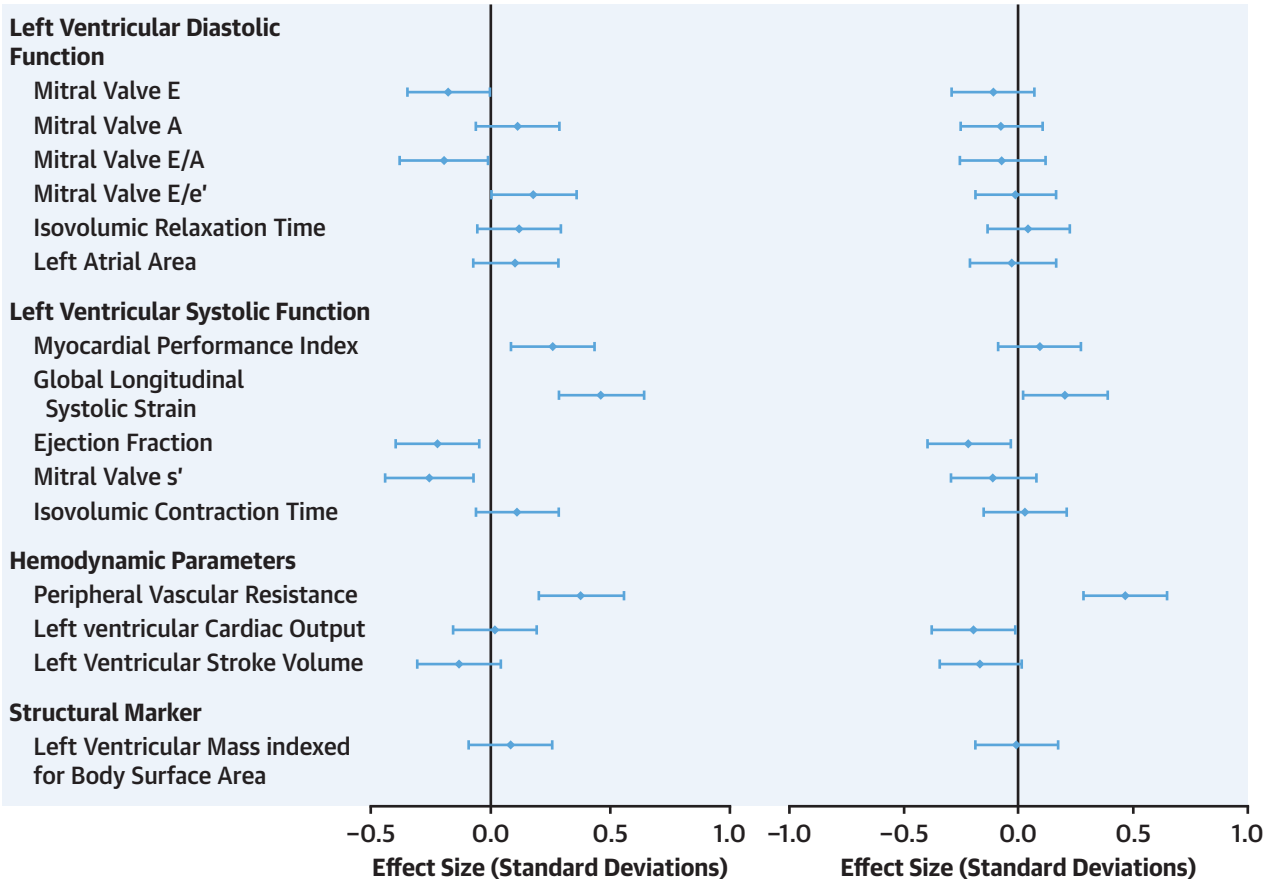
outcome and the gestational age at delivery with PE were included in the models. Backward elimination was used for variable selection. Variables relating to maternal characteristics and medical history, as indicated in the preceding paragraph, were used in the analysis. The partial residuals, after excluding the contribution of PE, comprised either the $\log_{10}$ MoM values or the deviations from the median (deltas), depending on the transformation of the cardiac outcome variable in the original model fitting. The association between maternal cardiac indices and markers of placental perfusion and function was assessed by regression analysis with the aim to assess the significance of association between the MoM or delta values of each cardiovascular index with the MoM values of MAP, UtA-PI, PlGF, and sFLT-1. The competing risks model was used to estimate the individual patient-specific risks of delivery with PE by a combination of maternal demographic characteristics and medical history with potential cardiovascular biomarkers (24). Detection rates of delivery with PE, at a 10% screening positive rate, were assessed for combinations of maternal factors; MAP, UtA-PI, and PlGF; and potential cardiovascular biomarkers.

The statistical software package R was used for data analyses (25).

RESULTS

STUDY PARTICIPANTS. During the study period, 4,866 pregnant women were screened, but 71 were excluded (3 had breast implants, 63 had cardiac or

FIGURE 1 Maternal Cardiovascular Indices and Development of Preeclampsia



Forest plot (mean and 95% CI) of cardiovascular indices unadjusted **(left)** and adjusted **(right)** for maternal characteristics and medical history in pregnancies that subsequently developed preeclampsia, plotted on an SD scale to allow for direct comparison between PE effect size in the different cardiac indices. The **vertical black line** corresponds to a mean of 0.0 for the unaffected pregnancies.

other significant fetal abnormalities, and 5 were unable to consent because of a language barrier or young age). The study population of 4,795 pregnancies contained 126 (2.6%) that developed PE, including 30 (0.6%) deliveries with PE at <37 weeks' gestation; there were 112 (2.3%) pregnancies that developed gestational hypertension (GH), and 4,557 were unaffected by PE or GH. Maternal and pregnancy characteristics of the study population are summarized in Table 1. None of the women had gestational diabetes at the time of the scan. In the PE group, compared to the unaffected pregnancies, there was a higher median maternal weight and body mass index and higher incidence of women with chronic hypertension, family history of PE, conception by in vitro fertilization, nulliparity, and previous history of PE. In the GH group, compared to the unaffected pregnancies, there was a higher median maternal weight and body mass index. In both the PE and GH groups, compared to the unaffected pregnancies, there was higher UtA-PI, systolic and diastolic blood pressure, and MAP (Table 1).

CARDIAC PROFILE IN WOMEN WITH PE (TERM AND PRETERM) AND THOSE WITH UNAFFECTED PREGNANCY. Analysis of cardiovascular indices unadjusted for maternal characteristics and medical history demonstrated that in the pregnancies that subsequently developed PE compared to those that did not develop PE or GH, there was a higher median myocardial performance index, global longitudinal systolic strain, and peripheral vascular resistance and a lower LV ejection fraction and mitral valve s′; there were no significant differences in the other cardiovascular indices (Figure 1, Table 2). LV end-diastolic dimensions were similar between groups.

TABLE 2 Maternal Cardiac Indices and Development of Preeclampsia

	Unadjusted Values			Adjusted (MoM or Delta)		
	No PE or GH (n = 4,557)	PE (n = 126)	*P* Value	No PE or GH (n = 4,557)	PE (n = 126)	*P* Value
Left ventricular diastolic function						
Mitral valve E, delta	92.55 (92.06 to 93.04)	89.73 (86.18 to 93.28)	0.126	0.0 (−0.48 to 0.48)	−2.50 (−5.92 to 1.01)	0.171
Mitral valve A, MoM	39.56 (39.21 to 39.92)	40.99 (38.81 to 43.29)	0.212	1.0 (0.99 to 1.01)	0.98 (0.93 to 1.03)	0.426
Mitral valve E/A, MoM	2.312 (2.29 to 2.34)	2.15 (1.98 to 2.33)	0.084	1.0 (0.99 to 1.01)	0.98 (0.91 to 1.05)	0.541
Mitral valve E/e′, MoM	6.16 (6.12 to 6.21)	6.41 (6.12 to 6.72)	0.108	1.0 (0.99 to 1.01)	0.99 (0.95 to 1.03)	0.584
Isovolumic relaxation time, delta	59.01 (58.63 to 59.38)	60.61 (58.06 to 63.16)	0.224	0.0 (−0.37 to 0.37)	0.22 (−2.33 to 2.77)	0.869
Left atrial area indexed for BSA, delta	7.79 (7.75 to 7.84)	7.69 (7.38 to 7.99)	0.494	0.0 (−0.05 to 0.05)	0.06 (−0.23 to 0.35)	0.708
Left ventricular systolic function						
Myocardial performance index, MoM	0.37 (0.37 to 0.38)	0.39 (0.38 to 0.41)	0.011	1.0 (0.99 to 1.01)	1.01 (0.98 to 1.05)	0.467
Global longitudinal systolic strain, delta	−23.96 (−24.03 to −23.88)	−22.86 (−23.35 to −22.37)	<0.0001	0.0 (−0.07 to 0.07)	0.46 (0.06 to 0.86)	0.026
Ejection fraction, delta	63.57 (63.4 to 63.75)	62.34 (61.28 to 63.39)	0.025	0.0 (−0.17 to 0.17)	−1.25 (−2.27 to −0.24)	0.019
Mitral valve s′, MoM	10.46 (10.41 to 10.51)	10.09 (9.78 to 10.41)	0.025	1.0 (0.99 to 1.005)	0.98 (0.95 to 1.01)	0.225
Isovolumic contraction time, delta	51.28 (50.95 to 51.61)	52.62 (50.52 to 54.72)	0.219	0.0 (−0.33 to 0.33)	0.53 (−1.52 to 2.59)	0.617
Hemodynamic parameters						
Peripheral vascular resistance, MoM	1,221 (1,214 to 1,229)	1329 (1,279 to 1,381)	<0.0001	1.0 (0.99 to 1.006)	1.10 (1.06 to 1.14)	<0.0001
Left ventricular cardiac output, MoM	5.53 (5.49 to 5.56)	5.55 (5.34 to 5.78)	0.817	1.0 (0.99 to 1.006)	0.96 (0.93 to 0.99)	0.020
Left ventricular stroke volume indexed for BSA, delta	42.89 (42.65 to 43.14)	40.3 (38.75 to 41.85)	0.002	0.0 (−0.23 to 0.23)	−1.24 (−2.68 to 0.19)	0.096
Structural marker						
Left ventricular mass indexed for BSA, delta	59.46 (59.18 to 59.74)	60.25 (58.51 to 61.98)	0.382	0.0 (−0.27 to 0.27)	−0.61 (−2.25 to 1.04)	0.479

Values are mean (95% CI) for both unadjusted cardiovascular indices and cardiovascular indices adjusted for maternal characteristics and medical history in pregnancies that did not develop PE and those that went on to develop PE. In view of multiple testing, significant difference between the 2 groups is indicated by $P < 0.0033$.

BSA = body surface area; GH = gestational hypertension; MoM = multiples of median; PE = preeclampsia.

Multivariable linear regression models were fitted to $\log_{10}$ values of A, E/A, E/e′, myocardial performance index, mitral valve s′, peripheral vascular resistance, and LV cardiac output and untransformed values of E, isovolumic relaxation time, left atrial area, global longitudinal systolic strain, LV ejection fraction, isovolumic contraction time, LV stroke volume, and LV mass indexed for body surface area. The effects of variables significantly contributing to measurement levels of each cardiovascular index are shown in Supplemental Table 1. Following multivariable analysis, global longitudinal systolic strain, LV ejection fraction, LV cardiac output, and left atrial area were lower, and peripheral vascular resistance was higher, in women who subsequently developed PE compared to those who did not; the other cardiovascular indices were not significantly altered in pregnancies that developed PE (**Figure 1, Table 2**). After accounting for multiple testing for all cardiac indices, peripheral vascular resistance was the only measurement that remained significantly higher in women with PE (**Table 2**). From the various cardiac indices, only left atrial area was associated with gestational age at delivery with PE; the overall median value of left atrial area in PE pregnancies was not significantly different from that of unaffected pregnancies, but in pregnancies with PE delivering preterm, the median value of the index was decreased, whereas in those delivering at term, the value was increased (**Figure 1**). In women who developed GH, compared to pregnancies without GH or PE and taking into account multiple testing for all cardiac indices, there was significantly increased peripheral vascular resistance; there were no other significant differences in systolic and diastolic indices (Supplemental Table 2).

CARDIOVASCULAR INDICES AND BIOMARKERS OF PLACENTAL PERFUSION AND FUNCTION. There were no significant associations between cardiovascular indices and markers of placental perfusion (UtA-PI) and function (serum PlGF and sFLT-1) (**Table 3**).

PERFORMANCE OF SCREENING. The detection rates, at a 10% screening positive rate, of delivery with PE at <37 weeks' gestation or delivery with PE at any gestational age in screening by maternal demographic characteristics and medical history or combinations of maternal risk factors with MAP, UtA-PI, PlGF, and sFLT-1 were not improved by the addition of peripheral vascular resistance (**Table 4, Central Illustration**).

TABLE 3 Association Between Cardiac Indices and Mean Arterial Pressure and Biomarkers of Placental Perfusion and Function

Cardiovascular Index	MAP MoM	UtA-PI MoM	PlGF MoM	sFLT-1 MoM
Peripheral vascular resistance, MoM	0.387 (0.354 to 0.419)	−0.022 (−0.06 to 0.016)	−0.017 (−0.055 to 0.021)	0.005 (−0.033 to 0.043)
Left ventricular ejection fraction, delta	−0.028 (−0.066 to 0.010)	−0.005 (−0.043 to 0.033)	0.022 (−0.016 to 0.06)	−0.007 (−0.045 to 0.031)
Global longitudinal systolic strain, delta	0.058 (0.020 to 0.095)	−0.011 (−0.049 to 0.027)	−0.017 (−0.054 to 0.021)	−0.005 (−0.043 to 0.033)
Left ventricular cardiac output,[a] MoM	−0.039 (−0.077 to −0.001)	0.009 (−0.029 to 0.047)	−0.003 (−0.041 to 0.035)	−0.005 (−0.043 to 0.033)
Left atrial area, delta	−0.014 (−0.051 to 0.024)	0.005 (−0.033 to 0.043)	−0.034 (−0.072 to 0.004)	0.008 (−0.030 to 0.046)

Values are correlation (95% CI) between cardiovascular indices and mean arterial blood pressure, uterine artery pulsatility index, placental growth factor, and soluble fms-like tyrosine kinase-1. [a]Indexed for body surface area.

MAP = mean arterial pressure; MoM = multiple of the median; PlGF = placental growth factor; sFLT-1 = soluble fms-like tyrosine kinase-1; UtA-PI = uterine artery pulsatility index.

DISCUSSION

PRINCIPAL FINDINGS OF THIS STUDY. In this prospective screening study, we performed detailed cardiac functional and structural assessment in an unselected population of pregnant women at 19 to 23 weeks' gestation. There are 5 main findings: First, women who subsequently developed PE compared to those who did not had evidence of vascular dysfunction as shown by increased peripheral vascular resistance and mildly lower cardiac systolic function. Second, the cardiovascular changes in the group that developed PE persisted after accounting for differences in maternal characteristics and medical history. Third, the cardiovascular indices were not associated with markers of placental perfusion and function. Fourth, most cardiovascular indices were not affected by gestational age at delivery with PE, except left atrial area, which was reduced in women who developed preterm PE and increased in those with term PE. Fifth, cardiovascular indices did not improve the performance of screening for PE, which was based on maternal characteristics and medical history or a combination of maternal risk factors and MAP, UtA-PI, PlGF, and sFlt-1.

These findings demonstrate that all the reported changes in cardiac indices were subtle and did not improve the performance of screening for PE.

INTERPRETATION OF RESULTS AND COMPARISON WITH FINDINGS OF PREVIOUS STUDIES. Over the last decade, there has been increasing interest in the identification of women at risk for PE because this condition has been associated with short- and long-term adverse outcomes for both the mother and fetus/child. For instance, Vaught et al (26) reported in 63 women that severe PE was associated with abnormal LV diastolic function and a decrease in right ventricular global longitudinal strain. Large epidemiologic studies, for example, have shown that women with a history of PE have increased risk for adverse cardiovascular outcome 5 to 15 years after pregnancy, but it remained unknown whether PE is an independent risk factor for adverse cardiovascular outcome or simply unmasks the pre-existing cardiovascular risk for these women (27,28). To address this issue, a few groups examined whether cardiac dysfunction precedes the development of PE. Vasapollo et al (12), in a study of 1,345 women identified as high risk for PE on the basis of Doppler findings of increased impedance to flow in the uterine arteries at midgestation, reported that women who later developed PE demonstrated mild LV dysfunction and an increase in LV mass and peripheral vascular resistance. The same group also reported in 526 high-risk women that measurement of peripheral vascular resistance can improve the predictive ability of UtA-PI in identifying women who develop PE and provided the first evidence that the maternal cardiac system might be involved in the pathophysiology of PE (11).

The findings of Vasapollo et al (12), were contradicted by the findings of a study by our group in 2,853 unselected women who underwent detailed cardiac assessment in midgestation; there was no significant contribution of maternal cardiac function in the pathogenesis of PE because the mild cardiac functional changes that were noted in women who subsequently developed PE, compared to those with uncomplicated pregnancies, were fully explained by differences in maternal characteristics (24). However, the number of cases of PE was relatively small, and the role of maternal cardiac function in the pathogenesis of PE could not be confidently rejected. In the current study, we expanded the phenotype to 4,795 women and increased our power by having more cases of term and preterm PE. We showed, consistent with findings in high-risk groups, that peripheral vascular resistance is increased in women who later developed PE compared to those without PE. In addition, we demonstrated a mild decrease in LV systolic functional indices by using conventional and novel echocardiographic techniques. Although

TABLE 4 Screening for Preeclampsia

Method of Screening	Preeclampsia, <37 weeks			All Preeclampsia		
	n/N	DR, % (95% CI)	AUC (95% CI)	n/N	DR, % (95% CI)	AUC (95% CI)
Maternal factors	16/30	53.3 (34.3-71.7)	0.800 (0.712-0.888)	48/120	40.0 (31.2-49.3)	0.758 (0.715-0.802)
+ PVR	16/30	53.3 (34.3-71.7)	0.796 (0.705-0.886)	48/120	40.0 (31.2-49.3)	0.766 (0.723-0.810)
+ MAP + UtA-PI + PlGF + sFLT-1	23/30	76.7 (57.7-90.1)	0.893 (0.817-0.970)	63/120	52.5 (43.2-61.7)	0.813 (0.772-0.853)
+ MAP + UtA-PI + PlGF + sFLT-1 + PVR	23/30	76.7 (57.7-90.1)	0.882 (0.801-0.964)	60/120	50.0 (40.7-59.3)	0.802 (0.760-0.844)

Detection rate of delivery with pre-eclampsia at <37 weeks' gestation and all preeclampsia, at a 10% screening positive rate, and areas under the receiver operating characteristic curve after screening at 19 to 23 weeks' gestation by maternal risk factors and mean arterial pressure, uterine artery pulsatility index, serum placental growth factor, and soluble fms-like tyrosine kinase-1, with and without the addition of maternal cardiovascular indices.

AUC = area under the curve; DR = detection rate; PVR = peripheral vascular resistance; other abbreviations as in Table 3.

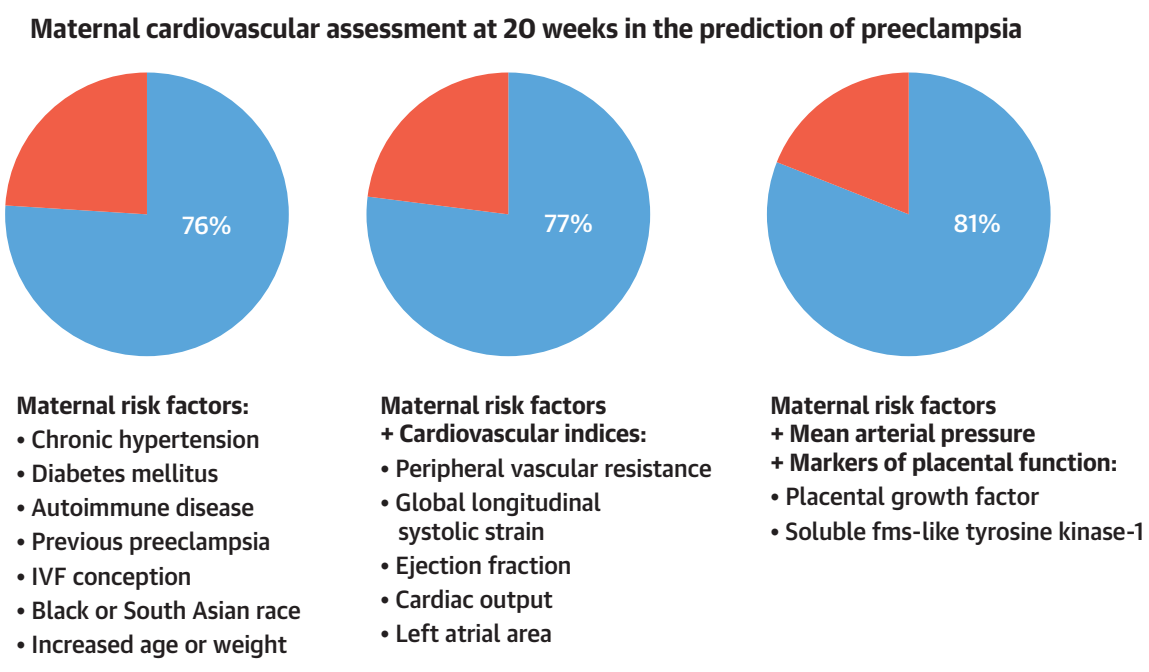
differences were small and possibly not clinically significant, these remained after accounting for differences in maternal characteristics, but after accounting for multiple testing, only peripheral vascular resistance was higher in women who developed PE or GH compared to those who did not, suggesting a similar pattern of cardiovascular changes in both conditions.

The gestational age at development of PE has also attracted a lot of interest in understanding the pathophysiology of the condition. In some relatively small studies, maternal hemodynamic adaptations were shown to differ between term and preterm PE, and it was implied that the 2 conditions constitute different disease entities. Valensise et al (11) reported that in 60 women with early PE, there was failed placental vascular remodeling with high peripheral vascular resistance and low cardiac output, whereas in 30 women with late PE, there was low peripheral vascular resistance and high cardiac output (11). Melchiorre et al (29) examined 269 women at 20 to 23 weeks' gestation and reported cardiac diastolic dysfunction only in 18 women who developed preterm PE but not in 28 women who developed term PE (29). More recently, Kalafat et al (30), in 298 women with chronic hypertension or gestational hypertension, demonstrated that those with high peripheral vascular resistance and normal or low cardiac output had higher risk of developing earlier PE compared to those with normal hemodynamic parameters (30). These findings, however, could not be confirmed in our study population. In our cohort, 96 women developed term PE, and 30 developed preterm PE. The pattern of cardiac adaptation was independent of the gestational age at delivery with PE apart from left atrial area, which was reduced in women who subsequently developed preterm PE and increased in those with term PE. These findings are in agreement with a smaller study where more advanced 3-dimensional imaging was used to characterize left atrial size and function (31,32). Considering that expansion of the left atrium is an independent predictor of diastolic dysfunction in patients with preserved LV systolic function, our findings would be consistent with more extensive cardiac functional changes in women with term rather than preterm PE.

In our study, in addition to the examination of cardiovascular function, we also measured a variety of biomarkers of placental perfusion and function. This provided the opportunity to assess the interrelationship between maternal cardiovascular and placental function but also to use these biomarkers along with maternal characteristics and medical history in the prediction of PE. We did not find any evidence of association between cardiac functional indices and placental markers, which would suggest that changes in maternal cardiac function do not operate through the placenta in promoting the development of PE.

STUDY STRENGTHS AND LIMITATIONS. To our knowledge, this study is the largest to perform detailed cardiovascular phenotyping and measurement of all potentially useful biomarkers of PE in an unselected cohort of pregnant women who were attending a routine hospital visit at midgestation. The incidence of PE in our cohort was 2.7%, which is comparable to figures previously reported in unselected populations in the United Kingdom, although variable numbers have been reported in different populations (1,33). Appropriately trained research fellows performed all cardiac measurements with a high degree of consistency in their analysis, as previously reported. A relatively large number of PE cases were identified, and this provided us with adequate power to detect a small reduction in LV systolic function and increase peripheral resistance in women who developed PE compared to those without PE, but the etiology of these findings remains unclear. Cardiac measurements were performed in midpregnancy; thus, it remains unknown whether

CENTRAL ILLUSTRATION **Screening for Preeclampsia**



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The figure demonstrates that maternal cardiac assessment at midgestation improves the performance of screening, which is based on maternal characteristics and medical history, by only 1% (area under the curve increased from 76% to 77%). Improved prediction of preeclampsia development can be achieved by a combination of maternal risk factors, mean arterial pressure, and markers of placental perfusion and function (area under the curve: 81%).

pregnancy potentially harms the cardiovascular system or simply exposes a pre-existing cardiac dysfunction. It is also possible that changes in echocardiographic parameters are the result of residual/unmeasured differences in inflammatory or cardiometabolic factors and provide further evidence supporting a heightened predisposition to hypertension in women who develop PE (34,35). In addition, after accounting for multiple testing, only peripheral vascular resistance provided strong evidence for a difference between women with PE and those without. Finally, despite the relatively large study population, the number of cases of preterm PE was small; consequently, there is a degree of uncertainty as to whether there are differences in cardiovascular indices between preterm and term PE.

CONCLUSIONS

Our study showed that women who developed PE, compared to those who did not, have increased peripheral vascular resistance and mild reduction in their LV systolic function long before the onset of the clinical manifestations of PE. Placental factors were strongly associated with the development of PE, whereas these were not associated with cardiac indices. This likely suggests that the contribution of maternal cardiac function in the development of PE is unlikely to be mediated through changes in placental perfusion and function.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Mild LV dysfunction precedes the onset of preeclampsia and is weakly associated with placental perfusion and function, suggesting that maternal cardiac function contributes to the pathophysiology of preeclampsia.

TRANSLATIONAL OUTLOOK: Because changes in maternal LV function are subtle, more sensitive measures of cardiovascular function in pregnancy are needed to identify women at risk of preeclampsia.

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KEY WORDS cardiac function, peripheral vascular resistance, preeclampsia, risk factor

APPENDIX For supplemental tables, please see the online version of this paper.