Original Article

Maternal Cardiac Assessment at 35 to 37 Weeks Improves Prediction of Development of Preeclampsia

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Abstract —Preeclampsia at term accounts for half of maternal deaths from hypertensive disorders. We aimed to assess differences in maternal cardiac indices at 35^{+0} to 36^{+6} weeks' gestation between women who subsequently developed preeclampsia at term compared with those with uncomplicated pregnancy and to evaluate whether cardiac indices offer incremental prognostic value to the available screening algorithm for preeclampsia. We recruited 1602 women with singleton pregnancies who attended for a routine hospital visit at 35^{+0} to 36^{+6} weeks' gestation between April and November 2018. We recorded maternal characteristics and preeclampsia-risk-score derived from a competing risks model and measured cardiac indices. Preeclampsia developed in 3.12% (50/1602) of participants. Women with preeclampsia, compared with those without, had increased mean arterial pressure (97.6, SD, 5.53 versus 87.9, SD, 6.82 mm Hg), systemic vascular resistance (1500, interquartile range, 1393–1831 versus 1400, interquartile range, 1202–1630 PRU) and preeclampsia-risk-score (23.4, interquartile range, 9.13–40 versus 0.9, interquartile range, 0.32–3.25). Multivariable analysis demonstrated independent association between the incidence of preeclampsia and E/e′ (hazard ratio, 1.19/unit [95% CI, 1.03–1.37]; P=0.018) as well as left ventricular mass indexed for body surface area (hazard ratio, 1.03/[g·m^2] [95% CI, 1.003–1.051]; P=0.029). Women with E/e′ ≥7.3 and left ventricular mass indexed for body surface area ≥63.2 g/m^2 had an increased risk for developing preeclampsia, despite low preeclampsia-risk-score <5% (hazard ratio, 20.1 [95% CI, 10.5–38.7], P<0.001). Increased left ventricular mass and E/e′ offer incremental information to available scoring systems and better stratify women at risk of developing preeclampsia at term. (***Hypertension*****. 2020;76:00-00. DOI: 10.1161/HYPERTENSIONAHA.120.14643.)** • Data Supplement

Key Words: diastolic function ■ morbidity ■ mortality ■ preeclampsia ■ pregnancy

Preeclampsia is a major cause of maternal and fetal mortality and morbidity.[1] A major challenge in modern obstetrics is early identification of pregnancies at high-risk of preeclampsia and undertaking the necessary measures to reduce the incidence of the disease. Extensive studies in the past decade have led to the development of first-trimester prediction of development of hypertensive disorders and their prevention through the prophylactic use of aspirin. Assessment of risk at 11 to 13 weeks' gestation by a combination of maternal demographic characteristics and medical history, maternal mean arterial pressure (MAP), uterine artery pulsatility index, and serum concentration of the angiogenic PLGF (placental growth factor), using a competing risks model, can identify a high-risk group comprising of 10% of the population that contains 90% of those that develop preeclampsia at <32 weeks' gestation (early-preeclampsia) and 75% of those that develop preeclampsia at <37 weeks (preterm-preeclampsia), but only 45% of preeclampsia at ≥37 weeks (term-preeclampsia).[2–4] Treatment of the high-risk group with aspirin (150 mg/day) from 12 to 36 weeks' gestation reduces the rate of early-preeclampsia by about 90% and preterm-preeclampsia by about 60% but has no effect on the incidence of term-preeclampsia, which is far more common than preterm-preeclampsia and contributes equally to adverse outcomes.[5] The reason for this discrepancy in the effectiveness of screening and prevention by aspirin of preterm-preeclampsia and term-preeclampsia remains unclear. It is possible that either the timing of the insult might be different or that additional factors beyond the placenta might have a key role in the pathophysiology of term-preeclampsia.

Many epidemiological studies have shown a strong relationship between preeclampsia and premature cardiovascular morbidity and mortality, which was initially attributed to the

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presence of a number of risk factors which are shared between the 2 conditions.[6–8] Later, it was hypothesized that the cardiovascular system may play a key role in the pathogenesis of hypertensive disorders and that development of preeclampsia may simply be the clinical consequence of a worsening cardiovascular adaptation to the strain of pregnancy.[9,10] To test causal relationships, the optimal approach would be to assess maternal cardiovascular function before pregnancy and examine the relationship with complications that occur during pregnancy. Foo et al[11] adopted this approach and reported differences in prepregnancy hemodynamic function in women who subsequently conceived and developed preeclampsia or fetal growth restriction during their pregnancy compared with those with normal outcome, but their findings were limited by a small number of complicated cases. Widespread cardiovascular screening for women before conception is unrealistic, and it is more reasonable to assess women during pregnancy and identify whether specific patterns of cardiovascular adaptation precede the development of preeclampsia.

We have previously demonstrated that routine assessment of pregnancy at 35 to 37 weeks' gestation is useful in the diagnosis of abnormal fetal growth patterns and prediction of term-preeclampsia by a combination of maternal factors, MAP, PLGF, and the antiangiogenic sFLT-1 (soluble fms-like tyrosine kinase 1), with detection rate of about 75% at false-positive rate of 10%.[12–14] In this study, we have performed detailed cardiovascular assessment in women at the same time as their routine scan to assess whether cardiovascular adaptations differ in women who are at imminent risk to develop preeclampsia and whether incorporation of maternal cardiac indices in the current screening protocol can improve the prediction for preeclampsia at term.

Methods

Study Design

This was a prospective observational study in women with singleton pregnancies attending for a routine hospital visit at 35^{+0} to 36^{+6} weeks' gestation at King's College Hospital, London, United Kingdom between April and November 2018. During this visit, we first recorded maternal characteristics, second, carried an ultrasound scan for fetal anatomy and growth, third, performed assessment of maternal cardiovascular function, and fourth, obtained a maternal venous blood sample for measurement of serum PLGF and sFLT-1. Exclusion criteria were the presence of hypertensive disorders before the scan and breast implants because these commonly compromise the echocardiographic acoustic windows.[15] Patients were also not eligible to participate if they were not fluent in English, and there was no available interpreter. All assessments were performed by seven fetal medicine fellows who were trained in performing both fetal ultrasound measurements and maternal echocardiography. The study protocol was approved by the National Research Ethics Committee (REC No 18/NI/0013) Integrated Research Application System ID:237936, and all patients provided written informed consent before participation. The data that support the findings of this study are available from the corresponding author upon request.

Maternal Characteristics

Maternal factors recorded during the clinic visit included age, height, weight, racial origin (white, black, and Asian), method of conception (spontaneous or assisted by in vitro fertilization or use of ovulation drugs), cigarette smoking during pregnancy, medical history, obstetric history (nulliparous if there was no previous pregnancy with delivery at ≥24 weeks´ gestation or parous with or without previous preeclampsia).

Mean arterial pressure was measured using validated automated devices and a standardized protocol.[16] Serum concentrations of PLGF and sFLT-1 were measured using an automated biochemical analyzer (Brahms Kryptor compact Plus, Thermo Fisher Scientific, Hennigsdorf, Germany). A competing risks model incorporating maternal factors, MAP, PLGF, and sFLT-1 was used to calculate a preeclampsia-risk-score for each woman.[12] Preeclampsia-risk-score >5% was considered to be a high risk for development of preeclampsia.

Maternal Cardiac Function

All subjects were studied by 2-dimensional, and Doppler transthoracic echocardiography at rest in the left lateral decubitus position and data were acquired during unforced expiration. The protocol included standard parasternal and apical views acquired with a Canon Aplio i900 scanner (Canon Medical Systems Europe BV, ZOETERMEER, the Netherlands) as per American Society of Echocardiography guidelines.[17,18] Reproducibility of the acquisition and analysis of the echocardiograms by 7 trained fellows was assessed in 10 participants and compared against an experienced cardiologist accredited in echocardiography.[19]

Pregnancy Outcomes

Pregnancy outcomes were obtained from the hospital delivery records or general medical practitioners. Fetal growth restriction was defined according to Gratacos classification, and fetuses were classified as small for gestational age if their birthweight was <2500 grams.[20] The diagnosis and severity of preeclampsia were based on the criteria defined American College of Obstetrics and Gynecology.[21] Birthweight for gestational age was converted to a *Z* score based on the Fetal Medicine Foundation fetal and birthweight chart.[22]

Statistical Analysis

Differences in maternal and fetal characteristics between pregnancies with and without development of preeclampsia were evaluated by independent samples *T* Test or Mann-Whitney test for continuous variables and χ^2 test for nominal variables.

Cox proportional hazards models were used to examine the association between individual baseline cardiovascular parameters and the subsequent development of preeclampsia (univariate Cox regression analysis). Data were censored at the time of the birth. Predictors in univariate analysis with significant or marginally significant (P <0.05) association with preeclampsia were further tested in a prespecified multivariable Cox regression model controlling for the preeclampsia-risk-score,[12] heart rate, and body mass index. Associations are presented as hazard ratio (HR) with 95% CI.

We further sought to analyze the prognostic value of left ventricular (LV) mass indexed to body surface area (LVMI) and E/e´ by deriving clinically relevant cutoff points from survival receiver operator characteristic curves. We also evaluated the incremental prognostic performance of LVMI and E/e´ variables on top of the competing risk model for term-preeclampsia by calculating the improvement in calibration indices (Akaike Information Criterion and likelihood ratio tests), the net reclassification index,[23] and the integrated discrimination improvement index.[24] We calculated integrated discrimination improvement index for both logistic and survival regression (package "survIDINRI" in R) models for preeclampsia.

Based on our previous studies showing ≈2.5% incidence of preeclampsia at term, we aimed to recruit ≈1600 women. This sample size would yield 40 cases with preeclampsia and would provide satisfactory power (ie, 80%) to establish a 2.5-fold unadjusted increase in HR for the main variable of interest (women with increased E/e´ or LVMI as compared to pregnancies with low diastolic and structural markers) towards the primary end point in Cox proportional hazards model (module "stpower" of STATA). In addition, we opted to retain a ratio of 5 to 10 events per covariate used in all Cox regression analyses to avoid model overfitting. None of the variables used in analyses had more than 5% missing values. Statistical calculations were performed by STATA package, version 13.1 (StataCorp, College Station, TX) and R version 3.4.0.

Results

Maternal Characteristics

The entry criteria were fulfilled by 1995 women, but 393 declined to participate in the study. Main reasons for refusal to participate included time constraints with concerns in prolonging clinic appointment and reluctance to perform screening for preeclampsia. In the study population of 1602 patients, 50 (3.12%) developed preeclampsia. The maternal and pregnancy characteristics are presented in Table 1. Women who developed preeclampsia, compared with those that did not, had higher prevalence of preexisting diabetes mellitus, preeclampsia-risk-score, weight, body mass index and sFLT-1 and lower PLGF, they more commonly delivered by cesarean section, and their babies had a lower birthweight.

Maternal Cardiac Function

Women who developed preeclampsia, compared with those that did not, had higher LVMI, MAP systemic vascular resistance, and lower heart rate but no significant difference in cardiac output (Table 2). From the various LV systolic functional indices, ejection fraction and Tissue Doppler Imaging were higher in women who developed preeclampsia compared with those who did not. From the diastolic LV functional indices, isovolumic relaxation time, E/A, E/e′, left atrial volume, and Tissue Doppler Imaging e′ were also higher in women who subsequently developed preeclampsia (Table 2). According to the American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines, none of the women had evidence of systolic dysfunction, 208 women had at least one criterion for diastolic dysfunction (intermediate

Table 1. Maternal and Pregnancy Characteristics of the Study Population

Variable	No Hypertensive Disorders (n=1552)	Preeclampsia (n=50)	*P* Value
Age, y, mean (SD), y	33 (5)	33 (6)	0.690
Weight, kg, mean (SD)	77 (70–87)	84 (78–91)	<0.001
Height, cm, median (IQR)	165 (161–170)	166 (162–170)	0.699
Body mass index, kg/m^2, mean (SD)	29.2 (4.6)	31 (3.8)	0.006
Racial origin			0.483
White, n (%)	1086 (73)	36 (72)	
Black, n (%)	267 (18)	11 (22)	
Asian, n (%)	134 (9)	2 (4)	
Mixed, n (%)	65 (4.19)	1 (2)	
Smoking, n (%)	36 (2)	0 (0)	0.276
Conception by in vitro fertilization, n (%)	85 (6)	6 (12)	0.050
Family history of preeclampsia, n (%)	68 (4)	2 (4)	0.897
Preexisting diabetes mellitus, n (%)	8 (0.52)	1 (2)	0.167
Gestational diabetes mellitus, n (%)	135 (9)	3 (6)	0.503
PLGF, pg/mL, median (IQR) (N=1412)	245 (129–455)	74 (51–114)	<0.001
sFLT-1, pg/mL, median (IQR) (N=1412)	2200 (1579–3291)	5800 (4216–8283)	<0.001
PLGF (multiple of the median; N=1412)	0.96 (0.53–1.77)	0.34 (0.21–0.53)	<0.001
sFLT-1 (multiple of the median; N=1412)	1.00 (0.75–1.49)	2.47 (1.76–3.24)	<0.001
Uterine artery PI (multiple of the median), median (IQR)	1.00 (0.84–1.20)	1.02 (0.77–1.21)	0.800
Preeclampsia-risk-score, n (%) (N=1412)	0.9 (0.32–3.25)	23.4 (9.13–40.0)	<0.001
Severe preeclampsia (ACOG criteria), n (%)		19 (38)	
Cesarean section delivery, n (%)	395 (26)	20 (40)	0.021
Gestational age at birth, wk, median (IQR)	40 (39–41)	40 (39–40)	0.196
Birth weight, g, median (IQR)	3400 (3130–3728)	3200 (2965–3480)	0.001
Birth weight, *Z* score (SD)	–0.07 (1.03)	–0.54 (1.16)	0.002
Estimated fetal weight, g (IQR)	2795 (2651–2950)	2724 (2704–3072)	0.04
IUGR, n (%)	44 (2.8)	6 (10.5)	0.001
SGA, n (%)	47 (3.0)	3 (7.5)	0.107

Measurements are presented as median (25th–75th percentile), mean (SD), or n (%). *P* values are derived from the nonparametric Mann Whitney *U* test or the Pearson χ^2 test. ACOG indicates American College of Obstetrics and Gynecology; IQR, interquartile range; IUGR, intrauterine growth restriction; PI, pulsatility index; PLGF, placental growth factor; sFLT-1, serum soluble fms-like tyrosine kinase 1; and SGA, small for gestational age.

Table 2. Maternal Cardiac Measurements in the Study Population

Variable	No Hypertensive Disorders (n=1552)	PE (n=50)	*P* Value
Mean arterial pressure, mm Hg, mean (SD)	87.9 (6.82)	97.6 (5.53)	<0.001
Heart rate, bpm, median (IQR)	82 (73 to 90)	75 (67 to 86)	<0.001
Systemic vascular resistance, PRU, median (IQR)	1400 (1202 to 1630)	1500 (1393 to 1831)	<0.001
Cardiac output, L/m, median (IQR)	5.05 (4.32 to 5.79)	5.03 (4.35 to 5.58)	0.734
Diastolic indices			
E, median, cm/s (IQR)	74.0 (64.0 to 85.9)	78.0 (68.5 to 88.7)	0.019
A, median, cm/s (IQR)	53.9 (46.4 to 63.0)	50.4 (41.3 to 64.0)	0.078
Isovolumic contraction time, ms, median (IQR)	58 (50 to 69)	56 (47 to 67)	0.134
Ejection time, ms, median (IQR)	256 (236 to 275)	263 (242 to 289)	0.015
Isovolumic relaxation time, ms, median (IQR)	72 (58 to 86)	81 (67 to 92)	0.007
E/A, median (IQR)	1.3 (1.2 to 1.6)	1.5 (1.2 to 1.9)	0.004
E/e′, median (IQR)	5.9 (4.9 to 7.0)	6.7 (5.8 to 8.0)	<0.001
e′ average, cm/s, median (IQR)	12.7 (11.1 to 14.5)	11.7 (10 to 12.9)	<0.001
A′ average, cm/s, median (IQR)	8.1 (7.0 to 9.1)	8.1 (7.1 to 9.3)	0.595
S′ average, median (IQR), cm/s	9.8 (8.7 to 10.9)	9.2 (8.3 to 10.2)	0.010
Left atrium volume indexed to body surface area, m^3, median (IQR)	17.6 (14.0 to 21.8)	19.6 (17.4 to 23.8)	0.001
Diastolic dysfunction, n (%)	189 (13)	19 (23)	0.010
Systolic indices and left ventricular mass			
Left ventricular outflow tract velocity time integral, ms, median (IQR)	19.7 (17.2 to 22.6)	21.1 (18.5 to 23.4)	0.016
Cardiac index, L/(min·m^2)	2.66 (2.31 to 3.03)	2.54 (2.21 to 2.83)	0.038
Myocardial performance index, median (IQR)	0.52 (0.44 to 0.60)	0.51 (0.44 to 0.60)	0.755
Stroke volume indexed to body surface area, %, median (IQR)	33.0 (28.3 to 38.3)	35.1 (28.8–40.0)	0.206
Ejection fraction, %, median (IQR)	58.3 (54.4 to 63.1)	60.7 (56.6 to 64.8)	0.002
GLS, %	−21.3 (−23.0 to −19.7)	−21.5 (−23.6 to −19.7)	0.644
GCS, %	−27.9 (−30.7 to −25.0)	−29.1 (−33.0 to −25.8)	0.052
Left ventricular mass indexed to body surface area, g/m^2, median (IQR)	61.2 (54.1 to 68.5)	64.6 (58.6 to 71.4)	0.001

Measurements are presented as median (25th–75th percentile), mean (SD), or n (%). *P* values are derived from the nonparametric Mann Whitney *U* test or the Pearson χ^2 test. A indicates mitral peak late diastolic flow velocity; A′, peak velocity of diastolic mitral annular motion as determined by pulsed-wave Doppler; E, mitral peak early diastolic flow velocity; e′, peak velocity of early diastolic cm/s mitral annular motion as determined by pulsed-wave Doppler; GCS, global circumferential strain; GLS, global longitudinal strain; IQR, interquartile range; PE, preeclampsia; PRU, peripheral resistance units (mm Hg×min×mL-1); and S′, peak velocity of systolic mitral annular motion as determined by pulsed-wave Doppler.

probability), whereas only 1 was positive for 2 (definite diagnosis).[17,18] Diastolic dysfunction was observed in a higher proportion of the group that developed preeclampsia, compared with those that did not (23.2% versus 12.6%; Table 2).

Reproducibility of Echocardiographic Measurements

Interobserver reproducibility of various cardiac indices between 7 different operators was moderate to excellent (intraclass correlation coefficient was 0.98 for mitral annular early diastolic velocity and 0.78 for LVMI). Reproducibility between the same fellow and an experienced cardiologist accredited in echocardiography was satisfactory to excellent (ICC was 0.85 for mitral annular early diastolic velocity, 0.83 for LVMI).

Prediction of Preeclampsia at Term

Preeclampsia occurred in 50 (3.1%) women at a median follow up period of 23 days (interquartile range:16-29). Cardiac

indices that were predictive for the development of preeclampsia in univariable and multivariable analysis are shown in Table 3. In the final multivariable model, accounting for all significant cardiac biomarkers, preeclampsia-risk-score, heart rate, and body mass index, only E/e′ (HR, 1.19 per 1 unit [95% CI, 1.03–1.37]) and LVMI (HR, 1.03 per g [95% CI, 1.003–1.051]) were independently associated with the incidence of preeclampsia. Dose-response curves indicated a linear association of E/e′ and LVMI with the risk of developing preeclampsia (P>0.05 for the nonlinear term in both cardiac markers, Figure S1A and S1B in the Data Supplement).

Survival receiver operator characteristic curve analysis demonstrated that the optimal cutoff point for E/e′ and LVMI to discriminate development of preeclampsia was 7.3 and 63.2 g/m^2, respectively (Figure S2A and S2B). These cutoff points for E/e′ and LVMI were associated with a >2-fold increase in the risk for preeclampsia, independently of the preeclampsia-risk-score and heart rate (Figure S3A and S3B). The combination of high E/e′ and LVMI progressively increased the risk for preeclampsia after controlling for the preeclampsia-risk-score and heart rate (HR, 3.09 per ascending group [95% CI, 2.06–4.62], P<0.001; Figure [A]).

Table 3. Cox Regression Analysis for the Incidence of Preeclampsia

	Univariable		*Multivariable	
Variable	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value
Heart rate, bpm (IQR)	0.956 (0.933–0.979)	<0.001	0.964 (0.942–0.987)	0.002
Systemic vascular resistance, PRU, median (IQR)	1.00 (1.00–1.00)	0.001	1.00 (0.999–1.00)	0.789
Cardiac output, L/min, median (IQR)	0.87 (0.68–1.12)	0.274	1.11(0.842–1.47)	0.452
Diastolic indices				
E, median (IQR), cm/s	1.02 (1.00–1.03)	0.020	1.01(0.994–1.03)	0.207
A, median (IQR), cm/s	1.00 (0.98–1.02)	0.774	1.003(0.98–1.03)	0.825
Isovolumic contraction time, ms, median (IQR)	1.00 (1.00–1.01)	<0.001	1(0.999–1.004)	0.170
Ejection time, ms, median (IQR)	1.01 (1.00–1.02)	0.006	0.999(0.987–1.01)	0.855
Isovolumic relaxation time, ms, median (IQR)	1.01 (1.00–1.02)	0.185	0.998(0.983–1.01)	0.762
E/A, median (IQR)	1.92 (1.29–2.84)	0.001	1.69(1–2.84)	0.050
E/e′, median (IQR)	1.32 (1.16–1.49)	<0.001	1.19(1.03–1.37)	0.018
e′ average, cm/s, median (IQR)	0.84 (0.75–0.94)	0.003	0.904(0.803–1.02)	0.096
A′ average, cm/s, median (IQR)	1.01 (0.85–1.19)	0.932	1.04(0.871–1.24)	0.666
S′ average, cm/s, median (IQR)	0.82 (0.68–0.98)	0.028	0.991(0.817–1.2)	0.927
Left atrium volume indexed to body surface area, m^3, median (IQR)	1.06 (1.01–1.11)	0.010	1.04(0.988–1.09)	0.141
Systolic indices				
Left ventricular outflow tract velocity time integral, ms, median (IQR)	1.05 (0.99–1.12)	0.135	0.999(0.924–1.08)	0.980
Myocardial performance index, median (IQR)	0.44 (0.05–4.18)	0.471	0.482(0.0473–4.91)	0.538
Stroke volume indexed to body surface area, %, median (IQR)	1.01 (0.98–1.05)	0.457	1.01(0.972–1.06)	0.534
Ejection fraction, %, median (IQR)	1.03 (0.99–1.08)	0.129	1(0.96–1.04)	0.993
GLS, %	0.97 (0.87–1.09)	0.631	1.04(0.937–1.16)	0.433
GCS, %	0.93 (0.87–0.99)	0.020	0.98(0.919–1.04)	0.536
Left ventricular mass indexed to body surface area, g/m^2, median (IQR)	1.03 (1.01–1.05)	0.009	1.03(1.003–1.05)	0.029

A indicates mitral peak late diastolic flow velocity; A′, peak velocity of diastolic mitral annular motion as determined by pulsed-wave Doppler; E, mitral peak early diastolic flow velocity; e′, peak velocity of early diastolic cm/s mitral annular motion as determined by pulsed-wave Doppler; GCS, global circumferential strain; GLS, global longitudinal strain; HR, hazard ratio; IQR, interquartile range; PRU, peripheral resistance units (mm Hg×min×mL-^{1}); and S′, peak velocity of systolic mitral annular motion as determined by pulsed-wave Doppler.

*Adjusted for preeclampsia-risk-score, heart rate, and body mass index.

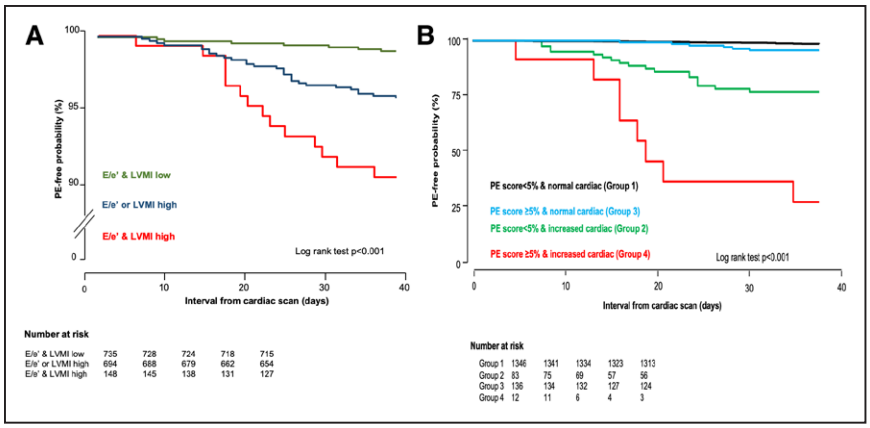

Figure. Kaplan-Meier curves for probability of preeclampsia (PE)-free pregnancy. (**A**) Combined values of mitral peak early diastolic flow velocity/peak velocity of early diastolic cm/s mitral annular motion as determined by pulsed-wave Doppler (E/e′) and left ventricular mass indexed to body surface area (LVMI) values at 35^{+0} to 36^{+6} wk, weeks and (**B**) combined use of PE-risk-score and cardiac markers. In **A**, the 3 groups represent low E/e′ <7.3 and LVMI <63.2g/m^2 (green line), high E/e′ ≥7.3, or LVMI ≥63.2 g/m^2 (blue line) and high E/e′ and LVMI (red line). In **B**, the 4 groups are created by combining high (>5%) or low (<5%) PE-risk-score with low and high (both E/e′ and LVMI) cardiac markers. *P* value was calculated by log-rank test.

Women with low preeclampsia-risk-score (<5%) and increased E/e′ (≥7.3) and LVMI (≥63.2 g/m^2) had substantially elevated risk for preeclampsia (HR, 20.1 [95% CI, 10.5–38.7]; *P*<0.001) as compared to pregnancies with both low preeclampsia-risk-score and low E/e′ (<7.3) and LVMI (<63.2 g/m^2; Figure [B]). Women with low preeclampsia-risk-score and high E/e′ and LVMI had higher incidence of preeclampsia compared with high preeclampsia-risk-score and low E/e′ and LVMI (HR, 5.89 [95% CI, 2.34–14.8]; *P*<0.001; Figure [B]).

Incremental Value of Cardiac Biomarkers to Available Screening Scoring System

Addition of E/e′ and LVMI improved the calibration for preeclampsia provided by the preeclampsia-risk-score alone (Table 4). The combination of increased E/e′ and LVMI conferred incremental reclassification value over the preeclampsia-risk-score for prediction of late preeclampsia (overall net reclassification index, 0.058, *P*=0.045); cardiac indices correctly reclassified 2 pregnancies that developed preeclampsia into higher risk category and additionally correctly stratified as low risk 27 uncomplicated pregnancies (Table S1). Addition of E/e′ and LVMI in the predictive model improved the detection rate for preeclampsia from 88% to 92% at the fixed false-positive rate of 25% (Table S2). Finally, increased E/e′ and LVMI improved the discriminative ability of the preeclampsia-risk-score for prediction of term-preeclampsia (overall integrated discrimination improvement index, 5.2, *P*<0.001 and survival integrated discrimination improvement index, 5.9 [95% CI, 2.6–13.1]; *P*<0.001; Table 4; Figure S4).

Discussion

This large prospective study has demonstrated that impairment in maternal cardiac diastolic functional indices and increase in LV mass precedes the development of preeclampsia in late pregnancy. In addition, we showed, for the first time, that measurement of LV mass and the simple and reproducible cardiac diastolic functional parameter of E/e′ at the time of a routine pregnancy visit at 35^{+0} to 36^{+6} weeks' gestation can provide incremental information to available scoring systems[12,14] and better stratify women at risk for developing preeclampsia. These findings support the hypothesis that maladaptation of maternal cardiovascular system precedes the development of preeclampsia and provide opportunities for further research to test whether more aggressive blood pressure treatment in high-risk women can modify cardiac adaptation and prevent the development of preeclampsia.

Understanding the pathophysiology of preeclampsia and predicting its occurrence has been an active area of research in the past few years. Data suggest that women who had preeclampsia in pregnancy are at increased risk for early development of adverse cardiovascular outcomes later in life.[9] However, whether the hypertensive event per se or the associated adverse cardiovascular risk profile that often coexists in these women is responsible for this association remains to be established. A number of studies, for instance, have shown

Table 4. Indices of Calibration, Discrimination, and Reclassification After Addition of Cardiac Markers on the PE-Risk Score for Prediction of Study's Outcomes

	Calibration		Discrimination					Reclassification	
	Akaike Information Criterion	Likelihood Ratio Test	IDI	Survival IDI				NRI	
		χ^2 (*P* Value)	Estimate (SE)	Events	Nonevents	Overall (95% CI)	*P* Value	Estimate (SE)	*P* Value
Preeclampsia									
PE-risk-score	601								
PE-risk-score +E/E′≥7.3 +LVMI ≥63.2 gr/m^2	582	22.9 (<0.001)	*5.2 (1.4)	5.7	−0.2	5.9 (2.6–13.1)	<0.001	0.058(0.029)	0.045

E indicates mitral peak early diastolic flow velocity; E′, peak velocity of early diastolic cm/s mitral annular motion as determined by pulsed-wave Doppler; IDI, integrated discrimination improvement; LVMI, left ventricular mass indexed to body surface area; NRI, net reclassification improvement; and PE, preeclampsia.

*P<0.001.

LV diastolic dysfunction, increased LV mass, and impaired longitudinal systolic function, in pregnant women following a hypertensive event and some of these cardiovascular changes seem to persist in the postpartum period and may increase the long term cardiovascular risk for these women.[25,26] In addition, few studies in high-risk pregnant women have demonstrated hemodynamic and subclinical cardiac dysfunction before the development of pregnancy complications, but the reported results were not consistent. For example, Vasapollo et al[27] examined 608 normotensive high-risk women at 20 to 22 weeks' gestation and demonstrated that measurement of peripheral vascular resistance offers incremental value to abnormal uterine artery Dopplers in the prediction of adverse pregnancy outcomes. In a subsequent study, by the same group, in 1345 pregnancies at 24 weeks' gestation, those who subsequently developed early or late preeclampsia had increased LV mass and higher diastolic functional indices than those with uncomplicated pregnancy.[28] In contrast, 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-preeclampsia but not in 28 women who developed term-preeclampsia.

To overcome potential bias by studying selective populations and to be able to distinguish physiological from maladaptive maternal cardiovascular responses, we performed detailed cardiovascular phenotype in a large unselected normotensive population of pregnant women who were attending a routine clinical visit in late pregnancy. From this prospective longitudinal assessment, we were able to demonstrate that few weeks before the development of preeclampsia, women had distinct hemodynamic and cardiovascular functional changes; MAP, peripheral vascular resistance, LVMI, and indices of LV diastolic function were increased. Although in the majority of women, the actual values remained within the normal range, the incidence of diastolic dysfunction as per American Society of Echocardiography/EACVI guidelines[17,18] was almost double in women who developed preeclampsia compared with those with uncomplicated pregnancy. From the various cardiac parameters assessed, LVMI and E/e′, which is considered one of the most reliable markers of diastolic function with high predictive value for later cardiovascular outcome in hypertensive nonpregnant adults,[30] had stronger associations with incidence of preeclampsia at term. Considering that E wave velocity was greater than in women with preeclampsia compared with normotensive pregnancies, these findings would be consistent with a change in passive myocardial compliance in the more hypertrophied ventricle. In the current study, we also confirmed previous data from our unit, where we reported that assessment of maternal hemodynamics (ie peripheral vascular resistance and cardiac output) does not improve performance of screening for preeclampsia.[31] Although maternal hemodynamic assessment is often used as a proxy for maternal cardiac function, the results of our study indicate that these should not be used interchangeably, and a more detailed cardiac functional assessment is needed to identify those at risk.

Increase in E/e′ and LVMI has been reported even in normal pregnancies in the third trimester, and this is thought to be the result of cardiac adaptation to the increase in volume loading, thus, making difficult the differentiation between physiological from maladaptive responses.[32] However, in our study, we were able to define threshold values, which may help clinicians to identify women at increased risk for preeclampsia. We showed that combination of E/e′ ≥7.4 and LVMI ≥63.5 g/m^2 at 35^{+0} to 36^{+6} weeks' gestation increases by >2-fold the likelihood for a pregnant woman to develop preeclampsia at term. Whether similar cardiac changes can be detected earlier in pregnancy and can assist in prediction of preeclampsia at term remains to be determined.

Women at imminent risk for preeclampsia, compared with those with uncomplicated pregnancy, had increased LV ejection fraction and circumferential strain. These findings would be consistent with the physiology noted in heart failure patients where ejection fraction is preserved in the presence of diastolic dysfunction as noted in our population and contradict studies in women with preeclampsia where lower global longitudinal strain has been reported.[25] It is possible that the discrepancy in these results is related to differences in the timing of assessment between studies, or it may suggest that the insult of hypertension is needed for more pronounced systolic functional changes to become apparent.

Development of preeclampsia is preceded by a decrease in the maternal serum concentration of the angiogenic factor PLGF and an increase in the level of the antiangiogenic factor sFLT-1.[33] Previously, our group has demonstrated that the use of competing risks model that combines maternal factors with MoM values of MAP, PlGF, and sFLT-1 when used at 35^{+0} to 36^{+6} weeks is superior to that of PlGF alone or the sFLT-1/PlGF ratio in predicting development of term-preeclampsia.[34,35] In this study, we showed that the addition of cardiac parameters to this model can improve discrimination and offer incremental value in identifying patients at high risk for development of preeclampsia at term.

Strengths of our study include, first, examination of a large population of women undergoing a routine clinical visit for assessment of fetal growth and second, detailed maternal cardiovascular functional assessment by trained operators that provided reproducible measurements validating the accuracy of our observations. The results of our study have important clinical implications, but they require validation in other cohorts before incorporating routine echocardiographic assessment during pregnancy because functional assessment of the maternal heart requires extensive training of operators and has economic implications. Appreciation of the importance of maternal cardiac adaptation during pregnancy has led to our previous work where we incorporated maternal hemodynamics into prediction models for the development of preeclampsia and the response to antihypertensive treatment.[31,36–38] The results of our current study demonstrate that diastolic function appears to be more sensitive and to precede the development of preeclampsia sooner than systolic function. It is, therefore, obvious that strategies for preeclampsia screening will improve further by the addition of diastolic functional indices to existing protocols; however, this will have to be validated in other cohorts.

In conclusion, we showed that women who are at risk of developing preeclampsia at term, compared with those with uncomplicated pregnancy, have distinct cardiac changes before their hypertensive event. In addition, we showed for the

first time that assessment of simple LV indices can improve risk stratification and discrimination of patients compared with current available competing risk models. Further studies are needed to determine the time course of the noted cardiac functional changes during pregnancy and to assess whether aggressive blood pressure treatment in high-risk women can modify cardiac adaptations, as shown in patients with even mild hypertension outside pregnancy,[39] and potentially reduce the incidence of term-preeclampsia.

Perspectives

In this prospective observational study, we demonstrated that women who developed preeclampsia compared with those who did not had increased preeclampsia-risk-score and increased LV mass indexed for body surface area and worse LV diastolic indices before the clinical onset of the disease. LV mass and E/e′ offer incremental information to available scoring systems and better stratify women at risk of preeclampsia.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Women who are at risk of developing preeclampsia at term, compared with those with uncomplicated pregnancy, have distinct cardiac changes before their hypertensive event.
- Impairment in maternal cardiac diastolic functional indices and increase in left ventricular mass precedes the development of preeclampsia in late pregnancy.

What Is Relevant?

- Women with E/e′ ≥7.3 and left ventricular mass indexed to body surface area ≥63.2 g/m^2 have increased risk for developing preeclampsia despite low preeclampsia-risk-score.
- Maladaptation of the maternal cardiovascular system precedes the development of preeclampsia and provides opportunities to test whether more aggressive blood pressure treatment in high-risk women can modify cardiac adaptation and prevent the development of preeclampsia.

Summary

Measurement of left ventricular mass indexed to body surface area and the simple and reproducible cardiac diastolic functional parameter of E/e′ at the time of a routine pregnancy visit at 35 to 36 weeks' gestation offer incremental information to available competing risk models and better stratify women at risk of preeclampsia.