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TITLE PAGE

Cardiovascular risk assessment in women at high risk for pre-eclampsia in first half of pregnancy

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KEYWORDS

Pre-eclampsia, angiogenic factors, echocardiography, cardiovascular risk, cardiac biomarkers.

ABSTRACT

Background: Women diagnosed with pre-eclampsia (PE), especially those with early-onset and severe forms, are at heightened risk of future cardiovascular disease (CVD). It is uncertain if women at high-risk for PE present cardiovascular impairment at the beginning of pregnancy. The aim of this study was to assess cardiovascular biomarkers and cardiac function in the first half of pregnancy in women at high-risk for PE.

Methods: This was a prospective cohort study including women attending first trimester screening for PE. Risk of PE in the first trimester was calculated using a previously validated model, which includes maternal factors and biophysical markers. A cut-off of 1 in 250 was used to classify high-risk for developing PE. Maternal echocardiographic function and morphometry were evaluated, and peripheral blood samples were obtained to assess hematological and biochemical variables, including lipid profile and cardiovascular and angiogenic factors.

Results: A total of 349 pregnant individuals were included; 257 at high-risk and 92 at low-risk for PE. Maternal echocardiography was performed at a mean ± SD gestational age of 14.9 ± 1.3 weeks and blood sampling at 16.3 ± 1.9 weeks. The high-risk PE group exhibited a significantly worse lipid profile (lower levels of high-density lipoproteins 69.7 ± 14.2 *vs* 74.0 ± 14.6 mg/dL, p=0.020), lower placental growth factor (0.89 ± 0.63 *vs* 1.15 ± 0.58 MoM, p<0.001), and significantly lower levels of N-terminal pro-brain natriuretic peptide (51.0 ± 2.1 *vs* 52.1 ± 2.0 ng/L, p=0.008). Echocardiographic evaluation indicated concentric remodeling, along with an altered diastolic pattern in the high-risk group.

Conclusions: Women at high risk of developing PE exhibit differences in lipid profile, angiogenic factors, and echocardiographic parameters, indicative of cardiac maladaptation or impairment during the first half of pregnancy. These findings suggest a link between subclinical cardiovascular dysfunction, PE development and later CVD risk.

MANUSCRIPT

INTRODUCTION

Heart disease and stroke cause 1 in 3 deaths among women each year - more than all cancers combined[1]. Although a reduction in mortality from cardiovascular disease (CVD) has been seen recently, the effect is less pronounced in women. Pregnancy complications such as preeclampsia (PE), are risk factors that are independently associated with CVD in women[2]. Women also have a significant window of opportunity after pregnancy to take proactive measures upon identifying their increased risk.

PE is a complication occurring in 2 to 8% of all pregnancies and remains a major cause of maternal morbidity and mortality[3,4] PE is commonly associated with abnormal placental pathology and placenta-mediated complications such as fetal growth restriction[5]. Severe PE is directly related to cardiac injury, characterized by cardiac remodeling, decreased myocardial relaxation and global left ventricular diastolic dysfunction[6]. Previous studies have shown that women with PE have an increased risk of developing CVD in the future; the risk being higher in those with early-onset and severe PE[7]. Multiple epidemiological studies have shown that PE is associated with development of cardiovascular (CV) risk factors, and outcomes like arterial hypertension, myocardial infarction or stroke, renal complications, vascular and metabolic dysfunction, during and in the subsequent years after the affected pregnancy[8]. Some studies show a 2-to-4-fold higher risk of developing CV disease in the short- and long-term in women with PE[8,9].

It is uncertain if women at high-risk of PE present CV impairment at the beginning of pregnancy or alternatively, CV changes observed are secondary to endothelial dysfunction and cardiac injury due to the condition[10,11]. Knowing the existing mechanisms behind cardiac remodeling in pregnant women at high-risk of PE is

important to identify those at increased risk of long-term CV disease, and to develop strategies to prevent or treat both early and late CV complications.

In this study, we assessed echocardiographic and CV biomarkers in the first half of pregnancy in women at high and at low risk for PE, to identify whether CV changes precede development of clinical PE.

METHODS

Study population

This was a prospective cohort study conducted at the Maternal-Fetal Medicine Department of Hospital Sant Pau, Barcelona, Spain as part of the AngioCor prospective cohort study[12]. Women were recruited from July 2020 to April 2023 upon first trimester screening for PE. Inclusion criteria were a singleton pregnancy in women between 18 and 45 years old, able to understand study requirements, and provide written informed consent. Women diagnosed with Type-1 diabetes mellitus, hyperthyroidism, renal disease or with history of thromboembolic events were excluded from the study. Likewise, fetal malformations and/or fetal chromosomal abnormalities were not included.

The AngioCor study is registered on the ClinicalTrials.gov website under NCT04162236. The Hospital's Ethics Committee approved the study protocol (September 27th, 2019; approval number EC/19/297/5698), and written informed consent was obtained from all women to participate in the study.

PE risk in the first trimester (between 11^{+0} to 13^{+6} weeks) was calculated using a multivariate Gaussian distribution model previously validated in our population[4]. Maternal factors (ethnicity, weight, height, waist/hip ratio, smoking status, parity, history

of PE, pre-existing diabetes, hypertension, thrombophilia, renal or autoimmune conditions), biophysical markers [mean arterial blood pressure (MAP) and mean uterine artery pulsatility index (UtA-PI)], and pregnancy-associated plasma protein A (PAPP-A) were included in the model, giving a numerical risk calculation. A cutoff point of 1 in 250 was considered as high-risk for developing PE[4,13]. In a subset of patients with intermediate risk for PE, placental growth factor (PlGF) was analyzed and included in the model, to refine the risk calculation. A detailed description of our risk calculation model can be found in **Appendix S1**.

Plasma biomarker analysis

Peripheral blood samples were obtained upon inclusion in the study. Routine hematological and biochemical variables, including lipid profile, were measured by standard, fully automated methods. Angiogenic factors (soluble fms-like tyrosine kinase-1 (sFLT-1); PlGF), high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured using automated electrochemiluminescence immunoassays on a Roche 711 cobas platform (Roche Diagnostics, Basel, Switzerland). Copeptin was measured using an automated immunofluorescent assay in a Kryptor instrument using two polyclonal antibodies directed to the 132.164 aminoacids of proAVP (BRAHMS Copeptin proAVP; ThermoFisher Scientific, Henningsdorf, Germany). All immunoassays showed appropriate accuracy and within- and between-batch precision in the internal and external quality control assessments.

Maternal echocardiography

Ultrasound examinations were performed at rest in the left lateral decubitus position using Affiniti 70G and EPIQ 7W (Philips Healthcare, Andover, MA, USA)

ultrasound systems. A 9 MHz sector probe (E10-2; Philips Healthcare,) was used. Images were acquired with duration of 5 cardiac consecutive cycles and frame rate of ≥60Hz. Clip acquisition was performed during maternal apnea. High-resolution images were acquired by an experienced obstetrician and post-processed by a cardiologist using dedicated software (Xcelera; Philips Healthcare, Andover, MA, USA). Cardiologists were blinded to the study group at the time of the analysis.

Two-dimensional (2D), M-mode and Doppler echocardiographic measurements were acquired according to standard protocols[14]. Standard echocardiographic measurements included left ventricle (LV) end-diastolic diameter (LVEDd), LV end-systolic diameter, LV end-diastolic volume, as well as end-diastolic wall thickness of the interventricular septum (IVS) and LV posterior wall thickness (PWT), LV outflow tract diameter, right ventricular diameter at the midlevel in the apical 4-chamber view, and 2D left atrial (LA) volume. LV mass was calculated using the formula 0.8 x (1.04 x ([IVS + LVEDd + PWT]^3 - LVEDd^3) + 0.6.

LV function was assessed by ejection fraction obtained by the Simpson method. Mitral annular peak systolic excursion (MAPSE) and tricuspid annular peak systolic excursion (TAPSE) were also measured. LV diastolic function was evaluated by transmitral flow velocities using pulsed Doppler, measuring early transmitral diastolic flow velocity (E) and flow velocity during atrial contraction (A), and calculating E/A ratio. LV filling pressure was predicted using average (septal and lateral) mitral E/E' ratio, obtained from pulsed tissue Doppler. Cardiac output was calculated using the formula: velocity-time integral (VTI) × cross-sectional area (CSA) × heart rate, in which the VTI is obtained through pulsed wave Doppler in the LV outflow tract, the CSA is of the LV outflow tract and heart rate (beats per min) is determined through automatic measurement of the R-R interval in the electrocardiogram[14,15].

Measurement of 2D global longitudinal strain (GLS), was conducted with automated tracking of myocardial motion, and was manually adjusted by correcting the endocardial borders, if deemed necessary.

Statistical analysis

Data distributions involved application of standard statistical tests. Variables manifesting non-Gaussian distributions underwent natural logarithm transformation, followed by reassessment of Gaussianity. Data are expressed as proportions, mean ± SD , or median and interquartile range. Disparities in proportions observed within high- and low-risk subgroups were subjected to analysis using the Z-test for large-sized samples or the chi-square test for small-sized samples. Comparisons between numerical variables were executed using either parametric (Student's *t*-test) or non-parametric (Mann-Whitney *U*-test) tests, contingent upon variable distribution. Correlation analyses were investigated using the Pearson method and confirmed by Spearman. To adjust for gestational age, angiogenic markers were transformed into multiples of the median (MoM) using a subset of control/low-risk patients.

Statistical significance was attributed to a *P*-value less than 0.05. Analysis was performed using IBM SPSS Statistics 25 (2017) statistical package (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 4196 pregnant patients were screened during the study period, identifying and inviting 433 high-risk patients to participate. In addition, 102 low-risk patients were also identified. This means that 10.3% of the screened population was deemed as high-risk for PE according to the model previously described[4]. A total of 349 women were included, of which 257 were classified as having a high risk and 92 as low

risk for PE according to their first trimester screening. A flowchart detailing patient inclusion in the study is shown in **Figure 1**.

Maternal characteristics

Maternal characteristics of high- and low-risk subgroups are shown in **Table 1**. There were no significant differences in terms of age or parity between the two groups. As expected, other maternal characteristics such as weight, body mass index (BMI), body surface area and systolic and diastolic blood pressures were significantly higher in the high-risk PE group, since these variables contribute directly to the calculated PE risk. After first trimester screening, aspirin prophylaxis was started in 97.3% of high-risk women.

Plasma biomarkers

Table 2 presents the plasma biomarkers associated with high and low-risk of PE. Blood samples were obtained at 16 ± 2 *vs* 15.9 ± 2 weeks' gestation in the high and low-risk groups, respectively. Platelet count was significantly higher in patients at high-risk for PE, with no other differences in the general blood count. Women at high-risk for PE had higher triglyceride and lower high-density lipoprotein concentrations. Copeptin and hs-cTnT showed significantly higher concentrations in the high-risk compared with the low-risk group. Of note, hs-cTnT was detectable (>3.0 ng/L) in 50.2% of women at high-risk for PE and in 40.9% of those at low-risk. In contrast, NT-proBNP concentration was lower in the high-risk group. Finally, PlGF was significantly lower in high-risk women compared with the control group, and the sFlt-1/PlGF ratio had a non-significant trend towards higher values in the high-risk group.

Maternal echocardiography

The results of the maternal echocardiographic measures are presented in **Table 3**. Maternal echocardiography was performed just after 1st trimester screening, at a mean ± SD gestational age of 14.9 ± 1.3 weeks. Measures were corrected for ethnicity and BMI or body surface area, considering disparity in both variables between the high- and low-risk groups. Regarding morphometric parameters, there were significantly thicker ventricular and posterior walls, as well as increased ventricular diastolic volumes in the high-risk group, while there were no differences in cardiac index. Significant differences were found in the high-risk group compared with the low-risk group for LV mass and LV mass index. Diastolic function parameters were significantly different between groups, with high-risk women showing an increased A wave velocity, decreased E/A ratio, and decreased tissue Doppler E' velocity in both lateral and septal mitral annuli, with increased E/E' ratio. LV ejection fraction and ventricular strain were not different between the high- and low-risk groups.

Correlation coefficients between biochemical markers (angiogenic factors, NT-proBNP, hs-cTnT, copeptin), and echocardiographic parameters are detailed in **Table S1**. Analysis revealed that there was no significant correlation between angiogenic factors and most maternal echocardiographic parameters. However, the sFlt-1/PlGF ratio demonstrated a positive correlation with LV mass and LV mass index, suggesting that a higher ratio is associated with increased LV mass. Notably, the sFlt-1/PlGF ratio also showed a significant positive correlation with strain parameters. Moreover, NT-proBNP displayed a significant positive correlation with tissue Doppler E' velocity in the LV lateralwall. This finding is consistent with our hypothesis that higher levels of NT-proBNP might offer a protective effect in hypertensive disorders during pregnancy. Copeptin also demonstrated a correlation with echocardiographic parameters analyzed, such as septal thickness and LV mass.

DISCUSSION

To our knowledge, this study is the first to prospectively compare CV function and biomarkers in early pregnancy between women at high-risk and at low-risk for PE. High-risk women showed echocardiographic differences, suggesting pre-existing or pregnancy-induced CV dysfunction. We observed expected differences regarding maternal characteristics, such as significantly higher blood pressure and BMI in the high-risk group, consistent with previous studies that have identified these factors as important contributors to the development of PE[16,17], which are associated with increased CV risk[16,18]. Our findings in the high-risk group support the idea that these factors may induce early cardiac changes even in early pregnancy.

This study confirms that women at high-risk for PE showed a more atherogenic lipid profile (lower high-density lipoprotein, higher triglycerides), aligning with other studies that support the role of lipid metabolism in early placental dysfunction and cardiac remodeling in PE pathogenesis[19,20]. The high-risk group also showed a significantly higher platelet count, potentially indicating increased inflammation or subclinical endothelial dysfunction, as elevated first-trimester platelet volume has been linked to PE, and may reflect endothelial function[21].

Regarding angiogenic factors, PlGF was lower in the high-risk group, with the sFlt-1/PlGF ratio showing a non-significant trend towards higher values. This may be explained because sFlt-1 rises until the third trimester in cases of PE. Previous studies have shown that vascular endothelial growth factor and PlGF contribute to cardiac remodeling during pregnancy[22]. Both factors are reduced in women with clinical PE and linked to adverse cardiac remodeling[23]. Other studies suggest that the angiogenic/anti-

angiogenic imbalance in PE may drive cardiac remodeling by disrupting endothelial growth and cell death. This may change heart structure and function, increasing ventricular mass and reducing diastolic function[24], as observed in this study.

Regarding cardiac enzymes, troponin is released from damaged heart cells and used as marker for acute myocardial infarction. Previous studies show elevated levels of troponin in pregnant women with *established* PE, associated with impaired cardiac function and adverse CV outcomes[25]. Women with PE had higher hs-cTnT levels than those with a normal pregnancy[25,26.] We observed similar hs-cTnT patterns in early pregnancy, suggesting its inclusion in PE prediction models may improve accuracy, though further studies are needed. Brain natriuretic peptide (BNP) is produced in the left atrium and ventricle in response to myocyte stretching due to volume expansion or pressure overload[27,28]. While BNP levels are typically normal throughout pregnancy, studies have shown higher concentrations in the first trimester compared with the third[29]. Elevated NT-proBNP levels in the first trimester correlate with lower risk for PE over a 2-7-year follow-up[30]. In this study, women at high-risk for PE had significantly lower NT-proBNP levels, aligning with recent studies linking higher NT-proBNP to a reduced risk of hypertensive disorders, even after adjusting for age, ethnicity, BMI, and aspirin use[30,31]. Finally, a metanalysis of 16 studies showed higher copeptin concentrations in PE women across all pregnancy trimesters[32], results that are in line with our findings. Cardiac enzymes may offer valuable insights into cardiac remodeling in women at high-risk for PE during early pregnancy, with ongoing research examining their progression into the third trimester.

Regarding echocardiography, Melchiorre et al.[33,34] reported elevated indices of cardiac effort and LV mass, which may indicate LV remodeling as a compensatory mechanism to sustain myocardial contractility in cases of established PE. However, no

studies have been conducted in early pregnancy in patients at high-risk for PE. One study reports significant differences in LV mass between those at high-risk and those at low risk for PE, but without laboratory parameters or additional echocardiographic measures evaluated[35]. In this study, both groups showed increased cardiac output, a normal hemodynamic change during pregnancy. We did not find differences in systolic LV functions, including ejection fraction and strain parameters. However, we observed significant differences in LV and LA dimensions, with larger volumes in the high-risk group. LA performance is impacted by LV loading changes, leading to reduced filling during diastole[36]. Increased LA volume in the high-risk group may be an early indicator of subclinical diastolic dysfunction. This suggests disrupted CV adaptation to pregnancy, causing atrial remodeling; LA enlargement is linked to poor CV outcomes in non-pregnant populations[37]. Worse Doppler patterns (i.e. LV A wave, E/A ratio, and E' velocities) were seen in the high-risk group, although still within normal ranges. Consistently, significant differences were found in LV mass and relative wall thickness (RWT). LV mass increase is attributed to adaptation of the ventricle to higher blood volume and peripheral vascular resistance. This adaptation may be pronounced in the high-risk group due to maladaptation and relative peripheral vasoconstriction, as demonstrated by higher blood pressure and lower cardiac adaptation, indicated by lower NT-proBNP levels. Notably, increased LV mass and RWT, are indicative of concentric remodeling rather than the usual eccentric remodeling[38]. In pregnancy, clinical significance of this finding may be magnified due to increased hemodynamic stress and CV changes. There is a clear trend to reduced cardiac adaptation in individuals at high-risk for PE, despite no evident pathological findings. Lack of pre-pregnancy data to assess whether changes were present before pregnancy, or develop during early pregnancy, is a limitation of this study.

Correlation coefficients between biochemical markers and echocardiographic parameters show interesting trends, however our sample size limits drawing conclusions. Another limitation is that PlGF was not included in the initial first-trimester screening in all patients, but measured later in a two-step process for intermediate-risk patients. While this method performs similarly to universal screening, the delayed measurement of PlGF could reduce external validation in settings where it is routinely included in first-trimester screening for PE.

In conclusion, women at high-risk for PE show early pregnancy differences in lipid profile, angiogenic factors, cardiac biomarkers, and echocardiography, suggesting subclinical CV dysfunction. Findings include low NT-proBNP, increased LV mass, concentric remodeling, and impaired diastolic function, highlighting CV adaptation in PE pathogenesis. Further research should assess persistence of these changes, their evolution with aspirin prophylaxis, and impact on PE and long-term maternal CV health.

TABLES

Table 1 Baseline characteristics of study population, according to risk for pre-eclampsia (PE)

Characteristic	PE risk		*P*
	High (n = 257)	Low (n = 92)	
GA at scan (weeks)	15 ± 1	14 ± 1	0.001
Maternal age (years)*	34 ± 5	34 ± 4	0.712
Nulliparous	171/256 (66.8%)	4/91 (4.4%)	0.967
Ethnicity			
Caucasian	164/255 (64.3%)	75/91 (82.4%)	0.001
Latin-American	80/255 (31.4%)	15/91(16.5%)	0.001
Asian	7/255 (2.7%)	0 (0)	—
Black	4/255 (1.6%)	1/91 (1.1%)	—
Smoker	5 (1.9%)	3/89 (3.4%)	0.469
Chronic hypertension	21 (8.2%)	0 (0%)	0.005
Pregestational diabetes	22/253 (8.7%)	3/89 (3.4%)	0.097
Previous PE	32/222 (14.2%)	2/82 (2.4%)	0.004
BMI (kg/m^2)†	28.4 ± 5.8	24.4 ± 3.6	< 0.001
Body surface area (m^2)†	1.81 ± 0.17	1.71 ± 0.14	< 0.001
Waist/hip ratio‡	0.86 ± 0.07	0.85 ± 0.07	0.154
Heart rate (bpm)‡	83 ± 12	81 ± 12	0.099
Systolic BP (mmHg)†	118 ± 12	111 ± 9	< 0.001
Diastolic BP (mmHg)†	71 ± 8	65 ± 8	< 0.001
Aspirin prophylaxis (%)	218/219 (99.5%)	1/219 (0.5%)	< 0.001

Data are given as mean ± SD, n/N (%) or n (%). *n = 254 for high-risk and n = 91 for low-risk group. †n = 255 for high-risk and n = 91 for low-risk group. ‡n = 250 for high-risk and n = 91 for low-risk group. BMI, body mass index; bpm, beats per minute; BP, Blood Pressure.

Table 2 Plasma biomarker profile of study population, according to risk for pre-eclampsia (PE)

Parameter	PE risk		*P*
	High	Low	
GA at blood draw (weeks)*	16 ± 2	15.9 ± 2	0.020
Hemoglobin (g/dL)*	12.1 ± 1.0	12.1 ± 0.9	0.540
Hematocrit (%)*	35 ± 2	35 ± 3	0.446
Platelets ($\times 10^{-9}$/L)†	264 ± 56	233 ± 52	< 0.001
Protein/creatinine ratio (mg/dL)*	201.7 ± 22.9	199.9 ± 0.0	1.000
Total cholesterol (mg/dL)‡	203.3 ± 34.6	203.5 ± 37.1	0.951
Low-density lipoproteins (mg/dL)§	107.3 ± 28.6	108.7 ± 31.4	0.714
High-density lipoproteins (mg/dL)‡	69.7 ± 14.2	74.0 ± 14.6	0.020
Triglycerides (mg/dL)‡	121 ± 1.46	98 ± 1.45	< 0.001
NT-proBNP (ng/L)¶	51.0 ± 2.1	52 ± 2.0	0.008
hs-cTnT (ng/L)**	3.1 (3.0–4.2)	3.0 (3.0–3.4)	0.010
Copeptin (pmol/L)††	3.4 ± 1.9	2.9 ± 1.4	0.044
sFlt-1 (MoM)*	0.95 ± 0.43	1.17 ± 0.59	< 0.001
PlGF (MoM)*	0.89 ± 0.63	1.15 ± 0.58	< 0.001
sFlt-1/PlGF ratio (MoM)*	1.32 ± 1.19	1.14 ± 0.60	0.086

Data are given as mean ± SD or median (interquartile range). *n = 249 for high-risk and n = 86 for low-risk group. †n = 248 for high-risk and n = 86 for low-risk group. ‡n = 248 for high-risk and n = 85 for low-risk group. §n = 248 for high-risk and n = 84 for low-risk group. ¶n = 227 for high-risk and n = 82 for low-risk group. **n = 227 for high-risk and n = 83 for low-risk group. ††n = 144 for high-risk and n = 65 for low risk group. GA, gestational age; NT-proBNP, N-terminal pro-brain natriuretic peptide; sFlt-1, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; MoM, multiples of the median; hs-cTnT, high-sensitivity cardiac troponin T.

295 **Table 3** Maternal echocardiographic measures of study population, according to risk for

296 pre-eclampsia (PE)

Parameter	High PE risk		Low PE risk		*P*
	Mean ± SD	*n*	Mean ± SD	*n*	
Electrocardiogram heart rate (bpm)	80 ± 12	174	76 ± 12	60	0.017
Septal thickness (cm)	0.90 ± 0.14	222	0.81 ± 0.12	87	< 0.001
LV posterior wall (cm)	0.85 ± 0.18	221	0.77 ± 0.13	87	< 0.001
LV end-diastolic diameter (cm)	4.4 ± 0.4	221	4.3 ± 0.4	87	0.02
LV end-diastolic volume (mL)	110 ± 23	215	102 ± 20	80	0.006
LV ejection fraction (%)	65.1 ± 4.8	216	64.2 ± 5.2	81	0.186
LV mass (g)	122 ± 32	223	104 ± 25	87	< 0.001
LV mass index (g/m^2)	67 ± 15	223	61 ± 12	87	< 0.001
Relative wall thickness	0.39 ± 0.08	220	0.36 ± 0.07	87	0.008
Cardiac output (L/min)	5.7 ± 1.2	199	5.2 ± 1.2	74	0.018
Cardiac output index	3.15 ± 0.73	201	3.08 ± 0.69	75	0.459
LV E wave velocity (cm/s)	94.3 ± 16.7	222	97.5 ± 19.7	87	0.182
LV A wave velocity (cm/s)	67.1 ± 15.1	221	59.6 ± 13.1	87	< 0.001
LV E/A ratio	1.5 ± 0.4	220	1.7 ± 0.5	87	< 0.001
Lateral mitral annular velocity E' (cm/s)	16.7 ± 3.4	224	17.7 ± 3.3	83	0.025
Septal mitral annular velocity E' (cm/s)	10.9 ± 4.5	222	11.8 ± 2.5	84	0.020
E/E' ratio	9.2 ± 2.4	218	8.6 ± 2.2	84	0.024
Left atrial biplanar volume (mL)	47 ± 13	161	43 ± 11	52	0.023
RV end-diastolic diameter (cm)	3.1 ± 0.4	149	3.0 ± 0.4	54	0.690
TAPSE (cm)	2.39 ± 0.36	228	2.38 ± 0.34	85	0.620
MAPSE (cm)	1.68 ± 0.25	223	1.69 ± 0.28	84	0.882
Global longitudinal strain (%)	−21.7 ± 2.8	173	−21.9 ± 3.1	63	0.782

297 LV: Left ventricle; RV: Right Ventricle; TAPSE, tricuspid annular plane systolic excursion;
298 MAPSE, mitral annular plane systolic excursion; bpm, beats per minute.

FIGURE LEGEND

Figure 1 Flowchart summarizing inclusion of patients at high and at low risk for pre-eclampsia (PE) in study. ECG, echocardiographic.

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SUPPORTING INFORMATION ON THE INTERNET

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

Appendix S1 Sample size estimation and multivariate distribution model for estimation of risk of pre-eclampsia (PE)

Table S1 Correlations between maternal cardiovascular biomarkers and echocardiographic measures evaluated in study population