Routine first-trimester pre-eclampsia screening and maternal left ventricular geometry

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CONTRIBUTIONS

What are the novel findings of this work?
A high screening risk for developing preterm pre-eclampsia (PE) in the first trimester is associated with an increased maternal left ventricular mass index when compared to participants with a low screening risk.

What are the clinical implications of this work?
As left ventricular mass is an independent risk factor for cardiovascular disease, women identified as being at high risk of preterm PE may benefit from further measures to optimize life-long cardiovascular health.

ABSTRACT

Objective Pre-eclampsia (PE) is a pregnancy complication associated with premature cardiovascular disease morbidity and mortality (i.e. before 60 years of age or in the first year postpartum). PE is associated with adverse left ventricular (LV) remodeling in the peri- and postpartum periods, an independent risk factor for cardiovascular disease. This study aimed to compare LV geometry by LV mass (LVM) and LVM index (LVMI) between participants with a high vs low screening risk for preterm PE in the first trimester.

Methods This was a prospective cohort study of singleton pregnancies between $11 + 0$ and $13 + 6$ weeks' gestation that underwent screening for preterm PE as part of their routine first-trimester ultrasound assessment at a tertiary center in London, UK, from February 2019 until March 2020. Screening for preterm PE was performed using the Fetal Medicine Foundation algorithm. Participants with a screening risk of ≥ 1 in 50 for preterm PE were classified as high risk and those with a screening risk of ≤ 1 in 500 were classified as low risk. All participants underwent two-dimensional and M-mode transthoracic echocardiography.

Results A total of 128 participants in the first trimester of pregnancy were included in the analysis, with 57 (44.5%) participants screened as low risk and 71 (55.5%) participants as high risk for PE. The risk groups did not vary in maternal age and gestational age at assessment. Maternal body surface area and body mass index were significantly higher in the high-risk group (all $P < 0.05$). The high-risk participants were significantly more likely to be Afro-Caribbean, nulliparous and have a family history of hypertensive disease in pregnancy as well as other cardiovascular disease (all $P < 0.05$). In addition, mean arterial blood pressure ($P < 0.001$), mean heart rate ($P < 0.001$), median LVM (130.06 (interquartile range, 113.62–150.50) g vs 97.44 (81.68–114.16) g; $P < 0.001$) and mean LVMI ($72.87 \pm 12.2\,g/m^2$ vs $57.54 \pm 12.72\,g/m^2$; $P < 0.001$) were significantly higher in the high-risk group. Consequently, those in the high-risk group were more likely to have abnormal LV geometry (37.1% vs 7.0%; $P < 0.001$).

Conclusions Early echocardiographic assessment in participants at high risk of preterm PE may unmask clinically healthy individuals who are at increased risk for future cardiovascular disease. Adverse cardiac remodeling in the first trimester of pregnancy may be an indicator of

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decreased cardiovascular reserve and subsequent dysfunctional cardiovascular adaptation in pregnancy. © 2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Pre-eclampsia (PE) is a medical condition that occurs during pregnancy. It is characterized by high blood pressure and damage to one or more organ systems. PE affects approximately 5–8% of all pregnancies and is a leading cause of maternal and fetal morbidity and mortality[1]. The risk of developing PE increases in women who have a history of high blood pressure, PE in a previous pregnancy, obesity, diabetes or renal disease. Other risk factors are maternal age over 35 years, multiple pregnancy and family history of PE[2]. Evidence is growing that pregnancy places a significant strain on the maternal cardiovascular system that can lead to maladaptation and result in the clinical phenotype of PE[3].

The ASPRE trial introduced a first-trimester screening algorithm for preterm PE that combines placental with maternal cardiovascular factors to identify women at high risk of uteroplacental dysfunction[4]. A clinical-effectiveness study demonstrated that prophylactic treatment with a daily dose of 150 mg of aspirin in women at high risk of preterm PE reduced the incidence of preterm PE by 80%[4,5]. This screening considers maternal factors that apply to the patient regardless of whether she is pregnant, such as age, ethnicity, obesity, cigarette smoking and comorbidity (e.g. chronic hypertension, diabetes, systemic lupus erythematosus, antiphospholipid syndrome); all of which are risk factors for cardiovascular disease[6,7]. PE has also been associated positively with chronic hypertension, obesity, elevated lipids and cardiovascular disease (myocardial infarction before the age of 60 years)[8,9]. This overlap of risk factors indicates that screening for PE encompasses overall cardiovascular health, rather than merely a pregnancy complication.

In normal pregnancy, the left ventricular (LV) mass (LVM) increases up to 50% until term[10]. LV hypertrophy is determined by LVM, which is a risk factor for cardiovascular disease, including heart failure, atrial fibrillation, myocardial infarction and stroke[11]. There is a continuous relationship between LVM and cardiovascular event rate in the general population[12]. This study aimed to compare LV geometry by LVM and LVM index (LVMI), which are risk factors for cardiovascular disease, between participants with a high *vs* low screening risk for preterm PE in the first trimester.

METHODS

Population

This was a prospective cohort study of singleton pregnancies between $11 + 0$ and $13 + 6$ weeks' gestation that presented for routine first-trimester ultrasound assessment from February 2019 until March 2020 at St George's University Hospitals NHS Foundation Trust, London, UK. Ethical approval for the study was given by the London–Brent Research Ethics Committee (19/LO/0794). All participants were offered first-trimester screening for preterm PE according to the Fetal Medicine Foundation algorithm, which includes maternal factors, mean arterial pressure (MAP), uterine artery Doppler pulsatility index (UtA-PI) and pregnancy-associated plasma protein-A (PAPP-A). It has been demonstrated previously that PAPP-A performs similarly to placental growth factor in preterm PE screening when applied in the clinical setting[13]. At the routine 11–13-week first-trimester ultrasound scan, gestational age was calculated according to crown–rump length, and MAP and UtA-PI were assessed according to established protocols[14–16]. Those with a screening risk of ≥ 1 in 50 for preterm PE were classified as the high-risk group. Participants with a screening risk of ≤ 1 in 500 were recruited and classified as the low-risk group. Participants < 18 years of age at presentation, those with pre-existing cardiac structural or functional abnormalities, multiple pregnancy, a major fetal anomaly at the time of the first-trimester screening and those who were not capable of providing written informed consent were excluded from the study.

Study protocol

All participants underwent transthoracic echocardiography at rest in the left lateral decubitus position using a GE Vivid E95 scanner (GE Healthcare, Horten, Norway). Two-dimensional (2D) M-mode echocardiography was performed following the guidelines of the American Society of Echocardiography[17]. For each acquisition, three cardiac cycles of non-compressed data were stored in cine-loop format and analyzed offline by one investigator (A.R.) on a dedicated workstation (EchoPAC version 202; GE Healthcare). Using the 2D parasternal long-axis view, the end-diastolic LV internal diameter (LVIDd, in cm), as well interventricular septum (IVSd, in cm) and the posterior wall thickness (PWT, in cm) were measured. LVM (g) was calculated using the equation: $0.8 \times (1.04 \times ((\text{LVIDd} + \text{PWT} + \text{IVSd})^3 - \text{LVIDd}^3) + 0.6)$, and indexed for maternal body surface area (BSA) to obtain LVMI. LV relative wall thickness (RWT) was calculated as follows: $\text{RWT} = 2 \times \text{PWT}/\text{LVIDd}$.

The participants' cardiac geometry was defined according to the following mutually exclusive categories: normal geometry (LVMI, ≤ 95 g/m^2 and RWT, ≤ 0.42); concentric remodeling (LVMI, ≤ 95 g/m^2 and RWT, > 0.42); eccentric remodeling (LVMI, > 95 g/m^2 and RWT, ≤ 0.42); and concentric hypertrophy (LVMI, > 95 g/m^2 and RWT, > 0.42). LVM was subdivided into the following groups: normal (66–150 g) and abnormal (> 150 g; mild increase (151–171 g), moderate increase (172–182 g), severe increase (> 182 g)). LVMI was subdivided into the following groups: normal (44–88 g/m^2),

abnormal ($\geq 89\,\mathrm{g/m^2}$; mild increase ($89–100\,\mathrm{g/m^2}$), moderate increase ($101–111\,\mathrm{g/m^2}$), severe increase ($\geq 112\,\mathrm{g/m^2}$)).

Statistical analysis

Variables were assessed for normality using the Shapiro–Wilk test and by visualizing their histograms. According to the data distribution, continuous data were compared using Student's *t*-test or the Mann–Whitney *U*-test, as appropriate, and expressed as mean $\pm$ SD or median (interquartile range). Categorical data were presented as *n* (%) and compared using the chi-square test or Fisher's exact test, as appropriate. Statistical significance was deemed *a priori* as $P < 0.05$. All data were analyzed using the statistical package for social sciences (SPSS version 29 for Windows; IBM Corp., Armonk, NY, USA).

RESULTS

Demographic and pregnancy characteristics

In total, 128 participants in the first trimester of pregnancy were recruited and included in the analysis, with 57 characterized as low risk and 71 high risk for PE. Demographic and pregnancy-related characteristics of the study groups are displayed in Table 1. There was no significant difference between low- and high-risk PE groups for maternal age or height, or gestational age at recruitment. However, at assessment, the high-risk group had significantly greater maternal BSA, maternal weight and maternal BMI.

Afro-Caribbean ethnicity, first pregnancy, assisted reproduction and a family history of hypertensive disorder of pregnancy as well as other cardiovascular diseases were significantly greater in the high-risk group. In addition, MAP and heart rate (HR) were significantly greater in the high-risk group at the first-trimester assessment (Table 1).

First-trimester LV geometry

When individual markers of LV geometry were considered, IVSd ($P < 0.001$), end-diastolic LV-PWT ($P < 0.001$), LVM ($P < 0.001$), LVMI ($P < 0.001$) and RWT ($P < 0.001$) were all significantly greater in the high-risk group compared to the low-risk group. The index of the LVIDd was decreased significantly ($P < 0.001$) in the high-risk compared to the low-risk group (Table 2 and Figure 1).

Qualitative assessment of LV dimensions revealed that there was a significantly higher proportion of cases with abnormal LVM ($P = 0.002$), LVMI ($P = 0.014$) and LV geometry ($P < 0.001$) in the high-risk group when compared with the low-risk group. A normal LVM was calculated in 54 (94.7%) participants in the low-risk group and 52 (74.3%) participants in the high-risk group ($P = 0.002$). A mild increase in LVM was calculated in three (5.3%) participants in the low-risk group and 11 (15.7%) participants in the high-risk group ($P = 0.061$). Three (4.3%) participants in the high-risk group had a moderate increase of LVM ($P = 0.114$) and four (5.7%) had a severe increase of LVM ($P = 0.067$). A normal LVMI was calculated in all low-risk participants and 63 (90.0%) participants in the high-risk group ($P = 0.014$). A mild increase in LVMI was calculated in six (8.6%)

Table 1 Demographic and maternal characteristics of 128 pregnancies at recruitment, stratified by high and low risk for pre-eclampsia

Characteristic	High-risk group (n = 71)	Low-risk group (n = 57)	P
Maternal age (years)	32.8 ± 5.1	32.5 ± 3.9	0.681
Maternal weight (kg)	72.00 (63.20–87.70)	63.00 (59.00–70.50)	< 0.001
Maternal height (cm)	164.2 ± 6.6	166.3 ± 6.6	0.072
Maternal body mass index ($\mathrm{kg/m^2}$)	27.60 (23.90–31.90)	23.00 (20.90–25.70)	< 0.001
Maternal body surface area ($\mathrm{m^2}$)	1.79 (1.67–1.96)	1.70 (1.63–1.81)	0.007
Nulliparous	51 (71.8)	23 (40.4)	< 0.001
Ethnicity			
Caucasian	44 (61.9)	51 (89.5)	< 0.001
Asian	9 (12.7)	4 (7.0)	0.292
Afro-Caribbean	18 (25.4)	2 (3.5)	0.001
Conception			0.003
Spontaneous	61 (85.9)	57 (100)	
Assisted	10 (14.1)	0 (0)	
Family history of cardiovascular disease			
Hypertensive disease of pregnancy	15 (21.1)	4 (7.0)	0.026
Other cardiovascular disease	34 (47.9)	17 (29.8)	0.038
Gestational age at recruitment (weeks)	12.60 ± 0.57	12.80 ± 0.62	0.118
PAPP-A (mIU/mL)	1.548 (0.968–2.785)	2.942 (1.764–4.477)	< 0.001
PAPP-A (MoM)	0.849 (0.536–1.291)	1.471 (0.888–1.908)	< 0.001
Average uterine artery PI	1.825 (1.475–2.175)	1.210 (0.969–1.508)	< 0.001
Mean arterial pressure (mmHg)	96.30 ± 8.28	81.35 ± 6.51	< 0.001
Heart rate (bpm)	78.4 ± 11.6	70.2 ± 8.7	< 0.001

Data are given as mean $\pm$ SD, median (interquartile range) or *n* (%). MoM, multiples of the median; PAPP-A, pregnancy-associated plasma protein-A; PI, pulsatility index.

Table 2 First-trimester left ventricular (LV) geometry markers in 128 pregnancies, stratified by high and low risk for pre-eclampsia

Parameter	High-risk group (n = 71)	Low-risk group (n = 57)	P
Interventricular septum diameter (cm)	0.90 (0.80–1.00)	0.60 (0.60–0.80)	< 0.001
End-diastolic LV internal diameter (cm)	4.51 ± 0.42	4.59 ± 0.34	0.266
End-diastolic LV internal diameter index (cm/m^2)	2.49 ± 0.27	2.67 ± 0.26	< 0.001
End-diastolic LV posterior wall thickness (cm)	0.90 (0.80–1.00)	0.70 (0.60–0.80)	< 0.001
End-systolic LV internal diameter (cm)	2.80 (2.60–3.15)	3.00 (2.80–3.30)	0.076
LV mass (g)	130.06 (113.62–150.50)	97.44 (81.68–114.16)	< 0.001
LV mass index (g/m^2)	72.87 ± 12.2	57.54 ± 12.72	< 0.001
Relative wall thickness (cm)	0.41 (0.37–0.46)	0.31 (0.27–0.35)	< 0.001

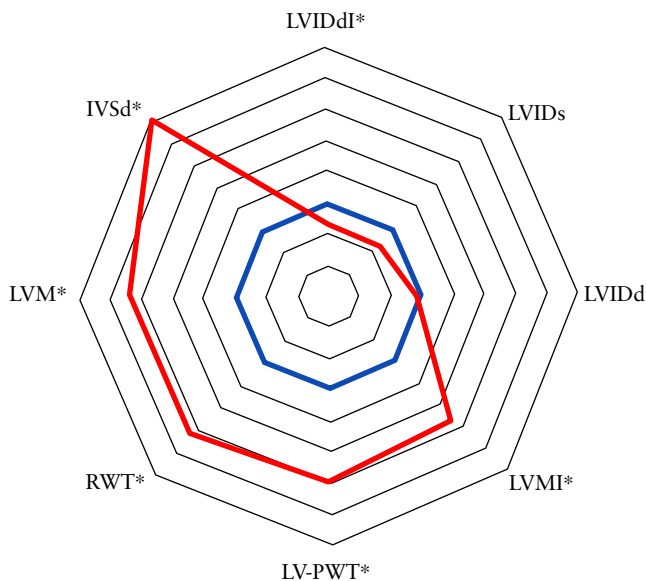Data are given as median (interquartile range) or mean ± SD.

Figure 1 Radar chart of important first-trimester left ventricular geometry measurements in those at high risk (——) compared to those at low risk (——) of pre-eclampsia. *$P < 0.05$. IVSd, interventricular septum diameter; LVIDd, end-diastolic left ventricular internal diameter; LVIDdI, end-diastolic left ventricular internal diameter index; LVIDs, end-systolic left ventricular internal diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; LV-PWT, end-diastolic left ventricular posterior wall thickness; RWT, relative wall thickness.

Table 3 Qualitative assessment of first-trimester left ventricular mass in 128 pregnancies*, stratified by high and low risk for pre-eclampsia

Parameter	High-risk group (n = 70)	Low-risk group (n = 57)	P
Left ventricular mass			0.002
Normal (66–150 g)	52 (74.3)	54 (94.7)	
Abnormal (> 150 g)	18 (25.7)	3 (5.3)	
Left ventricular mass index			0.014
Normal (44–88 g/m^2)	63 (90.0)	57 (100)	
Abnormal (≥ 89 g/m^2)	7 (10.0)	0 (0)	
Left ventricular geometry			< 0.001
Normal	44 (62.9)	53 (93.0)	
Abnormal	26 (37.1)	4 (7.0)	
Concentric remodeling	21 (30.0)	4 (7.0)	0.001
Eccentric remodeling	1 (1.4)	0 (0)	0.365
Concentric hypertrophy	4 (5.7)	0 (0)	0.067

Data are given as *n* (%). *One participant in high-risk group was excluded from analysis due to poor image quality.

participants in the high-risk group ($P = 0.024$) and one (1.4%) in the high-risk group had a moderate increase of LVMI ($P = 0.365$). Normal LV geometry was calculated in 53 (93.0%) participants in the low-risk group and 44 (62.9%) participants in the high-risk group ($P < 0.001$). Concentric remodeling was calculated in four (7.0%) participants in the low-risk group and 21 (30.0%) participants in the high-risk group ($P = 0.001$). Furthermore, one (1.4%) participant in the high-risk group showed eccentric remodeling ($P = 0.365$), while four (5.7%) participants in the high-risk group had concentric hypertrophy ($P = 0.067$). These results are summarized in Table 3.

DISCUSSION

This study demonstrates that participants with a high screening risk for preterm PE have a significantly increased LVM, LVMI and altered LV geometry compared to low-risk participants, which may impact short- and long-term cardiovascular disease risks.

Cardiovascular disease is a global health issue and a leading cause of morbidity and mortality worldwide. LV geometric abnormalities are well-known independent risk factors for cardiovascular disease and are associated with PE at term[18]. Not only do PE and cardiovascular disease share the same risk factors, but pre-existing cardiovascular disease is also the strongest risk factor for developing preterm PE. Women with a history of preterm PE have a higher risk of developing hypertension, stroke, ischemic heart disease and heart failure later in life compared to those with a normal pregnancy. One study reported that women who had preterm PE had a 2.5-fold increased risk of developing hypertension, a 3.5-fold increased risk of ischemic heart disease and a 1.7-fold increased risk of stroke, compared to women who did not have PE[19].

As demonstrated by this study, women who have been screened as high risk for developing preterm PE show significant signs of cardiac alterations, as early as the first trimester of pregnancy. Although abnormal trophoblast invasion has been proposed as the cause of PE by poor placentation since the 1960s, this study demonstrates that suboptimal cardiovascular adaptation

may be associated with poor placentation. Uteroplacental malperfusion through primary maternal cardiovascular dysfunction may still lead to syncytiotrophoblast damage by ischemic injury, with consequent abnormal placental signaling and development of the systemic inflammatory response occurring as PE. In this study, 37.1% of participants in the high-risk group demonstrated adverse cardiac remodeling and/or hypertrophy, 25.7% showed an abnormally increased LVM and even after correcting for BSA, 10.0% still had a pathological increase during the first trimester of pregnancy. Most of these individuals were young, clinically healthy pregnant women. In the low-risk group only 7.1%, 5.3% and 0% of participants showed these changes in LV geometry, LVM and LVMI, respectively.

Prior studies have shown the short-term (4–7 years) adverse effect of LV hypertrophy; specifically, the strong relationship of LV hypertrophy and heart failure, with variable association with coronary-artery-disease-related events[11,20–22]. Another study with longer follow-up (15 years) revealed that LV hypertrophy was associated independently with both non-coronary and coronary-related cardiovascular events (myocardial infarction, coronary artery disease-related death), as well as heart failure. Cardiovascular death rate was 7.5-times greater in participants with LV hypertrophy than in those without[23]. Increased LVM reflects diminished myocardial functional reserve due to a relative reduction in microvascular circulation/coronary flow reserve[24,25]. LVM increase also occurs in athletes to adjust to the increased cardiovascular strain during exercise; however, there are several distinctions between exercise-induced LV changes compared with hypertensive/maladaptive LV hypertrophy. For example, HR remains unaffected in the hypertensive heart, but is decreased in the athlete's heart[26]. In this study, participants in the high-risk group had a significantly higher HR. Furthermore, female athletes who engage in regular high-intensity exercise may experience an increase in LVM due to the demands placed on the heart to meet the increased oxygen demands of the body during exercise. However, studies have shown that the degree of LVM increase in female athletes is generally modest and within the normal range for healthy individuals[27,28].

Our results demonstrate that the inclusion of echocardiography during the screening process for preterm PE may unmask clinically healthy individuals who are at increased risk for cardiovascular disease. Therefore, these patients might benefit from preventative measures (such as maintenance of a healthy weight, exercise, diet, smoking cessation, blood pressure control, management of cholesterol levels, stress reduction) in order to reduce cardiovascular disease risk later in life. We hypothesize that the LV hypertrophy reported in the high-risk group in the first trimester of pregnancy, before the peak physiological volume overload of pregnancy occurs, may be an indicator of decreased prepregnancy cardiovascular capacity and dysfunctional cardiovascular adaptation in early pregnancy. One may even consider whether the screening for preterm PE is in fact a screen for the individual patient's cardiovascular disease risk. The development of improved screening, treatment and diagnostic strategies will be stagnant until better understanding of the cardiovascular etiology of PE is accepted widely.

Strengths and limitations

One of the strengths of this study was its prospective longitudinal design, as the study design and strict protocol allowed us to control for confounders that might affect cardiovascular assessment. Furthermore, this study provided a thorough examination of LV geometry in clinically healthy pregnant women. Thus, this study gathered important information on the cardiac profile of women who have been screened as high risk for developing preterm PE and may help lay the groundwork for future studies on cardiovascular markers for predicting PE.

However, the small sample size did not enable us to draw conclusions about the value of the cardiovascular markers assessed in this study for predicting PE. In addition, more participants are necessary to conduct further subgroup analyses; for example, a longitudinal study about women at high risk for developing preterm PE could subdivide participants who do and who do not develop diseases of the uteroplacental circulation. This might help further assess risk profiles in early pregnancy.

Conclusions

This study demonstrates that women with a high screening risk for preterm PE exhibit altered LV geometry and LVM/LVMI during the first trimester of pregnancy. These findings may have significant implications for the short- and long-term cardiovascular health of these women. Early identification of cardiac maladaptation during pregnancy may identify women at high risk of preterm PE and allow timely implementation of preventative measures to reduce cardiovascular disease risk.

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