Three-dimensional echocardiography and strain cardiac imaging in women with pre-eclampsia with follow up to six months postpartum

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Contribution

What are the novel findings of this work?

Women with preeclampsia, compared to those with normotensive pregnancy, have reduced left atrial strain, and increased left ventricular mass, as assessed by three-dimensional echocardiography. In women with preeclampsia, reduction in weight and systolic blood pressure during the postpartum period parallels improvement in cardiac indices.

What are the clinical implications of this work?

Women with preeclampsia have an adverse risk factor profile, with increase in weight and blood pressure. During pregnancy they have pronounced cardiac adaptations with reduction in diastolic indices and increase in left ventricular mass. Following delivery, there is decrease in weight and blood pressure within 2-3 days and this is further continued by 3 months. Right and left ventricular functional cardiac indices improve in postpartum period and improvement parallels reduction in risk factor profile.

ABSTRACT

Background: Epidemiological studies have established that women with preeclampsia (PE) are at increased long-term cardiovascular risk. Mild cardiac functional changes have been documented during pregnancy in women with PE, but how these are modified from transition to postpartum period remains poorly defined. The aim of this study is to determine biventricular cardiovascular changes using novel and sensitive 2D and 3D echocardiographic modalities in pregnancy and to track alterations in both risk factors and cardiovascular indices in the postpartum period.

Methods: We examined 59 women with PE at 34 (IQR 31, 37) weeks' gestation and at 2-3 days, 3 and 6 months postpartum. During pregnancy, 118 women with normotensive pregnancy were also recruited as controls. Biventricular ejection fraction and left ventricular mass were measured by 3D echocardiography. Biventricular global longitudinal strain and strain of the left atrium were assessed using speckle tracking imaging.

Results: In women with PE, compared to controls, there was lower left ventricular diastolic function (left atrial reservoir strain 44.1 vs. 49.2%) and increase in left ventricular mass (148 vs. 128 g/m2), but there was no significant difference in right ventricular functional indices. These alterations in cardiac indices were mostly explained by differences in maternal risk factors. In the postpartum period, most cardiac indices improved by 3 months. Multivariable linear mixed model analysis demonstrated that this improvement was mostly attributed to reduction in weight and blood pressure.

Conclusion: In women with PE there is postpartum improvement in cardiac functional and structural indices in parallel with improvement in risk factor profile.

INTRODUCTION

Women who have had preeclampsia (PE), compared with women who had a normotensive pregnancy, are at increased long-term risk for hypertension, ischemic heart disease and premature death[1,2]. However, there is controversy as to whether the reported long term cardiovascular risk of these women is independent of standard cardiovascular risk factors, such as obesity, chronic hypertension and diabetes mellitus[3].

During pregnancy, the maternal cardiovascular system adapts to increase in volume loading and serial cardiac assessments have shown that most women, even with uncomplicated pregnancy, show signs of cardiac maladaptation which resolve in the postpartum period[4]. Previously, our group has shown that women at risk for PE, compared to those with uncomplicated pregnancy, demonstrate even from 20 weeks' gestation, mild reduction in left ventricular diastolic function and increase in left ventricular mass[5,6]. However, the noted cardiac changes, were explained by differences in the underlying cardiovascular risk factor profile of the women, including increased age, weight and systolic blood pressure and preexisting chronic hypertension and diabetes mellitus. Later in gestation, in the third trimester, we have reported accentuated left ventricular functional alterations in women at risk for PE and other groups reported more pronounced cardiovascular adaptations in women after development of PE, but how these cardiac changes evolve following delivery remains poorly defined[7]. For instance, some groups have reported that in women who develop PE there is persistence of hypertension and cardiovascular alterations in the postpartum period, whereas, others have demonstrated improvement of risk factor profile and normalization of cardiac adaptations either by 6 months or 1 year postpartum[8-11]. In addition, in most studies changes in risk factor profile from antepartum to postpartum period has not been considered.

In the current study we set out to monitor women longitudinally starting from the time of development of PE to the postpartum period. Our aims were first, to determine early biventricular cardiovascular functional changes in women with PE compared to those with uncomplicated pregnancy, using sensitive and accurate 2D and 3D echocardiographic modalities, second, to assess the contribution of the underlying cardiovascular risk factor profile in the development of cardiovascular changes, and third, to track alterations in both risk factors and cardiovascular indices in women with PE in early (first 2 days) and late (3 and 6 months) postpartum period.

METHODS

Study design and participants

This was a prospective study in the Maternal-Fetal Medicine Unit of Hospital Clínico Universitario “Virgen de la Arrixaca” Murcia, Spain, between November 2019 and October 2021. Women who were diagnosed with PE, either during a routine antepartum visit or during hospital attendance as an obstetric emergency, were invited to participate in the study within 24 hours of diagnosis of PE (N=59). For every woman with PE, we recruited two women with normotensive uncomplicated pregnancy as controls at the same gestational age who attended the Fetal Medicine Unit. No formal matching for maternal characteristics was performed. Exclusion criteria were inability to consent or the presence of breast implants as these commonly obscure echocardiographic windows.

In addition to antepartum echocardiography the PE group was also longitudinally examined at 2-3 days and at 3 and 6 months after delivery with the aim to assess the pattern of change in cardiac indices from antepartum to peri and post partum. All participants signed an informed consent for the study which was approved by the Research Ethics Committee in Murcia (CI:2018-11-5-HCUVA).

Diagnosis and management of preeclampsia

The diagnosis of PE was made according to the American College of Obstetricians and Gynecologists guideline for Hypertension and Preeclampsia[12]. This requires the presence of hypertension (systolic blood pressure of $\geq$140 mm Hg or diastolic blood pressure of $\geq$90 mmHg) either new onset (on at least two occasions four hours apart developing after 20 weeks' gestation in previously normotensive women) or chronic hypertension together with at least one of the following: proteinuria (≥300 mg/24h or protein to creatinine ratio $\geq$30 mg/mmoL or $\geq$2 + on dipstick testing), renal insufficiency with serum creatinine >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 <100,000/µL), neurological complications (e.g. cerebral or visual symptoms), or pulmonary edema.

Severity of preeclampsia was defined according to established criteria which included systolic blood pressure of 160mmHg or higher or diastolic blood pressure of 110mmHg or higher on 2 occasions at least 6 hours apart on bed rest, thrombocytopenia (platelet count

<100,00/microliter), impaired liver function or fetal growth restriction, oliguria<500ml in 24hours, proteinuria≥5g in a 24 hour urine specimen or ≥3+ on 2 random urine samples collected at least 4 hours apart, cerebral or visual symptoms, pulmonary edema or cyanosis, epigastric or right upper quadrant pain.

Management of PE was based on close monitoring of blood pressure, renal, hepatic and hematolgical function in the mother and growth and wellbeing of the fetus. If there was evidence of severe disease then delivery was carried out soon after presentation. Otherwise, delivery was aimed at 37 weeks' gestation.

Maternal characteristics

We recorded information on maternal age, racial origin (White, Black, Asian and mixed), method of conception (natural or assisted by *in vitro* fertilization or ovulation induction drugs), history of chronic hypertension and diabetes mellitus, cigarette smoking during pregnancy and parity (parous and nulliparous if there was no previous pregnancy with delivery at ≥24 weeks´ gestation). At the clinic visit we measured systolic and diastolic blood pressure on the right arm as per published protocol [13]. Weight and height were measured and calculated the body mass index.

Maternal cardiac functional analysis

We performed maternal echocardiography using X5-1 transducer, EPIC 7G, EPIQ ELITE (Philips Bothell, WA, USA) according to the European Association of Cardiovascular Imaging /American Society of Echocardiography guidelines[14] and the protocol included measurements of the left ventricle and atrium that were obtained in the standard four chamber apical view. To achieve high frames per rate, the field of view was optimized by reducing sector width and depth and appropriate use of zoom. Speckle tracking echocardiography was used to assess global longitudinal strain of the left and right ventricle[15]. In the left ventricle measurements were obtained in the four chamber, two chamber and three chamber views. Starting from the initial end-systolic contour, the software uses an established speckle tracking algorithm to automatically detect the endocardial borders on all frames of the selected cardiac cycle. Measurements were performed at 50-70 frames per second[16]. Left atrial strain measurements were performed according to the European Association Cardiovascular Imaging guidelines[17]. The clips were exported in the original frame per rates in an external hard drive and then transferred for offline analysis using Qlab advanced quantification and QStation software. Longitudinal right ventricular functional assessment was also performed by calculating the tricuspid annular systolic plane excursion (TAPSE) and fractional area change (FAC).

From 3D echocardiography, the ejection fraction of left and right ventricle were calculated as well as left ventricular mass[18]. Left ventricular mass was indexed to body surface area. Left atrial volume was also calculated from 3D echocardiography. Reproducibility in the acquisition and analysis of images was previously reported from the same group[19]. Analysis was performed by one fellow (AC) who was blinded to participant characteristics and study design.

Statistical analysis

Data were assessed for normality using histograms and quantile-quantile plots Continuous variables were presented as mean (standard deviation) and variables not following normal distribution as median (interquartile range). Nominal variables were summarized as counts and percentages. Comparison of cardiac measurements between PE and controls was made using T-test for normally distributed variables and Mann-Whitney U Test and the chi-squared test for continuous not-normally distributed and categorical variables, respectively. General linear regression models were used to assess the association between PE and a range of echocardiographic parameters after adjusting for maternal characteristics.

Comparison of changes in echocardiographic parameters before and after pregnancy was performed using linear mixed models with two random effects (random intercept and random slope) with unstructured variance-covariance matrix; analysis was further adjusted for a pre-specified set of confounders including maternal age, race, change in weight and blood pressure and time elapsed to postnatal visit from baseline measurement and gestational age of PE development. Statistical analysis was conducted using STATA package, version 13.1 (StataCorp, College Station, Texas USA). Statistical significance was set at $p<0.05$. All tests were 2-tailed.

RESULTS

Participant characteristics

We studied 59 women with PE and 118 women with uncomplicated pregnancy. The mean gestational age at prenatal assessment was 34 weeks. Women with PE, compared to the controls, had a higher mean weight, systolic and diastolic blood pressure and higher prevalence of chronic hypertension and diabetes mellitus (Table 1). In the postpartum period, 5 women were discharged before day 3. Fourty nine women had ≥3 visits whereas 10 had less than 3 visits (Flow diagram, Figure 1). There was no difference in maternal characteristics at baseline between participants who attended the follow up visits and those who did not (Supplementary Table 1) Twenty-seven women developed PE before 34 weeks' gestation and 32 at or after 34 weeks.

Cardiac indices in women with preeclampsia and normotensive controls

Women with PE, compared to controls, had lower left atrial strain, and increased left ventricular mass; left ventricular systolic function and right ventricular function were not significantly different (Table 2). Multivariable analysis, after adjustment for age, weight, height, racial origin, method of conception, systolic blood pressure and diabetes mellitus, showed no significant differences in cardiac indices between the PE group and controls (Table 2). Additional analysis revealed that there were no differences in cardiac indices when analysis was stratified into early PE < 34 weeks' gestation and late PE ≥ 34 weeks (Table S1).

Postpartum findings in women with preeclampsia

In the postpartum period, compared to the prenatal period, there was a substantial decrease in mean maternal weight (5.8 Kg) and systolic blood pressure (16.5 mmHg) within 2-3 days of delivery and further decrease by 3 months (8.9 kg and 30.3 mmHg, respectively), but by 6 months there was no further reduction in either (Table 3). At 2-3 days, 39 women were on antihypertensive treatment, whereas only 11 were at 3 months and 8 at 6 months.

In terms of systolic and diastolic cardiac indices, by linear mixed model analysis there was no significant change at 2-3 days postpartum, compared to the prenatal period, but there was significant improvement in most indices at 3 months with no further improvement at 6 months (Table 3). Following multivariable analysis, after taking into account changes in weight and blood pressure, alterations in cardiovascular outcomes were attenuated (Table 4, Table S2).

DISCUSSION

Principal findings of this study

The main findings of this study are: first, during pregnancy, women with PE, compared with normotensive controls, had increase in left ventricular mass and reduction in left atrial strain an increase in left atrial volume; but these abnormalities were mostly accounted by differences in the cardiovascular risk factor profile between groups; second, we did not identify any differences in cardiac indices according to gestational age at development of PE; third, longitudinal assessment in the postpartum period in women with PE revealed that cardiac indices improved by 3 months and this improvement was mostly attributed to reductions in weight and blood pressure.

Comparison with findings of previous studies and interpretation of results

In pregnancy, a number of studies have assessed cardiac function in women with PE and controls using conventional echocardiographic modalities which can be affected by loading conditions but none used 3D echocardiography and strain longitudinally as performed in the current study. For instance, Buddeberg *et al.*[9], reported that in 30 women with term PE, compared to 40 women with uncomplicated pregnancy, there was mild left sided diastolic impairment, using pulse Doppler indices, and increase in left ventricular mass as measured by M-Mode. Muthyla *et al.*[20], used conventional echocardiography and tissue Doppler imaging to examine 120 women with PE and 30 normotensive controls at 28-36 weeks' gestation; in 21% of the PE group there was diastolic dysfunction, but none of these progressed to heart failure or pulmonary edema. Other groups using speckle tracking echocardiography demonstrated that in women with PE there is reduction in left ventricular global longitudinal strain and left atrial remodelling[21,22]. Caglar *et al.*, reported that in 67 women with PE, compared to 46 controls, there was both left and right ventricular dysfunction[23].

In the current study, we elected to use only novel techniques, speckle tracking imaging which is less affected by loading conditions, to characterize early myocardial functional alterations in the left and right ventricle and 3D echocardiography to accurately evaluate ventricular volumes and estimate ventricular mass[15,18]. We showed that women with PE had greater volume loading in both the right and left ventricle but this did not affect their systolic function. Biventricular ejection fraction and left and right longitudinal systolic strain were preserved and this contradicts results from a recent study in which women with PE had significantly reduced ventricular strain measurements compared to controls but no clear reason for this discrepancy could be identified[24]. Differences in ventricular volumes in women with PE, compared to controls, were mostly abolished when adjustment for risk factors was made in the multivariable analysis; this demonstrates that maternal characteristics and in particular weight and blood pressure contribute to changes in maternal cardiac function.

In the assessment of left ventricular diastolic function we elected to examine the functional performance of the left atrium. Recent data in hypertensive adults demonstrate that reduction in functional properties of the left atrium, as measured by strain imaging, precedes structural volumetric alterations[24,25]. Additionally, reduction in left atrial strain in patients with preserved left ventricular ejection fraction, as in our population, can provide useful information about left ventricular end diastolic pressure[26,27] and might predict postpartum persistent hypertension[26]. Consistent with a previous study[22,28], we showed that in women with PE, compared to women with uncomplicated pregnancy, left atrial strain was reduced and mild alterations remained after accounting for differences in maternal characteristics. This finding would suggest that women with PE might be at risk for left atrial fibrosis and stiffening which occurs in the context of hypertension and presents before any detectable changes in left atrial size[26].

In the postpartum period, there was significant reduction in weight and blood pressure but some women, remained hypertensive at 6 months and required antihypertensive therapy; this is consistent with results of previous studies[8]. The remodelling process in cardiac functional indices was apparent by 3 months and there was no further improvement in either right or left ventricular cardiac function by 6 months. Previous studies have also reported postpartum recovery in cardiac indices but the time interval for such recovery was up to one year[28,29]. Other groups have shown that women with early PE (<34 weeks) or severe PE have persistent cardiac changes in the postpartum period, but such finding could not be confirmed in our cohort[30,31]. The improvement in cardiac indices could be explained by the reduction in volume loading, maternal weight and improvement in blood pressure. Stratified analysis by gestational age of PE development, did not reveal any difference in the pattern of cardiac changes between women who experience early and late PE. In addition, our results are consistent with results from a recent study in a smaller group of women with hypertensive disorders[32]. In this study, in early peripartum period cardiac functional indices in women with hypertensive disorders remained unchanged which would imply possibly persistent cardiovascular changes in women with PE[32]; however, our finding of improvement in cardiovascular profile by 6 months would argue against it.

Strengths and limitations

The main strengths of the study are: first, use of novel echocardiographic modalities to characterize left and right ventricular function and accurately assess changes in left ventricular mass; second, longitudinal cardiac monitoring of women with PE, using linear mixed models, which allowed monitoring of cardiac remodelling in the early and late postpartum period. A limitation of the study was lack of postnatal follow up in women with uncomplicated pregnancy, which precluded us from being able to establish whether the timing and pattern of cardiac remodelling differs in women with PE compared to those with uncomplicated pregnancies. In addition, our population was predominantly of White race and consequently our findings may not be representative of changes noted in different racial groups. Our population was relatively small and some women did not attend all the follow up visits. Although no difference in maternal characteristics and severity of PE could be identified between participants who attended for follow up and those who did not, we could not exclude a potential selection bias in the screening population. We elected to use only novel techniques such as left atrial strain, which is a measure of left atrial function which is relatively independent of tethering effects and less load dependent. Although recent studies suggest that changes in strain precede any other functional alterations, the lack of conventional modalities, precluded us from performing direct comparisons with other published studies and provide more global information on left ventricular diastolic function.

Perspective

Women with PE, compared to those with normotensive pregnancy, had reduced left atrial strain, and increased left ventricular mass, as assessed by 3D echocardiography. However, these cardiac changes were mostly attributed to differences in maternal characteristics. In women with PE, reduction in weight and systolic blood pressure during the postpartum period paralleled improvement in cardiac indices. Our findings would support that improvement of maternal underlying cardiovascular risk factor profile both in antepartum and postpartum period may translate in cardiovascular benefit[33]. However, the changes in left atrial strain and left ventricular mass would support the increased risk of these women for development of chronic hypertension.

Conclusion

This study used novel and sensitive echocardiographic techniques and demonstrated that women with PE, compared to those with normotensive pregnancy, have preserved left and right ventricular function and show mild reduction in left atrial strain and increase in left ventricular mass. The cardiac changes were attributed to differences in risk factor profile between the PE and normotensive groups. After delivery, there is decrease in weight and blood pressure; these physiological changes are followed by improvement in cardiovascular function in women with PE.

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FIGURE LEGENDS

Figure 1 Flow chart of participants

Table 1: Demographic characteristics of the study population at baseline

Characteristic	Controls N=118	Preeclampsia N=59	P value
Age (years)	32.6 (6.5)	33.8 (6.8)	0.256
Weight (kg)	75.8 (10.8)	92.0 (19.1)	<0.001
Height (cm)	162.9 (5.6)	162.7 (5.8)	0.849
Body mass index (kg/m^2)	28.6 (3.8)	34.6 (6.3)	<0.001
Racial origin			0.075
White	116 (98.3)	54 (91.5)	
Black	2 (1.7)	4 (6.8)	
Mixed	-	1 (1.7)	
Method of conception			0.183
Natural	110 (93.2)	51 (86.4)	
Ovulation drugs	-	1 (1.7)	
In vitro fertilization	8(6.8)	7 (11.9)	
Smoking	16 (13.6)	3 (5.1)	0.086
Chronic Hypertension	-	9 (15.3)	<0.001
Diabetes mellitus	-	2 (4)	0.044
Nulliparous	52 (44.1)	33 (55.9)	0.136
Gestational age (weeks)	34.1 (4.1)	34.0 (4.4)	0.800
Systolic blood pressure (mmHg)	115.8 (12.7)	154.0 (14.0)	<0.001
Diastolic blood pressure (mmHg)	71.8 (8.7)	94.3 (9.2)	<0.001

Values expressed as mean (standard deviation) or n (%)

Table 2: Comparison of two-dimensional strain and three-dimensional echocardiographic indices in women with preeclampsia and normotensive controls. In colums 2-4 the raw data are compared and in the last two columns comparison was performed after multivariable adjustment.

Echocardiographic index	**Controls N=118**	**Preeclampsia N=59**	**P value**	**Multivariable adjustment**	
				Regression coefficient (95% CI)	**P value**
LV global longitudinal strain (%)	-20.2 (-21.8, -18.6)	-19.8 (-21.1, -18.1)	0.159	0.4 (-1.6, 2.5)	0.673
LV end systolic volume (mL)	59 (51, 67)	70 (56, 77)	<0.001	-1.8 (-8.5, 4.9)	0.597
LV end diastolic volume(mL)	138 (123, 153)	153 (141,170)	<0.001	3.0 (-8.8, 14.9)	0.612
LV ejection fraction (%)	57.5 (52, 62)	56 (52, 59)	0.102	2.0 (-1.4, 5.4)	0.249
LV mass (g /m^2)	128 (23.1)	148 (24.7)	<0.001	8.7 (-3.0, 20.4)	0.143
LV cardiac index (L/min/m2)	3.4 (3.0, 3.8)	3.3 (2.9, 3.6)	0.156	-0.1 (-0.5, 0.4)	0.774
LA volume (mL)	46.6 (13.7)	57.5 (16.2)	<0.001	2.3 (-5.6, 10.2)	0.565
LA ejection fraction (%)	67 (62, 72)	63 (59, 67)	0.003	-4.1 (-8.8, 0.7)	0.092
LA reservoir strain (%)	49.2 (41.2, 56.3)	44.1 (33.7, 53.0)	0.009	0.6 (-6.0, 7.2)	0.849
LA conduit strain (%)	-34.5 (-41.5, -28.4)	-26.6 (-32.3, -20.7)	<0.001	1.8 (-3.1, 6.7)	0.474

LA contraction strain (%)	-14.4 (-18.2, -11.2)	-16.9 (-22.6, -11.3)	0.022	-2.3 (-6.1, 1.5)	0.232
Tricuspid annular plane systolic excursion (mm)	19.9 (17.4, 22.5)	20.4 (15.7, 23.0)	0.832	1.3 (-1.3, 4.0)	0.328
RV fractional area change (%)	43.8 (39.8, 47.8)	43.7 (40.7, 45.5)	0.503	1.1 (-2.2, 4.4)	0.505
RV end diastolic volume (mL)	103 (21.3)	119 (28.9)	<0.001	9.6 (-2.7, 21.8)	0.124
RV end systolic volume (mL)	50.3 (10.9)	60.1 (16.4)	<0.001	5.5 (-0.9, 11.9)	0.094
RV ejection fraction (%)	50.6 (48.2, 54.1)	50.2 (46.9, 52.1)	0.100	-0.1 (-2.5, 2.3)	0.945
RV global longitudinal strain (%)	-23.9 (-26.6, -21.7)	-23.5 (-26.4, -20.6)	0.359	0.4 (-2.0, 2.7)	0.769

LV: left ventricle, RV: right ventricle

Values expressed as median (interquartile range). Comparison of raw data was made using Kruskal Wallis test. In the last two columns, inverse ranking normalization was used for all outcome measures. Analysis was adjusted for age, weight, height, racial origin, method of conception, systolic blood pressure and diabetes mellitus.

Table 3: Univariable models with changes in weight, systolic blood pressure and cardiac indices in women with preeclampsia between those during pregnancy (baseline) and the postpartum period.

Variable	**Mean change between baseline and 2-3 days**	**P value**	**Mean change between baseline and 3 months**	**P value**	**Mean change between baseline and 6 months**	**P value**
Weight (kg)	-5.8 (-7.0, -4.6)	<0.001	-8.9 (-10.6, -7.1)	<0.001	-8.9 (-11.1, -6.6)	<0.001
Systolic blood pressure (mmHg)	-16.5 (-21.1, -11.9)	<0.001	-30.3 (-35.3, -25.2)	<0.001	-28.9 (-33.9, -23.8)	<0.001
LV global longitudinal strain (%)	1.6 (0.5, 2.7)	0.004	0.1 (-1.1, 1.3)	0.820	-0.5 (-1.7, 0.7)	0.405
LV end systolic volume (mL)	5.7 (1.1, 10.4)	0.067	-8.7 (-13.9, -3.5)	0.001	-10.8 (-16.2,-5.5)	<0.001
LV end diastolic volume(mL)	5.0 (-1.4,11.4)	0.126	-17.4 (-24.7,-10.1)	<0.001	-20.3 (-28.2, -12.4)	<0.001
LV ejection fraction (%)	-2.0 (-4.0, 0.1)	0.065	0.9 (-1.4, 3.2)	0.433	2.2 (-0.2,4.5)	0.068
LV mass (g /m^2)	3.0 (-5.5, 11.5)	0.484	-7.4 (-0.6, -0.2)	<0.001	-13.3 (-24.3, -2.3)	0.018
LV cardiac index (L/min/m2)	0.2 (-0.03, 0.4)	0.104	-0.4 (-0.6,-0.2)	<0.001	-0.5 (-0.7,-0.2)	<0.001
LA volume (mL)	2.9 (-1.6, 7.5)	0.208	-11.3 (-16.2, -6.3)	<0.001	-13.3 (-18.3, -8.3)	<0.001
LA ejection fraction (%)	-0.7 (-3.6, 2.2)	0.632	5.4 (2.2,8.7)	0.011	3.2 (-0.4,6.7)	0.079
LA reservoir strain (%)	-0.3 (-4.4, 3.8)	0.887	6.1 (1.5,10.6)	0.009	6.4 (1.8,10.9)	0.006
LA conduit strain (%)	-0.9 (-4.0,2.2)	0.562	-6.6 (-9.9,-3.2)	<0.001	-5.8 (-9.2,-2.5)	<0.001

LA contraction strain (%)	1.2 (-1.0,3.4)	0.294	0.5 (-1.9,2.9)	0.685	-0.7 (-3.1,1.8)	0.601
Tricuspid annular plane systolic excursion (mm)	-0.9 (-2.4,0.6)	0.223	0.2 (-1.5,1.8)	0.857	-1.2 (-2.8,0.4)	0.153
RV fractional area change (%)	-0.6 (-9.1,7.9)	0.895	1.3 (-8.9,11.5)	0.808	9.3 (-1.3,19.9)	0.087
RV end diastolic volume (mL)	0.1 (-7.6,7.7)	0.991	-17.8 (-26.6,-9.1)	<0.001	-19.9 (-28.1,-11.6)	<0.001
RV end systolic volumen (mL)	1.1 (-3.2,5.4)	0.605	-9.6 (-14.5,-4.7)	<0.001	-10.4 (-15.0,-5.8)	<0.001
RV ejection fraction (%)	-1.1 (-2.6, 0.5)	0.183	0.8 (-0.9, 2.6)	0.353	0.4 (-1.3, 2.1)	0.627
RV global longitudinal strain (%)	0.4 (-1.2,1.9)	0.633	-0.5 (-2.2,1.1)	0.528	-2.1 (-3.8,-0.5)	0.011

LV: left ventricle, RV: right ventricle

Values expressed as median (interquartile range). Analysis was performed using linear mixed models.

Table 4: Multivariable models with changes in cardiac indices in women with preeclampsia between those during pregnancy (baseline) and the postpartum period.

Echocardiographic index	Mean change between baseline and 2-3 days	P value	Mean change between baseline and 3 months	P value	Mean change between baseline and 6 months	P value
LV global longitudinal strain (%)	1.0 (-0.2, 2.2)	0.115	-1.2 (-2.7, 0.4)	0.148	-1.7 (-3.2, -0.2)	0.029
LV end systolic volume (mL)	9.2 (3.9, 14.5)	0.001	-4.3 (-11.2, 2.6)	0.218	-6.1 (-12.9, 0.8)	0.081
LV end diastolic volume(mL)	10.3 (3.0, 17.6)	0.005	-10.3 (-19.9, -0.7)	0.036	-12.6 (-22.4, -2.9)	0.011
LV ejection fraction (%)	-2.9 (-5.2, -0.6)	0.015	-0.3 (-3.3, 2.7)	0.845	0.9 (-2.0, 3.8)	0.549
LV mass (g /m^2)	8.2 (-1.2, 17.7)	0.089	-1.1 (-13.7, 11.5)	0.865	-6.9 (-19.8, 6.1)	0.298
LV cardiac index (L/min/m2)	0.2 (-0.1, 0.4)	0.174	-0.4 (-0.7, -0.2)	0.002	-0.5 (-0.7, -0.2)	0.001
LA volume (mL)	6.4 (1.4, 11.4)	0.012	-5.8 (-12.3, 0.6)	0.078	-7.9 (-14.2, -1.6)	0.014
LA ejection fraction (%)	-0.9 (-4.0, 2.3)	0.597	5.4 (1.2, 9.6)	0.011	2.9 (-1.4, 7.3)	0.181
LA reservoir strain (%)	-0.8 (-5.4, 3.8)	0.727	5.4 (-0.5, 11.3)	0.072	5.4 (-0.3, 11.1)	0.065
LA conduit strain (%)	0.2 (-3.1, 3.6)	0.895	-5.3 (-9.6, -1.1)	0.013	-4.1 (-8.2, 0.02)	0.051
LA contraction strain (%)	0.5 (-2.0, 3.0)	0.683	-0.3 (-3.5, 2.9)	0.851	-1.5 (-4.7, 1.6)	0.337
Tricuspid annular plane systolic	-0.5 (-2.1, 1.2)	0.558	1.0 (-1.3, 3.2)	0.408	-0.4 (-2.5, 1.7)	0.705

excursion (mm)						
RV fractional area change (%)	-1.3 (-10.9, 8.3)	0.790	0.1 (-13.4, 13.6)	0.984	8.3 (-4.9, 21.5)	0.221
RV end diastolic volume (mL)	3.6 (-4.7, 11.8)	0.396	-13.6 (-24.7, -2.5)	0.017	-14.8 (-25.1, -4.5)	0.005
RV end systolic volume (mL)	3.1 (-1.6, 7.8)	0.194	-7.3 (-13.7, -0.9)	0.026	-7.7 (-13.6, -1.8)	0.010
RV ejection fraction (%)	-1.3 (-3.1, 0.4)	0.136	0.5 (-1.9, 3.0)	0.657	0.04 (-2.2, 2.3)	0.969
RV global longitudinal strain (%)	0.3 (-1.3, 2.0)	0.686	-0.4 (-2.5, 1.8)	0.721	-2.1 (-4.2, -0.1)	0.045

LV: left ventricle, RV: right ventricle,

Values expressed as median (interquantile range). Analysis for cardiac indices was performed using linear mixed models and adjustment was performed for age, racial origin, method of conception, diabetes mellitus, gestational age of preeclampsia development and change in weight and systolic blood pressure.

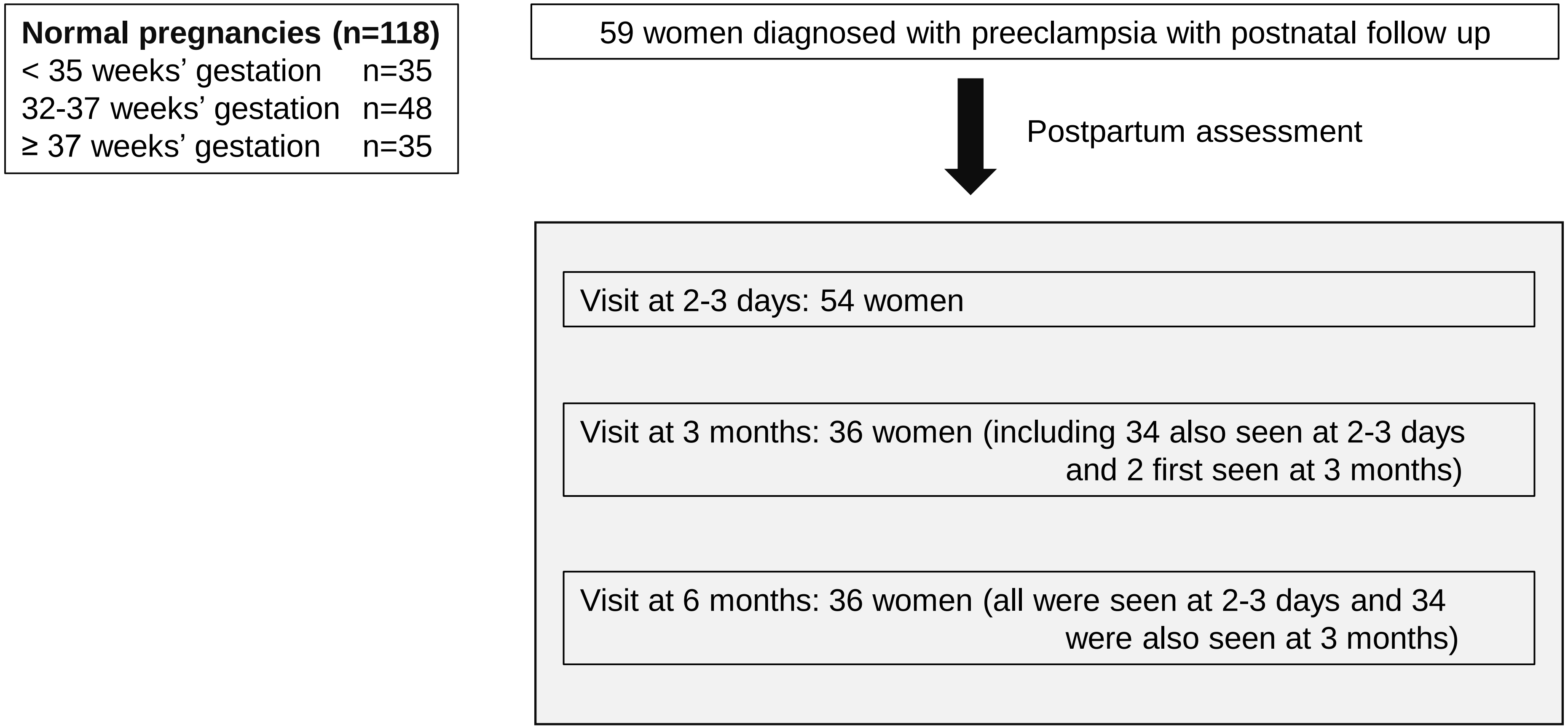

Figure 1. Flow chart of participants