**Left atrial mechanics following preeclamptic pregnancy**

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Short title: Postpartum LA mechanics in preeclampsia

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**ABSTRACT**

**Background:** Preterm preeclampsia is a pregnancy complication associated with myocardial dysfunction and premature cardiovascular disease morbidity and mortality. Left atrial (LA) strain is a non-invasive index of left ventricular end diastolic pressure and early marker of heart failure risk. This study aimed to evaluate LA strain during the postpartum period in participants with and without preterm preeclampsia and to assess whether this varied in the presence of hypertension and/or cardiac dysfunction.

**Methods:** In this longitudinal cohort study, 321-women from 28-hospitals with preterm preeclampsia (cases) underwent cardiovascular assessment 6-months postpartum. This is a secondary analysis of the PHOEBE study (ISRCTN01879376). An uncomplicated pregnancy control group (n=30) were recruited from a single centre for comparison. A full cross-sectional transthoracic echocardiogram was performed and from these images, myocardial strain of the left atrium, including reservoir, conduit and contractile strain as well as left atrial (LA) stiffness were calculated.

**Results:** At 6 months postpartum, compared to controls, prior preeclampsia was associated with a significantly attenuated LA reservoir, conduit and contractile strain, as well as increased LA stiffness (all $p<0.001$). LA strain was further reduced in preeclamptic women who had and had not developed hypertension, systolic and diastolic dysfunction at 6-months postpartum (all $p<0.05$).

**Conclusions:** LA mechanics were significantly attenuated at 6 months postpartum in participants with preterm preeclampsia, whether or not they remained hypertensive or had

evidence of ventricular dysfunction. Further studies are needed to determine whether postnatal LA strain may identify women at greater risk for future cardiovascular disease.

Key words: Hypertensive disorders of pregnancy, left atrial mechanics, left atrial stiffness, left atrial strain, preeclampsia.

**NONSTANDARD ABBREVIATIONS AND ACRONYMS**

BMI – Body mass index

BP – Blood pressure

Ea – Arterial elastance

EF – Ejection fraction

EDV – End diastolic volume

ESP – End systolic pressure

EDV – End diastolic volume

FAC – Fractional area change

GLS – Global longitudinal strain

LA – Left atrial

LV – Left ventricular

PACS – Peak atrial contraction strain

PALS – Peak atrial longitudinal strain

RA – Right atrial

RV – Right ventricular

TTE – Transthoracic echocardiography

VAC – Ventricular arterial coupling

## INTRODUCTION

Preeclampsia is a hypertensive disorder of pregnancy that is associated with postpartum maternal cardiovascular risk and dysfunction, including hypertension, heart failure, coronary artery disease and premature mortality.[1-5] Preeclampsia affects 3-5% of all pregnancies and is responsible for 70,000 maternal deaths worldwide, justifying its inclusion as an important cardiovascular disease risk factor in current cardiology guidelines.[6-8] Indeed, the PHOEBE study demonstrated that at 6 months after a preeclamptic pregnancy, the prevalence of systolic dysfunction, diastolic dysfunction and persistent hypertension was 10%, 20% and 71%, respectively.[5] These observations are supported by longitudinal studies[2, 9] and confirm that preeclampsia is not a self-limiting disease of pregnancy, with chronic hypertension being the most prevalent postpartum risk factor.

Preeclampsia is associated with adverse cardiac remodelling, diastolic dysfunction and reduced global longitudinal strain (GLS) which may all signal future cardiovascular health risks in women with a history of preeclampsia.[2, 10, 11] Despite these overt echocardiographic findings in women with preeclampsia, most previous data show minimal change in left atrial (LA) volume, unlike with overt chronic hypertension, where it contributes to the development of subsequent heart failure. However, long-term follow up of women with pregnancies complicated by preeclampsia have demonstrated LA volume index changes a decade after giving birth.[12]. In a number of cardiac diseases, LA dysfunction precedes the development of LA enlargement and is a mediator of impaired cardiac dynamics. Growing evidence suggests that impaired LA function is actively involved in symptoms and cardiac disease progression. The left atrium is vulnerable to sustained volume and pressure overload following increases in left ventricular (LV) filling pressure.[13] Quantification of LA mechanics using strain can offer important intrinsic functional information, which can detect

LA functional impairment in its early stages.[14] Indeed, in patients with hypertension and diabetes, despite normal LA size, impaired LA mechanical function was reported.[15] In addition, LA strain has demonstrated prognostic utility in the general population.[16, 17]

There is a paucity of information on LA strain in pregnancy and preeclampsia. It is not evident whether LA strain is impaired even in the absence of extensive remodelling and/or hypertension in women after preeclampsia. Studies of exercise response in young adults with suboptimal blood pressure demonstrated changes in LA strain as a possible sensitive marker of early haemodynamic changes.[18] If LA mechanics are affected in preeclampsia, this could affect cardiac function and signal an increased risk for cardiovascular disease even in women with no other abnormal cardiovascular features. The aim of this study was to investigate LA mechanical function in women six months after birth with normal and preeclamptic pregnancies.

## METHODS

*Study Design and Participants*

The data that support the findings of this study are available from the corresponding author upon reasonable request. The PHOEBE study[5] was a parallel group, multicentre (28 consultant-led maternity units in England and Wales), mechanistic study, embedded within a randomised controlled trial of women with preeclampsia who were managed by planned delivery against usual care, which is expectant management (ISRCTN registry number: ISRCTN01879376). As published, the trial confirmed that the relatively short delay in those expectantly managed compared with planned delivery did not worsen cardiovascular dysfunction. A woman was eligible for the study if she was between $34^{+0}$ weeks and $36^{+6}$ weeks of gestation, had a diagnosis of preeclampsia or superimposed preeclampsia (as

defined by the International Society for the Study of Hypertension in Pregnancy),[19] with a singleton or dichorionic diamniotic twin pregnancy and at least one viable fetus, was aged 18 years or older, and was able to give written informed consent. The only exclusion criterion of the original study was if a decision had already been made to deliver within the next 48 hours. The study was approved by the South Central - Hampshire B Research Ethics Committee (no. 13/SC/0645) and the main findings have been previously described.[5] Participants with an uncomplicated normal pregnancy who underwent a matched cardiovascular assessment 6-months post-partum were recruited outside of the PHOEBE study from St George's University Hospitals NHS Foundation Trust between February 2019 and August 2021. The Brent Research Ethics Committee (19/LO/0794) approved the study protocol, and participants provided written informed consent.

*Procedure*

Site research teams approached women to confirm eligibility and provided verbal and written information. A trained research midwife or clinician obtained written informed consent. A research team member entered baseline data on a web-based database. All other aspects of pregnancy management were expected to be in accordance with the UK national guidelines at the discretion of the responsible clinician.[20] Outcomes were recorded on a web-based trial database through case-note review by trained researchers after maternal primary hospital discharge. Women were invited to return to their local hospital at least 6 months following delivery for transthoracic echocardiography (TTE) assessment, performed within an 8-week window of the 6-month timepoint. At this assessment, a brief medical history was recorded, blood pressure (BP) assessed, and TTE undertaken. Echocardiography was performed locally according to a standard operating procedure circulated by the research team and according to current guidelines.[21] All TTE assessments were anonymized and sent to the lead

echocardiographer (JOD) for analysis, who entered results onto the web-based trial database. Every tenth TTE from the PHOEBE study was second read, by an echocardiographer at the University of Oxford, and findings compared by the trial lead cardiologist (PL) to ensure consistency. When TTE assessment demonstrated potentially concerning features that may have impacted on clinical care, the findings were escalated and reviewed by the lead cardiologist (PL) and communicated back to the lead clinician at the recruiting site with a recommendation for clinical follow-up.

*Outcomes*

The primary outcome of the PHOEBE study was a composite of systolic and diastolic function classified according to the American College of Cardiology as assessed by TTE six months' postpartum, which has been previously reported.[5] Analysis of the TTE images using speckle tracking for measures of LA mechanics was a predetermined secondary outcome of the study.

*Echocardiography with strain analysis*

All participants underwent comprehensive 2-dimensional TTE with Doppler and tissue Doppler imaging at the time of the study,[5] with systolic and diastolic function graded according to current guidelines.[21, 22] Images were acquired at end expiration in the left lateral decubitus position using a commercially available GE Vivid or Philips scanner. For each acquisition, 3-cardiac cycles of non-compressed data at a frame rate between 60 and 90 frames·s$^{-1}$ were stored in cine-loop format for offline analysis. Left atrial strain was calculated from a non-foreshortened apical 4-chamber view as recommended.[23] Speckle tracking analysis of the LA phasic functions, including peak atrial longitudinal strain (PALS; reservoir phase), peak atrial contraction strain (PACS; contraction phase) and LA conduit

strain (conduit phase) was performed using commercially available dedicated atrial strain software (2D Cardiac Performance Image Arena version 4.6, TomTec Imaging System). The LA endocardial boarder was traced manually at end-diastole and then the software automatically tracked speckles along the endocardial border and myocardium throughout the cardiac cycle. Adequate tracking of the region on the contour was verified and normal PALS values have been reported to be between 39.4% and 46.8%.[24, 25] LV, right ventricular (RV) and right atrial (RA) strain was also calculated as recommended.[23, 26] Left atrial stiffness was estimated using the formula, LA stiffness = (E/E')/PALS;[27] end systolic pressure (ESP) was estimated from systolic BP x 0.9[28] and ventricular elastance (Ees) = ESP/end systolic volume; arterial elastance (Ea) = 0.9 x systolic BP/stroke volume; and ventricular arterial coupling = Ea/Ees.[29, 30] The intraobserver and interobserver coefficient of variation for our measures of reservoir, conduit and contractile strain were 6.7% and 6.9%, 8.3% and 9.9%, and 7.3% and 7.4%, respectively.

*Statistical Analysis*

Unless otherwise stated, continuous variables were expressed as mean ± standard deviation. Distribution of all continuous variables were assessed and log transformations were used as appropriate. Simple and multiple regression models were used to compare groups, with adjustments for age, BMI, and blood pressure. Study power calculation is reported previously.[5] Statistical significance was deemed a priori as $p<0.05$. Data analyses were performed with STATA/SE version 15.1.

## RESULTS

In total, 623 women with preeclampsia were eligible for the study, of whom 420 (67%) were recruited across 28 maternity units in England and Wales. Of the preeclampsia participants recruited, 321 (76.4%) and 30 normal pregnancy controls completed their 6-month follow-up and underwent TTE assessment (see Table 1 for participant characteristics). Briefly, normal pregnant participants were significantly older, weighed less, had lower body mass index and lower blood pressure. At 6-months follow-up, 71% (n=299) of preeclampsia women remained hypertensive, defined as being on anti-hypertensive medication or a systolic BP of >140 mmHg and/or diastolic BP of >90 mmHg, 10% (n=31) had LV systolic dysfunction, defined as a left ventricular ejection fraction <55%, and 50% (n=162) had diastolic dysfunction when LV global longitudinal strain indices were incorporated.

Compared to women who had a normotensive pregnancy (n=30), formerly preeclamptic women (n=321) had significantly higher estimated LV filling pressure (E/E'; 7.1±1.9 vs. 5.4±0.8, $p$<0.001) and LV geometry, including LV mass (125.0±32.1 vs. 100.7±20.5 g, $p$<0.001) and relative wall thickness (0.35±0.1 vs. 0.27±0.1, $p$<0.001). In preeclampsia participants with and without sustained postnatal hypertension, there were no significant differences in estimated LV filling pressure or LV geometric parameters. LV mass was significantly greater in preeclampsia women with LV systolic dysfunction at 6-months follow-up (142.9±39.3 vs. 123.2±30.8 g, $p$=0.007). The estimated LV filling pressure (E/E'; 7.8±2.1 vs. 6.4±1.6, $p$<0.001) and LV geometry, including LV mass (131.2±34.0 vs. 118.6±27.7 g, $p$<0.001) and relative wall thickness (0.37±0.1 vs. 0.34±0.1, $p$<0.001) was significantly greater in preeclampsia participants with compared to without diastolic dysfunction, respectively.

*Echocardiography speckle tracking analysis*

All deformation indices of the LA were significantly different (Table S1) in healthy vs. preeclampsia participants. This included LA reservoir (Figure S1A), conduit, and contractile strain (all $p<0.001$) and LA stiffness ($p<0.001$; Figure S1B), but there were no statistically significant differences in RA myocardial deformation indices between healthy and preeclampsia participants. Analysis of differences in ventricular deformation demonstrated significant attenuation in both LV and RV global longitudinal strain (GLS) in preeclampsia participants compared to healthy pregnant participants and significantly elevated arterial elastance (all $p<0.001$).

In preeclampsia participants with hypertension, LA reservoir ($p=0.048$ and $p<0.001$ Figure 1A) and contractile strain ($p=0.014$ and $p<0.001$) were significantly attenuated compared to non-hypertensive preeclamptic participants and normal healthy pregnancy control participants 6-months postpartum, respectively. However, LA stiffness (Figure 1B) was only significantly different compared to normal healthy pregnancy control participants 6-months postpartum (Table 2). There were no statistically significant differences in LV GLS, RA or RV deformation between preeclamptic participants with and without hypertension 6-months postpartum.

In preeclampsia participants with LV systolic dysfunction at 6-months postpartum, LA reservoir ($p<0.001$ and $p<0.001$, Figure 1C), conduit ($p<0.001$ and $p<0.001$) and contractile strain ($p<0.001$ and $p<0.001$) were significantly attenuated and LA stiffness ($p<0.001$ and $p<0.001$, Figure 1D) was significantly elevated compared to preeclamptic participants without impaired LV function and normal healthy pregnancy control participants 6-months postpartum, respectively (Table 3). LV GLS was significantly attenuated in those with LV

systolic dysfunction ($p$<0.001 and $p$<0.001), with statistically significant differences in ventricular ($p$<0.001 and $p$<0.001) elastance and ventricular arterial coupling ($p$<0.001 and $p$<0.001) compared to preeclamptic participants without impaired LV function and normal healthy pregnancy control participants 6-months postpartum, respectively. There was also significant differences in RV deformation ($p$<0.001 and $p$<0.001) and right ventricular fractional area change ($p$=0.023 and $p$=0.004) compared to preeclamptic participants without impaired LV function and normal healthy pregnancy control participants 6-months postpartum, respectively.

In preeclampsia participants with LV diastolic dysfunction 6-months postpartum, LA reservoir ($p$=0.005 and $p$<0.001, Figure 1E) and conduit strain ($p$<0.001 and $p$<0.001) were significantly attenuated and LA stiffness ($p$<0.001 and $p$<0.001, Figure 1F) was significantly elevated compared to preeclamptic participants without impaired diastolic function and normal healthy pregnancy control participants 6-months postpartum, respectively (Table 4). LV GLS ($p$<0.001 and $p$<0.001) and RA reservoir ($p$<0.001 and $p$=0.049) strain were significantly attenuated in preeclampsia participants with compared to those without impaired diastolic function normal healthy pregnancy control participants 6-months postpartum, respectively.

When participants were divided according to normal pregnancy (n=30), preeclamptic pregnancy (n=52) with no cardiovascular conditions (hypertension, systolic dysfunction, and/or diastolic dysfunction) and preeclamptic pregnancy (n=269) with hypertension, systolic dysfunction, and/or diastolic dysfunction (Stage A and B heart failure[31]) at 6-months postpartum, there is a stepwise significant attenuation in LA reservoir strain (48±10% vs. 39.6±8.8 vs. 35.2±9.3, respectively) and stepwise significant increase in LA stiffness index

(0.12±0.03% vs. 0.18±0.06 vs. 0.22±0.12, respectively) (see Figure 2 and Central Figure). 26 participants in the preeclampsia cohort had chronic hypertension prior to pregnancy. However, in sensitivity analysis, exclusion of these women from analysis did not alter the findings.

## DISCUSSION

This large multicentre prospective study demonstrates that LA phasic mechanics are significantly attenuated, with increased LA stiffness in women with preeclampsia at 6-months postpartum compared to participants with an uncomplicated normal pregnancy. These alterations are exacerbated in formerly preeclamptic women with compared to those without cardiovascular impairment, with evidence of sustained hypertension, LV systolic dysfunction and LV diastolic dysfunction (Stage A and B heart failure) at 6-months post-partum.

Women with preeclampsia experience adverse cardiovascular events up to 2-decades earlier compared to women with gestational hypertension, which suggests preeclampsia increases the risk of cardiovascular disease independently of traditional risk factors.[32] Identification of mechanisms accelerating this increased cardiovascular disease risk could help identify early markers that predict future risk. For example, a recent meta-analysis demonstrated that subclinical cardiac dysfunction can be identified before structural alterations using simple and reproducible tools, which may be of clinical value in women with preeclampsia.[33] In our study, women who had preeclampsia had reduced LA reservoir strain[24, 25] and LA stiffness index[25] at 6 months post-partum, with indices typical for those 2 to 3-decades older. Greater reductions in strain indices were evident in those women who had evidence of cardiovascular risk factors or cardiac dysfunction at 6 months. LA strain is a powerful prognosticator of all-cause mortality in the general female population,[17] and in those with cardiovascular

disease.[34-37] LA stiffness has been shown to be a better predictor than other TTE indicators of diastolic dysfunction of adverse clinical outcomes including long-term mortality and hospitalisation for heart failure, even after adjustment for clinically relevant parameters.[38]

Recent research has identified several TTE parameters at delivery that are able to identify women with hypertensive disorders of pregnancy who are significantly more likely to exhibit cardiovascular dysfunction 6-months postpartum. These include adverse LV geometry, diastolic dysfunction and attenuated LV GLS.[10] Our results highlight a potential additional role for LA strain in risk prediction. LA strain is known to be a precursor of more severe LA dysfunction including LA dilatation, which is associated with increased risk of mortality in low cardiovascular disease risk populations.[39, 40] LA dilatation is also associated with an increased risk of various cardiovascular diseases including coronary artery disease, heart failure with preserved and reduced ejection fraction, atrial fibrillation and stroke,[41] which are also pertinent in women with pregnancies complicated by preeclampsia.[42, 43] We have previously identified significant LA dilatation, independent of blood pressure variation, in women 5-10 years following a hypertensive disorder of pregnancy.[12] Therefore, although LA size did not differ in our current study, the presence of impaired LA reservoir strain and LA stiffness during the postnatal period might explain why LA dilatation subsequently emerges over the next 10 years. As such, LA strain might provide an early predictor of women at the greatest risk of subsequent development of cardiovascular disease and who may benefit from early intensified risk factor management.

*Limitations*

Our results should be interpreted in the context of some limitations. The normal pregnancy control group participants were recruited from a single centre and a healthier volunteer

selection bias is possible. However, the uncomplicated normal pregnancy participants have values that match normative data from other sources. Although the preeclampsia cohort were recruited from multiple UK centres, whether these findings generalize to other ethnic/racial populations requires further research. Without a longer follow-up period, it is unclear if LA reservoir strain and LA stiffness remain important parameters for the prediction of long-term cardiovascular disease risk. Some data that may be relevant to understanding potential confounders in the association were also not available, such as breast feeding status at the time echocardiographic imaging,[44] and this needs to be explored further. The cross-sectional design leaves open the possibility that differences in LA mechanics may differ preconception and/or during gestation in women who subsequently develop preeclampsia. Furthermore, whether findings extrapolate to term preeclampsia and/or gestational hypertension requires further study. The design also does not explain why LA mechanics differ. However, we hypothesize that failure to 'reverse remodel' after severe preeclampsia may lead to permanent changes in cardiovascular structure and function relevant to long term risk. Our initial trials suggest this maybe preventable with early post-partum intervention. In addition, although the LA strain analysis algorithm used has good reproducibility,[45] other vendor algorithms may provide different values.

**PERSPECTIVES**

In this longitudinal observational cohort study, left atrial mechanics are significantly attenuated at 6 months postpartum in women with preterm preeclampsia compared to an uncomplicated normal pregnancy. These maladaptation's are intensified in preeclamptic women with evidence of sustained hypertension, left ventricular systolic and/or diastolic dysfunction compared to preeclamptic women without cardiovascular impairment at 6-months post-partum. Impaired LA mechanics may be an important early haemodynamic

signal to identify women at greatest risk of future cardiovascular disease. These findings emphasise the importance of echocardiographic assessment as part of a structured postpartum follow up programme for risk factor management and early intervention strategies in this population.

*Conclusion*

LA reservoir strain is attenuated and LA stiffness increased in participants with preterm preeclampsia compared to an uncomplicated normal pregnancy. This dysfunction is exacerbated in formerly preeclamptic women who present with diastolic dysfunction, systolic dysfunction or chronic hypertension at 6-months postpartum. Impaired LA mechanics may be an important early haemodynamic signal of reduced compliance that negatively impacts both pulmonary (pressure and compliance) and systemic (left ventricular filling pressure and cardiac output) circulation. The addition of LA strain and LA stiffness measures during echocardiographic assessment may be of additional value to identify formerly preeclamptic women who are at greatest cardiovascular disease risk.

**Data availability**

The data underlying this article will be shared on reasonable request to the corresponding author.

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## NOVELTY AND RELEVANCE

### What Is New?

In women with preterm preeclampsia, left atrial mechanics are significantly attenuated at 6 months postpartum compared to an uncomplicated normal pregnancy. These alterations are exacerbated in preeclamptic women with evidence of sustained hypertension, left ventricular systolic and/or diastolic dysfunction compared to preeclamptic women without cardiovascular impairment at 6-months post-partum.

### What Is Relevant?

Women who had preeclampsia had indices of left atrial mechanics at 6 months post-partum typical for those 2 to 3-decades older.

### Clinical/Pathophysiological Implications?

The addition of left atrial strain and stiffness measures during echocardiographic assessment may be of value for the early identification of preeclamptic women who are at greatest cardiovascular disease risk and who may benefit from early intensified risk factor management.

**Figure Legends**

Figure 1: Left atrial mechanical differences in normal and preeclamptic pregnancy. Box plots compare left atrial reservoir strain and left atrial stiffness index between women following normal pregnancy and preeclamptic pregnancy without and with hypertension (A and B, respectively), normal pregnancy and preeclamptic pregnancy without and with systolic dysfunction (C and D, respectively), and normal pregnancy and preeclamptic pregnancy without and with diastolic dysfunction (E and F, respectively) 6-months postpartum.

Figure 2: Left atrial mechanical differences in normal and preeclamptic pregnancy with and without hypertension or cardiac dysfunction. Box plots compare left atrial reservoir strain (A) and left atrial stiffness index (B) between women with normal pregnancy, preeclamptic pregnancy with no risk factors (hypertension, systolic dysfunction, or diastolic dysfunction) and preeclamptic pregnancy with hypertension, systolic dysfunction, or diastolic dysfunction (Stage A and B Heart Failure) at 6-months postpartum. Note: PE = preeclampsia; Stage A and B heart failure defined according to Heidenreich et al. (2022).[31]