CARDIAC MALADAPTATION IN TERM PREGNANCIES WITH PREECLAMPSIA

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ABSTRACT

Objectives: To study biventricular cardiac changes with conventional echocardiography and new echocardiographic speckle tracking technologies such strain, twist and torsion in pregnant women with preeclampsia at term and normotensive control term pregnant women.

Study design: For this prospective single centre case-control study, we consecutively recruited 30 women with preeclampsia at term as cases and 40 healthy control term pregnant women. All women underwent transthoracic echocardiographic examination at the time point of inclusion into the study.

Main outcome measures: Signs of systolic and/or diastolic cardiac maladaptation to the increased volume load associated with pregnancy.

Results: Conventional echocardiography revealed mild left sided diastolic impairment in the form of significantly increased E/E' in preeclampsia (7.58±1.72 vs. 6.18±1.57, p=0.001) compared to normotensive controls, but no evidence of systolic impairment. With speckle tracking analysis, significant decreases in left ventricular global (-13.32±2.37% vs. -17.61±1.89%, p<0.001), endocardial (-15.64±2.79% vs. -19.84±2.35%, p<0.001) and epicardial strain (-11.48±2.15% vs. -15.73±1.66%, p<0.001) as well as left ventricular longitudinal strain rate (-0.84±0.14s^{-1} vs. -0.98±0.12s^{-1}, p<0.001) and left ventricular early diastolic strain rate (0.86±0.30s^{-1} vs. 1.24±0.26s^{-1}, p<0.001) could be observed in women with term preeclampsia.

Conclusions: The findings of this study demonstrate that pregnant women with term preeclampsia with minimal functional changes on conventional echocardiography, demonstrated significant subclinical myocardial changes on speckle tracking analysis. Post-natal cardiac follow-up might therefore be advisable even in women with preeclampsia at term.

Key words: pregnancy, preeclampsia, echocardiography, speckle tracking, cardiac dysfunction

INTRODUCTION

Preeclampsia is a multisystem disorder affecting 3-5% of all pregnancies and remains one of the main factors contributing to maternal morbidity and mortality in women[1-4]. Despite decades of research and a clearer understanding of clinical risk factors as well as genetic predispositions, the cause of preeclampsia still remains unknown[5, 6]. Preeclampsia is defined as new onset hypertension after twenty weeks of pregnancy plus involvement of at least one organ system. Onset before 34 weeks is classified as early onset, onset after 34 weeks as late onset preeclampsia – but proteinuria is no longer a mandatory diagnostic criteria in most guidelines[7, 8]. This recognises that preeclampsia can affect any organ system of the expectant mother and manifest not only with renal, but also with hepatic, neurological, haematological, pulmonary or cardiac symptoms or as utero-placental dysfunction[9].

In pregnancy, the cardiovascular system has to adapt to a state of chronic volume overload. The volume load is significantly increased while the resistance load (total vascular resistance) is decreased. Echocardiographic studies have shown that even healthy pregnant women at term may sometimes show signs of cardiac maladaptation to volume overload, which resolve within the first year postpartum[10, 11]. In preeclampsia, cardiovascular maladaptation is more pronounced with overt diastolic dysfunction appearing in up to 40-45% of preeclamptic women[12, 13]. In contrast to the echocardiographic findings in healthy pregnant women, changes in women with preeclampsia do not resolve entirely after delivery[14, 15].

New echocardiographic technologies such as speckle tracking are more sensitive in detecting subclinical cardiac changes than conventional techniques[16, 17]. Speckle tracking has been shown to be a sensitive tool to quantify even subtle changes in cardiac function[18-21]. The existing literature included a very limited number of strain measurements only[18, 19], and focused on left ventricular function and early-onset preeclampsia[20, 21]. The aim of the present study is to use speckle tracking and ventricular torsion assessment to determine biventricular cardiac function in women with term preeclampsia compared to healthy term pregnancies.

METHODS

This prospective case-control study was carried out at St. George's University Hospitals NHS Foundation Trust in London over a 12-month period from April 2016 until March 2017. The local institutional review committee approved the study (ID 12/LO/0810) and all participants provided written informed consent. Women with singleton pregnancy and preeclampsia at term were recruited as cases. Only women without any cardiovascular co-morbidity and before starting any antihypertensive medication were asked to take part in the study. Preeclampsia was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy (ISSHP)[8]. Normotensive healthy term pregnant women without any co-morbidities were recruited as controls. Blood pressure was measured manually from the brachial artery according to the guidelines of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy[22].

Echocardiography

Echocardiographic examination and analysis were performed by a single operator (BSB) using a GE Vivid Q® ultrasound machine equipped with a 3.5-MHz transducer. Images were acquired at rest in the left lateral decubitus position from standard parasternal and apical views. Digital loops of 3 cardiac cycles with associated electrocardiogram information were stored on the hard disk of the ultrasound machine and transferred to a GE EchoPac® workstation for offline analysis. Analysis was performed according to existing guidelines[23-25]. Interventricular septum thickness, left ventricular posterior wall thickness, left ventricular systolic and diastolic diameter were measured in the parasternal long axis view. Left atrial volume (LAV) and left ventricular volume in diastole (LVEDV) were calculated from apical views. Right atrial area, right ventricular basal and mid cavity diameter and right ventricular longitudinal diameter were measured from apical views. Proximal and distal right ventricular outflow tract (prox. and dist. RVOT) were measured in parasternal short axis views. TAPSE was measured from apical M-Mode images. Right ventricular fractional area change was calculated from apical views. Doppler images were used to measure early and late mitral and tricuspid valve inflow velocities (E and A, RV E and RV A), mitral and tricuspid inflow deceleration time (DT, RV DT), isovolumetric relaxation time (IVRT), systolic and diastolic flow in the pulmonary veins, duration of the late mitral valve inflow (A dur),

duration of the flow in the pulmonary vein during atrial contraction (AR dur) and acceleration time of the flow through the pulmonary valve (PV acc. time). Tissue Doppler images were used to measure systolic (S'), early diastolic (E') and late diastolic (A') tissue velocities at the septal and lateral mitral valve and at the right ventricular free wall. Left ventricular mass was calculated using the Devereux formula $0.8(1.04[([LVEDD + IVSd + PWd]^3 - LVEDD^3)]) + 0.6v$, where LVEDD is left ventricular end diastolic diameter, IVSd is thickness of the intraventricular septum in diastole and PWd is posterior wall thickness in diastole. Relative wall thickness was calculated with the formula (2*PWd)/LVEDD. Total vascular resistance was (TVR) was calculated with the formula 80*MAP/(CO/1000), where MAP is mean arterial pressure and CO cardiac output.

Speckle tracking echocardiography

The myocardium was traced manually and the EchoPac software then suggested an area of interest by delimiting the endocardium and epicardium. The operator readjusted this area before the software calculated deformation. LV global strain, LV endocardial global strain, LV epicardial global strain, RV global strain, RV endocardial global strain, RV epicardial global strain, LV longitudinal strain rate, LV early and late diastolic strain rate, RV longitudinal strain rate and RV early and late diastolic strain rate as well as LV and RV diastolic strain rate ratio were calculated from apical views. Negative values indicate fibre shortening, positive values indicate fibre lengthening. LV apical rotation, LV basal rotation, LV apical (de-) rotation rate and LV basal (de-) rotation rate were calculated from apical and basal parasternal short axis views. Negative values indicate rotation in the clockwise direction; positive values indicate rotation in the counter-clockwise direction. LV twist is the difference between the apical and the basal rotation, LV torsion is LV twist divided by left ventricular length in diastole (measured from an apical view). If >1 segment was rejected, subjects were excluded from statistical analysis. Figure 1 illustrates speckle tracking in the apical 4 chamber view in a control and in a preeclamptic participant.

Statistical analysis

Descriptive statistics were performed. Continuous data were presented as mean (standard deviation, SD). Normal distribution was assessed using Shapiro-Wilk test. Categorical data

were presented as number (%) and were compared using the Chi square test. Comparisons between the groups were performed using either unpaired t-test or Mann Whitney U test for continous data, depending on distribution of data. IBM SPSS statistics version 24 was used.

RESULTS

We enrolled a total of 70 pregnant women, 30 women with term preeclampsia and 40 women with healthy term pregnancy. Conventional echocardiographic evaluation of the left ventricle could be performed in all women, and right ventricular images could not be obtained in three controls and six preeclamptic women. Speckle tracking analysis could not be performed in 11 control (five left ventricle, six right ventricle) and 16 preeclamptic (six left ventricle, 10 right ventricle) women. Twist and torsion analysis was not available in 10 control and 11 preeclamptic women.

The demographic characteristics of the control and preeclamptic groups are shown in Table 1. As expected, women developing preeclampsia at term had significantly higher systolic and diastolic booking blood pressures. Total vascular resistance (TVR), total vascular resistance index (TVRI), left ventricular mass (LVM), left ventricular mass index (LVMI) and relative wall thickness and E/E' as a surrogate parameter for increased left ventricular filling pressures were all significantly higher in the preeclamptic group than in the normotensive control group (Table 2, Figure 2). Speckle tracking analysis demonstrated significantly lower LV global strain, LV endocardial global strain, LV epicardial global strain, LV longitudinal strain rate and LV early diastolic strain rate in the preeclamptic group. No difference could be observed in the right heart findings or biventricular twist and torsion measurements (Table 2 and Supplementary Table I).

DISCUSSION

Summary of study findings

The findings of this study demonstrate that preeclampsia at term is associated with more evidence of cardiac maladaptation to increased cardiac work in pregnancy than healthy term pregnant controls. The earlier preeclampsia manifests in pregnancy, the more severe the course of the disease typically. It is therefore not surprising that cardiac changes detected by conventional 2D echocardiography are subtle in this group of women and only affect the left side of the heart. However, when applying strain measurements to detect subclinical changes, left ventricular longitudinal strain is reduced in all three myocardial layers in term preeclamptic women. The additional finding of increased E/E' and reduced early left ventricular diastolic strain rate, indicates that subclinical diastolic dysfunction is present in term preeclampsia.

The current study demonstrated principally mild diastolic impairment in preeclampsia, unlike previous work which showed more severe impairment[12, 13, 26]. The latter can be explained by the exclusion of women with comorbidities, on hypertensive medication and those with preterm preeclampsia. These findings also apply to the right heart, where existing literature documented right heart impairment only in women with preterm preeclampsia[26, 27]. Global longitudinal strain has been shown to be significantly reduced in women with preterm preeclampsia[21], or in cohorts of women with early and late-onset preeclampsia[18]. Our study demonstrated that similar changes are seen in women with term preeclampsia. Furthermore, myocardial layer-specific impairment of longitudinal strain has only previously been documented in early-onset preeclampsia by Cong *et al.*[20]. Our study shows that these changes are seen in term preeclampsia and that in addition, left ventricular diastolic strain rate is also impaired. Orabona *et al.* studied women with a history of preeclampsia between 6 months and 4 years postpartum and were able to demonstrate persistent reduction in ventricular torsion mechanics[14]. Impairment was associated with gestational age at preeclampsia diagnosis, possibly explaining why in our cohort at term, we did not find any changes in twist mechanics.

Study limitations and strengths

Our study included a small number of women (n=70) and preeclamptic women were scanned a week earlier than controls (38.3 weeks vs. 39.3weeks). However, previous work has shown that cardiac maladaptation to chronic volume overload of normal pregnancy increases towards term[28]. If the difference in the gestational age had an effect on the results, it should have served to reduce the difference seen in the preeclamptic group. The strengths of our study are that we only included pregnancies at term, therefore controlling for the higher prevalance of cardiac maladaptation towards term[28]. Moreover, we excluded women with cardiovascular comorbidities or on antihypertensive medication, and therefore we reduced the likelihood that the observed changes are secondary to these factors. The novelty of this study was the comprehensive biventricular systolic and diastolic assessment with speckle tracking analysis as well as formal twist and torsion.

Conclusion

Women with preeclampsia at term demonstrate subclinical myocardial impairment detectable predominantly by speckle tracking analysis. There is already increasing awareness that women with early-onset severe preeclampsia are at significantly increased long-term risk of cardiovascular disease. As term preeclampsia is 4-5 times more common than the early-onset variety, our study findings suggest that postnatal cardiac follow-up might be advisable even in women with preeclampsia at term.

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DECLARATION OF INTEREST

None

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