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Long-term follow-up of women with early onset pre-eclampsia shows subclinical impairment of the left ventricular function by two-dimensional speckle tracking echocardiography

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ABSTRACT

Objectives: This study compares differences in the long-term myocardial function between women with early (EOPE) and late onset preeclampsia (LOPE) and age matched normotensive controls using two-dimensional speckle tracking echocardiography.

Methods: The study population comprised 93 women who gave birth at Department of Gynecology and Obstetrics, Randers Regional Hospital between 1998 and 2008. The women were grouped as EOPE (n = 31), LOPE (n = 22), and women with previous normotensive pregnancies (n = 40). All women underwent comprehensive blinded echocardiographic assessment of myocardial function.

Results: The median time since delivery was 12 years [9;15]. Left ventricular (LV) ejection fraction did not differ between groups. In contrast, LV longitudinal systolic myocardial function by LV global longitudinal strain (LVGLS) magnitude was significantly lower in EOPE women than controls (−18 ± 3% versus −21 ± 2%, $p < 0.001$) and LOPE women (−18 ± 3% versus −21 ± 2%, $p < 0.01$). In alignment with systolic parameters, the diastolic filling pattern indicated more restrictive filling pattern in EOPE women than controls and LOPE women. Thus, EOPE women had lower septal e′ velocities leading to lower mean e′ and subsequently higher E/e′ ratio ($p < 0.01$) than controls and LOPE women. LVGLS was the echocardiographic parameter with the strongest association with EOPE in ROC curves.

Conclusions: Women with a history of EOPE are more likely to have subclinical impairment of left ventricular function 12 years after PE than are those with a history of LOPE and controls. LVGLS was the echocardiographic parameter with the strongest association with EOPE.

1. Introduction

Preeclampsia (PE) affects 5–8% of all pregnancies [1]. Still, the clinical severity of PE varies immensely, which furthermore leads to guideline differences in PE severity definitions [2]. It is well established that women with a history of PE have increased cardiovascular disease (CVD) risk later in life [3–5]. However, studies suggest the cardiovascular risk profile to be different in two subgroups i.e. early onset PE (EOPE: onset before 34 weeks) and late onset PE (LOPE: onset at or after 34 weeks) [6]. Systematic reviews support the epidemiological findings and demonstrate an approximately doubled risk of ischemic heart disease, cerebrovascular incidents and mortality of cardiovascular disease after PE [1]. The gestational age at PE onset has been shown to be negatively associated with markers of subclinical

Abbreviations: BMI, Body mass index; CVD, Cardiovascular disease; DM, Diabetes mellitus; EOPE, Early onset PE; PWT, Infero-lateral wall thickness; IVS, Interventricular septum; LOPE, Late onset PE; LV, Left ventricular; LVEF, Left ventricular ejection fraction; LVGLS, Left ventricular global longitudinal strain; LVID, Left ventricular internal diameter; e′, Peak diastolic mitral annular velocities; S′, Peak systolic mitral annular velocities; PE, Preeclampsia

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atherosclerosis [7]. However, the association between PE and the premature CVD is incompletely understood. Studies have shown that PE is a vascular disease related to traditional CVD risk factors such as hypertension, dyslipidemia and obesity. Nonetheless, how early the CVD develop and the underlying hemodynamic explanation and ways to evaluate these still remains unresolved.

Solid evidence supports echocardiography as a valuable tool to stratify risk and to guide management and counseling in the preclinical and clinical phases of gestational hypertension and PE. Changes in cardiac function and morphology are recognizable at an asymptomatic early stage and correlate with disease severity and adverse outcomes [8]. PE is associated with left ventricular (LV) hypertrophy and LV diastolic dysfunction when compared to normotensive individuals [9,10].

However, traditional LV systolic parameters have shown limited value in the evaluation of myocardial dysfunction long-term post PE despite abnormal loading conditions [11]. Therefore, there is a need for novel and sensitive parameters of myocardial dysfunction in the long term follow-up of women with previous PE. The introduction of two-dimensional (2D) speckle-tracking echocardiography (STE) has enabled LV global longitudinal strain (GLS) assessment as a useful and robust marker of systolic myocardial function. Notably, LV GLS proves a valuable tool in detecting subclinical myocardial dysfunction despite normal LV ejection fraction (EF) [12,13]. Therefore, recent echocardiographic guidelines recommends routine LV GLS assessment while evaluating systolic myocardial performance [14].

Our objective was to compare the myocardial function between groups (EOPE vs. LOPE vs. normotensive controls) 12 years after index pregnancy using STE to assess the LV function.

2. Methods

2.1. Study population

Present study was based on an observational cohort study recruiting women giving birth at Department of Gynecology and Obstetrics, Randers Regional Hospital 1998–2008 [7]. Originally, a total of 185 (75 controls, 55 LOPE and 55 EOPE) eligible participants were identified in The National Patient Registry and The Medical Birth Registry using relevant ICD-10 diagnosis codes resulting 98 participating women. Subsequently, 93 women were included in present study after having provided written informed consent in pursuance of the Helsinki Declaration principles. Of the 5 non-participating women, one had undergone breast cancer surgery, one was pregnant and 3 refused to participate. These women were grouped as early onset PE (EOPE, n = 31), late onset PE (LOPE, n = 22), and controls (n = 40).

Exclusion criteria at follow-up were pregnancy, breastfeeding, natural menopause or address more than 100 km away from the study site. All eligible women with late-onset preeclampsia and with normotensive pregnancies were identified to match eligible early-onset women (age ± 2 years) and time since delivery (± 1 year) and then randomly selected for participation. The women with normotensive pregnancies were randomly selected from eligible matched unexposed women in the source population. Women with normotensive pregnancies were excluded if they before index pregnancy experienced gestational hypertension, preeclampsia, HELLP syndrome or eclampsia. No women with EOPE or LOPE had chronic hypertension during pregnancy. All eligible women were invited to participate in the current study by mail.

The study protocol was approved by the local Medical Ethics Committee and The Danish Data Protection Agency. The study was registered at: www.clinicaltrials.gov as NCT02337049.

2.2. Preeclampsia definitions

During 1998–2008, preeclampsia diagnosis was defined as new-onset hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) and proteinuria (≥300 mg/24 h or ≥30 mg/mmol albumin: creatinine random urine or ≥1 + on repeat dipstick). Early-onset preeclampsia was defined as symptoms occurring before 34 weeks of gestation and late-onset preeclampsia at or after 34 weeks of gestation [15].

2.3. Echocardiography

We used a commercially available ultrasound system (Vivid E9 XDclear, GE Healthcare Horten, Norway) with a 3.5-MHz-phased array transducer (M5Sc).

All women underwent a comprehensive echocardiographic assessment according to current guidelines [14] and volumetric measurements were indexed to body surface area when appropriate. We obtained M-mode or 2D-guided linear measurement of LV interventricular septum (IVS), infero-lateral wall thickness (PWT), and LV internal diameter (LVID) at end-diastole. LV mass was estimated using the linear method by Cube formula as

$$\text{LV mass} = 0.8 \times 1.04 \times [(\text{IVS} + \text{LVID} + \text{PWT})^3 - \text{LVID}^3] + 0.6\,\text{g}.$$

2D LV ejection fraction (LVEF) was calculated using Simpson's biplane method of discs. Peak systolic mitral annular velocities (S′) were estimated from the tissue Doppler velocity images as an average of septal, lateral, anterior, and posterior velocities. Peak diastolic mitral annular velocities (e′) was estimated both septal, lateral, and as the average of septal and lateral velocities. In the assessment of E/e′ ratio we used the average e′.

The magnitude of peak systolic left ventricular global longitudinal strain (LVGLS) [16] was obtained in standard 2D cine-loops using frame-by-frame tracking of speckle patterns throughout the left-sided myocardium with a frame rate > 60 frames/s. We manually adjusted the speckle area of interest for optimal tracking results. We excluded segments with an unacceptably low tracking quality. LVGLS was calculated using a 17-myocardial segment model [17]. Fig. 1 shows examples of LVGLS plots in a EOPE patient, a LOPE patient, and a control subject. The LVGLS magnitude is expressed as a negative value. Thus, the more negative LVGLS value the better myocardial deformation.

The echocardiographic assessment and data analysis was performed blinded to PE status. The data were analyzed offline using dedicated software by a single observed BBL (EchoPAC PC SW-Only, 201, GE-Healthcare, Milwaukee, Wisconsin, USA).

2.4. Blood sampling and blood pressure measurement

At follow-up both fasting and non-fasting blood samples were collected and analyzed according to standard laboratory protocols. A fully automatic oscillometric device (Omron MIT Elite; Omron Healthcare Co; Kyoto; Japan) with appropriate cuff size was used to arterial blood pressure measurements following 10 min rest in upright position. Measurements were performed three times with 3-minutes interval and repeated if values differed more than 5 mmHg. The mean of the last two blood pressure measurements is the reported value.

2.5. Statistical analysis

Normally distributed data are presented as mean ± standard deviation; non-normally distributed data are presented as median and interquartile range. Categorical data are presented as absolute values with percentages. Histograms and Q-Q plots were used to check continuous values for normality. Between-group differences were assessed using the *t*-test and ANOVA for normally distributed data, the Mann-Whitney *U* test and Kruskal-Wallis test for non-normally distributed data, and the chi^2 test for dichotomized data. A linear regression model was used to compare continuous variables. In a multivariable regression model we adjusted for blood pressure and body mass index. Area under ROC curve was used to compare the predictive ability of the parameters