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ARTICLE

Inappropriate left ventricular mass after preeclampsia: another piece of the puzzle Inappropriate LVM and PE

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Abstract

Excessive left ventricular (LV) mass (LVM) increase results in inefficient LV work with high energy waste and a negative prognostic effect. We aimed to investigate the presence of inappropriate LVM and to calculate the myocardial mechanoenergetic efficiency index (MEEi) in asymptomatic women with a history of early-onset (EO) or late-onset (LO) pre-eclampsia (PE). Among all women diagnosed with PE in the years 2009-2013, after applying inclusion/exclusion criteria and cost-effectiveness analysis, we randomly selected thirty women who experienced EO-PE, thirty with a previous LO-PE and thirty healthy controls to undergo echocardiography from 6 months to 4 years after delivery. Data regarding gestational age (GA) and mean uterine artery (UtA) pulsatility index (PI) at PE onset were collected from medical records. All women were free from cardiovascular risk factors. LVM excess was calculated as the ratio between observed LVM and predicted LVM (by sex, stroke work and height), while MEEi was calculated as the ratio between stroke work and "double product" (to approximate energy consumption), indexed to LVM. Concentric remodeling was present in 60% of EO-PE and 53% of LO-PE. LVM excess was significantly more often present in the EO-PE group than in the control group. LVM was inappropriate in 52% of EO-PE and 17% of LO-PE. MEEi showed a tendency towards lower values in the EO-PE group. Multivariate regression analysis showed that both LVM excess and MEEi were independently associated with lower GA and higher mean UtA PI at PE onset. Inappropriate LVM with a tendency towards reduced MEEi in the first 4 years after delivery may partially explain the elevated cardiovascular risk in former pre-eclamptic women compared to the general population.

Keywords Pre-eclampsia · left ventricular mass · inappropriate · echocardiography · mechanoenergetic efficiency · remodeling

Introduction

Preeclampsia (PE) is one of the leading causes of maternal and perinatal morbidity and mortality worldwide [1]. The impact of PE does not end with delivery, as it is associated with a 2- to 7-fold increased risk for premature onset of cardiovascular (CV) disease [2]. Previous studies reported a high prevalence of persistent postpartum impairment in left ventricular (LV) geometry after PE [3–11], including concentric remodeling and hypertrophy, which may, at least in part, explain the elevated associated CV risk after PE. LV hypertrophy represents the structural adaptation to cardiac overload thanks to a higher compensatory LV mass (LVM). However, in some cases, LVM exceeds the need to sustain cardiac workload, resulting in "inappropriate LVM", which is linked to functional cardiac impairment, resulting in energy waste and reduced LV mechanoenergetic efficiency

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(MEE) [12–14]. Moreover, it is associated with a sub-optimal CV risk profile [15–18] and cardiac adverse events [19, 20].

The aim of the present study was to assess the presence of inappropriate LVM and the extent of MEE in women with a history of early-onset (EO) and late-onset (LO) PE. We also aimed to investigate the relationship between LVM excess and MEE and obstetric parameters, including gestational age (GA) at PE onset, intrauterine growth restriction (IUGR) and uterine artery (UtA) Doppler velocimetry.

Methods

Subjects

This was a cross-sectional single-center case–control study, in compliance with the 1975 Declaration of Helsinki, approved by the local Medical Ethics committee and conducted according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [21]. We retrospectively searched our electronic database for all women diagnosed with PE at the Maternal Fetal Medicine Unit of the Department of Obstetrics and Gynecology, University of Brescia, Italy between January 2009 and December 2013. PE was defined, according to the International Society for the Study of Hypertension in Pregnancy, as a blood pressure of at least 140/90 mmHg, on two occasions 4–6 h apart, after the 20th week of gestation, in previously normotensive women, accompanied by proteinuria ≥ 300 mg/24 h [22]. EO-PE was defined as PE requiring delivery before 34 weeks of gestation.

All women were approached by phone between 6 months and 4 years after delivery to assess their eligibility. We excluded women with any of the following CV risk factors: smoking habit, dyslipidemia, overweight/obesity, diabetes mellitus, or chronic hypertension, as well as those who had multiple pregnancy, fetal aneuploidy or malformation, maternal cardiopathy, nephropathy or immune disorder, or PE superimposed on chronic hypertension. In addition, we only included women with normal blood pressure values and the absence of pathological proteinuria 6 months after delivery. Considering the sample-size calculation, cost-effectiveness and available resources, only 60 subjects (30 EO-PE and 30 LO-PE) were randomly selected and requested to attend for postpartum follow-up. Thirty healthy women matched for age, body mass index and parity and without CV risk factors who delivered in our hospital during the same days as the enrolled cases were selected as controls.

Demographic and clinical data during pregnancy were collected from obstetric charts of all included subjects. Small-for-gestational age infants were defined as a birth weight below the 10th percentile for GA on the basis of national growth charts [23]. IUGR was defined as fetal abdominal circumference < 10th percentile, according to local standards [23], with umbilical artery pulsatility index (PI) > 95th percentile at sonography. All prenatal ultrasound scans had been performed by experienced sonographers using an iU22 ultrasound system equipped with a V6-2 curved-array volume transducer (Philips Healthcare, Bothell, WA, USA). UtA Doppler measurements were obtained at the apparent crossover of the uterine and external iliac arteries. The PIs of both UtAs were measured, and their mean was calculated.

After providing written informed consent to participate, all women underwent peripheral blood pressure measurement and echocardiography at our Cardiology Unit, in a single, temperature-controlled room. To limit intra- and interobserver variability, the study was carried out by a single expert echocardiographer (E.V.) who was blinded to the patients' prior medical history.

Blood pressure measurement

Blood pressure was assessed using a standard, calibrated, electronic sphygmomanometer (OMRON Healthcare, Hoofddorp, The Netherlands), with the woman in a resting state and sitting at a 45° angle. Systolic blood pressure (SBP) was considered to be high if it was ≥ 140 mmHg, while high diastolic blood pressure (DBP) was defined as a value ≥ 90 mmHg. BP was measured initially in each arm, and the arm with the highest sitting DBP reading was used for a further two measurements, with the mean of the three measurements recorded. Every effort was made to have the same staff member obtain blood pressure measurements in every patient, at the same time of day, using the same equipment. Mean arterial pressure (MAP) was calculated as: $(SBP + 2 \times DBP)/3$.

Echocardiography

Echocardiographic examinations were performed using a Vivid 7 ultrasound machine (GE Healthcare, Milwaukee, WI, USA), equipped with a 3.5-MHz transducer. Digital loops were stored on the hard disk of the ultrasound machine and transferred to an EchoPac workstation (GE Healthcare) for offline analysis. Participants were placed in the left lateral decubitus position, and images were acquired from standard parasternal and apical views. LV dimensions, volumes and LVM were obtained according to current guidelines [24], and the LV ejection fraction (LVEF) was calculated using Simpson's biplane method [24]. LV diastolic function was defined according to published guidelines, assessing transmitral Doppler inflows and tissue

Doppler imaging at basal segments [25]. Valvular alterations were screened according to published guidelines [26, 27].

Inappropriate LVM and myocardial MEEi

LVM (in g) was obtained by the equation $0.8 \times (1.04 \times ((\mathrm{LVEDD} + \mathrm{IVST} + \mathrm{PWT})^3 - \mathrm{LVEDD}^3)) + 0.6$, and relative wall thickness (RWT) was calculated as $2 \times \mathrm{PWT}/\mathrm{LVEDD}$, where LVEDD is LV end-diastolic diameter, IVST is the interventricular septal thickness and PWT is the posterior wall thickness, at end-diastole [24]. Concentric remodeling was defined by $\mathrm{RWT} > 0.42$ with a normal LVM, and concentric hypertrophy by $\mathrm{RWT} > 0.42$ and LVM index $> 95\ \mathrm{g/m^2}$ (for females) [24].

Predicted LVM (pLVM) was calculated from stroke work (SW), sex and body size (as height (h) in meters to the 2.7 power) by the following validated equation:[28, 29] $\mathrm{pLVM\ (in\ g)} = 55.37 + (6.64 \times \mathrm{h}^{2.7}) + (0.64 \times \mathrm{SW}) - (18.07 \times \mathrm{sex})$. SW can be computed as: $\mathrm{SW} = \mathrm{SBP} \times \mathrm{SV} \times 0.0144$, where SV is echocardiographic stroke volume, calculated using the z-derived method to estimate LV volumes [30]. The term 0.0144 converts $\mathrm{mmHg} \times \mathrm{cm}^3$ to $\mathrm{g} \times \mathrm{m}$. Sex was assigned the values of 1 for men and 2 for women. An excess of LVM was calculated as the ratio between the observed LVM and pLVM. The excess of LVM over 128% of the value predicted from individual hemodynamic load was defined as "inappropriate LVM", whereas a LVM/pLVM ratio < 73% as "inadequate LVM" [28].

The mechanical efficiency of a system is the ratio between developed work and the corresponding energy consumption. To estimate myocardial MEE, two factors are required: work and energy consumption, as previously demonstrated [14, 31]. Total external myocardial work can be estimated as SW, as indicated above (Fig. 1). Energy consumption would ideally be determined by coronary sinus catheterization to measure real-time myocardial oxygen consumption ($\mathrm{MVO_2}$). More simply, $\mathrm{MVO_2}$ can be calculated as the so-called "double product" (DP), that is, $\mathrm{SBP} \times \mathrm{HR}$. Thus, myocardial MEE—as the ratio between developed external work and an estimate of $\mathrm{MVO_2}$ – can be expressed as: $\mathrm{MEE} = \mathrm{SW/DP} = \mathrm{SV/HR}$. HR can also be expressed in seconds, as the time of the cardiac cycle by dividing HR by 60. Thus, myocardial mechanical efficiency can be measured as the ideal amount of blood pumped by one single heart beat in 1 s. Due to the strong relationship between MEE and LVM, MEE can be divided by LVM to obtain an estimate of myocardial MEE per gram of LVM [i.e., MEE index (MEEi), expressed in mL/s per g].

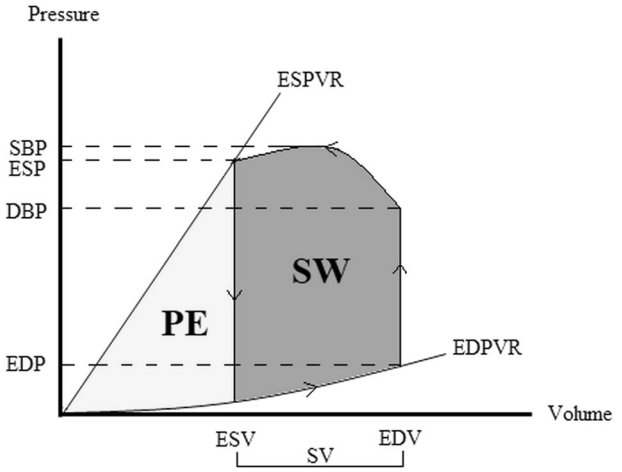

Fig. 1 Left ventricular pressure–volume curve. Myocardial energy is the sum of external work (namely, stroke work, in orange) and elastic potential energy (in yellow). DBP diastolic blood pressure, EDP end-diastolic pressure, EDPVR end-diastolic pressure–volume relationship, EDV end-diastolic volume, ESP end-systolic pressure, ESPVR end-systolic pressure–volume relationship, PE potential energy, ESV end-systolic volume, SBP systolic blood pressure, SV stroke volume, SW stroke work

Statistical analysis

Continuous variables were visually tested for normality using Q–Q plots and are expressed as the means and standard deviations (SDs); categorical variables are expressed as frequencies (n) and percentages of the sample.

After Levene's test for homoscedasticity, Welch's unequal variances analysis of variance (ANOVA) was performed to analyze the difference between means for continuous variables (independent samples Welch's *t* test if two groups), and Dunnett C test for *post hoc* analysis. The χ^2 test was used for assessing differences between proportions.

Multivariate regression analysis using the "enter" method was performed to assess the association between LVM/pLVM and MEEi from 6 months to 4 years after delivery (as the dependent variables) and pregnancy data from both PE groups as the independent variables (GA, SBP, DBP, UtA-PI at diagnosis of PE, birth weight percentile). No a priori sample size calculation was possible due to the lack of data for the parameters investigated in this clinical setting. *Post hoc* sample size calculation showed that the statistics were adequate with an 85% power and a 0.05 Type I error risk for all parameters. Statistical analysis was performed using IBM SPSS Statistics 20 for Windows (SPSS, Inc., Chicago, IL). All values were two-tailed; statistical significance was set at $p < 0.05$.

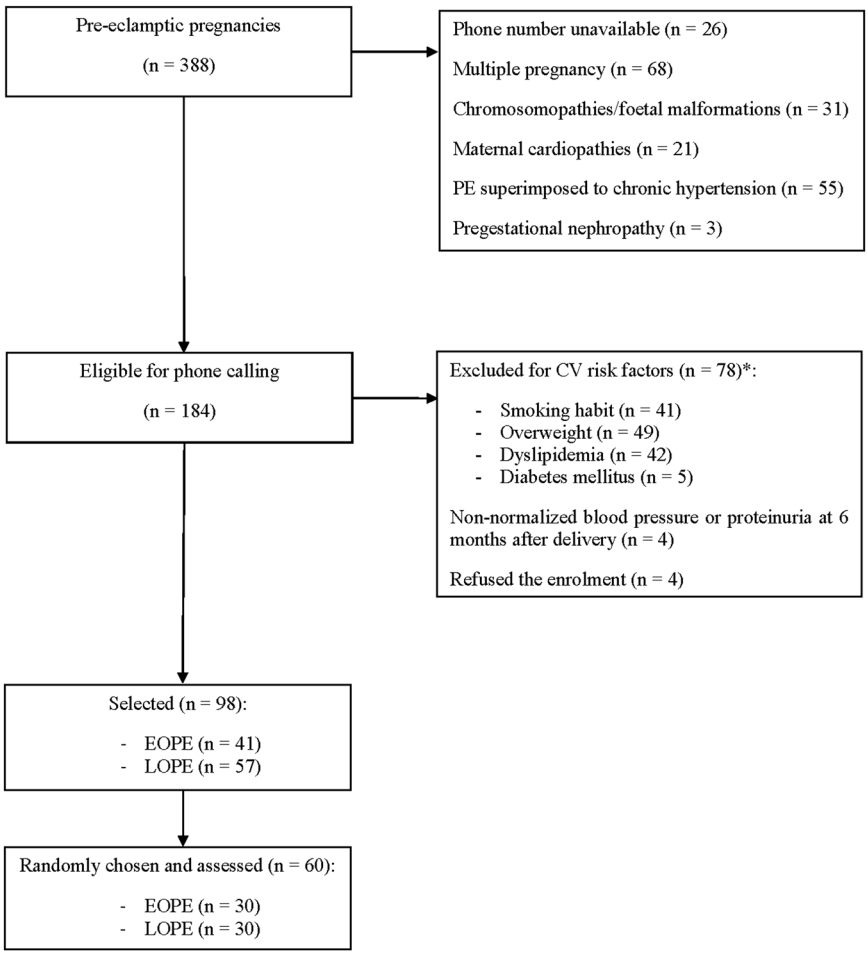

Fig. 2 Flowchart of pre-eclamptic pregnancies considered for inclusion in the study. *Fifty-eight subjects had more than one cardiovascular (CV) risk factor. BP blood pressure, EO-PE early-onset pre-eclampsia, LO-PE late-onset preeclampsia, PE preeclampsia

Results

In our electronic database, we identified 388 women with a previous pregnancy complicated by PE between January 2009 and December 2013. Among these women, 41 who experienced EO-PE and 57 who had had LO-PE were eligible for the study. According to cost-effectiveness 30 cases from each group were randomly included (Fig. 2). All women were free from any medication at the time of cardiologic assessment, including oral contraceptives. Pregnancy data and baseline patient characteristics are reported in Table 1. Blood pressure measurements, although within the normal range (<140/90 mmHg), were significantly higher in the EO-PE group than in the LO-PE group; DBP was also higher than in the controls.

Table 2 shows that all patients had normal LVM and pLVM, with statistically nonsignificant tendencies towards higher LVM in both PE groups than in the controls. No woman had LV hypertrophy. However, concentric remodeling was higher in both PE groups than in the controls (60% vs 53% vs 0%, respectively; $p < 0.001$). Consequently, LVM/pLVM was significantly increased in these groups, with a significant difference between EO-PE and the controls. LVM was more often inappropriate in the EO-PE group compared to the other two groups (53 vs. 17 vs. 0%, respectively; $p < 0.001$). MEE and MEEi did not show any significant differences among the three groups, with a tendency towards lower values in the EO-PE group. No woman had inadequate LVM. Grade I diastolic dysfunction was present in only 10% of the EO-PE group ($p = 0.045$)

The results of the multivariable analysis are reported in Table 3. GA at the diagnosis of PE, as well as blood pressure at PE onset, UtA-PI and birth-weight percentile were all independently associated with LVM excess (LVM/pLVM) and MEEi.

Discussion

The main findings of the present study are that: (1) even in the absence of LV hypertrophy, approximately half of women with a previous EO-PE and one-sixth of those with a previous LO-PE showed inappropriate LVM; (2) women with a previous EO-PE had a tendency towards lower MEEi

Table 1 Demographic and clinical characteristics of study population of women with previous singleton pregnancy complicated by early-onset (EO) or late-onset (LO) pre-eclampsia (PE) and controls, obtained retrospectively

Variable	EO-PE group ($n = 30$)	LO-PE group ($n = 30$)	Controls ($n = 30$)	P value
Maternal age at delivery (years)	36 ± 4	34 ± 6	35 ± 4	0.061
Maternal age at assessment (years)	38 ± 4	36 ± 6	37 ± 4	0.084
Time from delivery (years)	2.3 ± 0.7	2.5 ± 0.8	2.2 ± 0.6	0.115
BMI (kg/m^2)	23.2 ± 2.3	22.3 ± 2.4	23.1 ± 2.5	0.329
BSA (m^2)	1.68 ± 0.14	1.67 ± 0.12	1.62 ± 0.08	0.112
SBP (mmHg)	125 ± 13‡	116 ± 11	119 ± 8	0.007
DBP (mmHg)	80 ± 9*‡	73 ± 9	74 ± 6	0.003
MAP (mmHg)	95 ± 10*‡	87 ± 9	89 ± 4	0.001
HR (bpm)	78 ± 9	77 ± 10	79 ± 7	0.604
Parity				0.136
Nulliparous	18 (60.0%)	24 (80.0%)	21 (70.0%)	
Primiparous	9 (30.0%)	3 (10.0%)	6 (20.0%)	
Multiparous	3 (10.0%)	3 (10.0%)	3 (10.0%)	
GA at diagnosis of PE (weeks)	$27^{+5} \pm 2^{+4}$	$36^{+4} \pm 1^{+2}$	-	< 0.001
Mean UtA-PI at diagnosis of PE	1.56 ± 0.39	1.13 ± 0.43	-	0.001
SBP at diagnosis of PE (mmHg)	161 ± 27	163 ± 13	-	0.007
DBP at diagnosis of PE (mmHg)	117 ± 33	104 ± 18	-	0.003
Proteinuria (mg/24 h)	3258 ± 926	3012 ± 2618	-	0.841
GA at delivery (weeks)	$30^{+6+} \pm 3^{+6}$*	$37^{+1} \pm 1^{+2\dagger}$	$39^{+1} \pm 1^{+0}$	0.033
Cesarean section	30 (100.0%)*‡	17 (56.7%)†	5 (16.7%)	< 0.001
IUGR	23 (76.7%)	13 (43.3%)	-	< 0.001
Male sex	15 (50.0%)	10 (33.3%)	17 (56.7%)	0.405
Birth weight (g)	928 ± 539‡	2483 ± 561†	3315 ± 485	< 0.001
Birth-weight percentile	14.1 ± 20.7*	20.7 ± 22.3†	48.0 ± 21.9	0.022
Maternal complications				—
HELLP syndrome		—	—	
Eclampsia	—	—	—	
Placental abruption	1 (3.3%)	—	—	
Disseminated intravascular coagulation	1 (3.3%)			

The data are given as mean ± SD, *n* (%)

BMI body mass index, *BSA* body surface area, *DBP* diastolic blood pressure, *DIC* disseminated intravascular coagulation, *GA* gestational age, *HR* heart rate, *IUGR* intrauterine growth restriction, *MAP* mean arterial pressure, *PI* pulsatility index, *SBP* systolic blood pressure, *UtA* uterine artery

Post-hoc two-sample comparison of groups: *$P < 0.05$, EO-PE vs. controls, †$P < 0.05$, LO-PE vs. controls, ‡$P < 0.05$, EO-PE vs. LO-PE

than LO-PE and controls; and (3) GA and UtA-PI at PE onset and birth-weight percentile were independently associated with LVM excess and MEEi.

Women with a previous pregnancy complicated by PE, particularly EO-PE, are characterized by a relatively high proportion of asymptomatic LV systolic and/or diastolic dysfunction [3–11, 32, 33]. More in detail, Melchiorre *et al*. demonstrated 40 and 20% prevalence rates of unfavorable LV remodeling and/or hypertrophy one year postpartum in EO-PE and LO-PE, respectively [3]. These abnormalities were associated with the development of clinical hypertension in 50% of cases within 1 to 2 years after pregnancy [3]. Similarly, Ghossein-Doha *et al*. found that the development of hypertension in initially normotensive formerly pre-eclamptic women was preceded by the increase of LVM and that PE was an independent predictor for developing structural cardiac remodeling 4–7 years later [34]. We recently extended these data, describing a frequent subclinical impairment in LV contractility and relaxation at short-medium term after delivery [33]. In contrast to the subjects studied by Melchiorre *et al*., our cohort was normotensive and characterized by the absence of LV hypertrophy. Nevertheless, we hereby demonstrated that many apparently healthy women show an excess of LVM that

Table 2 Demographic and clinical characteristics of study population of women with previous singleton pregnancy complicated by early-onset (EO) or late-onset (LO) pre-eclampsia (PE) and controls, obtained retrospectively

Variable	EO-PE group (n = 30)	LO-PE group (*n* = 30)	Controls (*n* = 30)	*P*
LVEF (%)	56 ± 7*‡	61 ± 5	63 ± 4	< 0.001
Stroke volume (mL)[a]	46 ± 11	50 ± 15	48 ± 18	0.669
LVM (g)	109.9 ± 29.4	108.1 ± 17.1	97.9 ± 17.5	0.081
LVMi (g/m^2)	64.7 ± 13.6	64.7 ± 8.2	61.2 ± 10.8	0.389
RWT	0.42 ± 0.09*	0.44 ± 0.11†	0.36 ± 0.06	0.238
Concentric remodelling	18 (60.0%)*	16 (53.3%)†	0 (0.0%)	< 0.001
E/A ratio	1.24 ± 0.19	1.27 ± 0.25	1.18 ± 0.09	0.212
E wave deceleration time (ms)	208 ± 70	185 ± 42	185 ± 13	0.136
E/E'	7.20 ± 1.34	7.37 ± 0.63	6.78 ± 1.13	0.091
Grade I diastolic dysfunction	3 (10.0%)*‡	0 (0.0%)	0 (0.0%)	0.045
pLVM (g)[a]	96.7 ± 12.6	97.7 ± 16.2	95.1 ± 19.2	0.820
LVM/pLVM (%)[a]	123 ± 36*	112 ± 15	104 ± 16	0.020
Inappropriate LVM[a]	12 (52.2%)*‡	5 (16.7%)†	0 (0.0%)	0.002
MEE (mL/s)[a]	35.2 ± 10.2	39.4 ± 13.6	36.7 ± 14.4	0.502
MEEi (mL/s/g)[a]	0.41 ± 0.27	0.47 ± 0.14	0.48 ± 0.12	0.498

Data are given as mean ± SD, *n* (%)

LV left ventricular, *LVEF* left ventricular ejection fraction, *LVM* left ventricular mass, *LVMi* left ventricular mass index, *MEE* mechano-energetic efficiency, *MEEi* mechano-energetic efficiency index, *pLVM* predicted left ventricular mass, *RWT* relative wall thickness

Post-hoc two-sample comparison of groups: *$P < 0.05$, EO-PE vs. controls, †$P < 0.05$, LO-PE vs. controls, ‡$P < 0.05$, EO-PE vs. LO-PE

[a]Data available only in 23/30 (76·7%) EO-PE

Table 3 Multivariate regression analysis, run on the 60 cases with previous pre-eclamptic pregnancy, to assess linear association between LVM excess and MEEi (as dependent variables) and obstetric data (as independent variables). 95% confidence intervals are also shown

	LVM excess (LVM/pLVM)		MEEi	
	β	*P* value	β	*P* value
GA	−1.013 (−2.156 to −0.009)	0.049	0.013 (0.007 to 0.019)	< 0.001
SBP	2.090 (1.557 to 2.624)	< 0.001	−0.006 (−0.009 to −0.003)	< 0.001
DBP	2.825 (2.359 to 3.290)	< 0.001	−0.012 (−0.014 to −0.009)	< 0.001
BW percentile	−0.519 (−0.849 to −0.189)	0.004	0.002 (0.000 to 0.004)	0.028
UtA-PI	57.649 (46.846 to 68.453)	< 0.001	−0.277 (−0.338 to −0.216)	< 0.001

BW birth weight, *DBP* diastolic blood pressure at diagnosis, *GA* gestational age at diagnosis, *LVM* left ventricular mass, *MEEi* mechano-energetic efficiency index, *pLVM* predicted left ventricular mass, *SBP* systolic blood pressure at diagnosis, *UtA-PI* mean uterine artery pulsatility index at diagnosis

cannot be expected by hemodynamic load based on blood pressure or body composition. We attempt to explain this issue considering two aspects. First, these women showed high prevalence rates of endothelial dysfunction and arterial stiffness [35–37], with impaired aortic elastic properties [36] and increased aortic elastance (i.e., stiffness) [33]. This phenotype is responsible for increased afterload and reduced ventricular-arterial coupling during the ejection phase, thus favoring an inappropriately high LVM. Second, the presence of LV fibrosis documented in these women may increase LVM without a corresponding increase in LV work [38]. As a consequence, the left ventricle is more stiffened (high LV elastance), which leads to impaired diastolic function [33]. This effect could be the consequence of a relative myocardial ischemia due to the mismatch between increased afterload and reduced coronary perfusion in diastole, both related to arterial stiffness. A fibrotic, stiffened and remodeled left ventricle works at low efficiency and wastes energy. If the aorta is rigid, as it is in this case, the efficiency is even lower, as we demonstrated [33, 36]. Furthermore, we found a statistically nonsignificant tendency towards reduced MEEi in the EO-PE group, suggesting a low contraction efficiency at the myocyte level.

Inappropriate LVM has been extensively studied in hypertensive subjects, as it is associated with LV geometric and functional abnormalities [12, 13], thus favoring wasted LV energy and reduced MEE [14]. Moreover, inappropriate

LVM is associated with a high-risk CV profile [15–18] and predicts adverse events [19, 20]. From epidemiological studies, pregnancies complicated by PE are associated with a higher risk of CV events later in life with a two-fold CV mortality (eight-fold if EO-PE) [2, 39]. For this reason, a history of PE has been added to traditional CV risk factors [40]. It may be that inappropriate LVM may play a role in increasing the CV risk of these women.

Our study suffers from some limitations. First, a small number of patients was involved. Second, the lack of a preconceptional and gestational echocardiographic evaluation to compare our findings prevented us from definitely knowing if the LVM excess with reduced MEE is a consequence of PE or indicates an alteration already present before pregnancy. Moreover, SV measured by M-mode echocardiography may be imprecise. However, in an epidemiological study, M-mode SV was very closely related to Doppler SV (mean difference 1.6 ± 5.0 mL/beat), which was validated against invasive SV [41]. Finally, in order to relate external work with MVO_2 and to estimate MEE, we used simple formulas based on simple assumptions, which have already been used in many different circumstances [12–20, 28–31] and validated against invasive methods [42–45].

In conclusion, to the best of our knowledge, this is the first study to assess LVM excess and MEE in asymptomatic women with a history of PE. Our findings suggest that EO-PE is characterized by LVM excess at short-medium term after delivery, with a tendency towards reduced MEE. These findings can provide another possible explanation for the higher risk of CV events later in life in these women with respect to the general female population of the same age.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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