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Pre-eclampsia: an important risk factor for asymptomatic heart failure

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KEYWORDS: heart failure; metabolic syndrome; pre-eclampsia; pregnancy; prehypertension

ABSTRACT

Objectives *Pre-eclampsia (PE) is associated with both postpartum structural asymptomatic heart disease (i.e. heart failure Stage B (HF-B)) and conventional cardiovascular (CV) risk factors. We aimed to evaluate the extent to which PE, adjusted for conventional CV risk factors, is associated independently with asymptomatic cardiac abnormalities postpartum.*

Methods *In this cross-sectional cohort study, 107 formerly pre-eclamptic women and 41 women with uneventful previous pregnancy (controls) were invited for CV risk assessment 4–10 years postpartum. This included cardiac ultrasound, blood pressure (BP) measurement and evaluation of metabolic syndrome determinants. Asymptomatic structural and functional cardiac abnormalities were classified as HF-B, according to the American Heart Association guidelines. Prehypertension was defined as systolic BP of 120–139 mmHg and/or diastolic BP of 80–89 mmHg. Univariate and multivariate regression analyses were performed to calculate associations of PE and conventional risk factors with HF-B.*

Results *The prevalence of asymptomatic HF-B was approximately 3.5-fold higher in the PE group compared with controls (25% vs 7%, $P < 0.01$); 67% of this group had concentric remodeling and 22% had mildly impaired ejection fraction. After adjustment for postpartum interval, hypertension and high-density lipoprotein, PE was significantly associated with HF-B (adjusted odds ratio, 4.4 (95% CI, 1.0–19.1)). Moreover, in the formerly pre-eclamptic group, prehypertension was associated significantly with HF-B (odds ratio, 4.3 (95% CI, 1.4–12.7)), while metabolic syndrome determinants were not.*

Conclusion *PE is associated with a four-fold increased female-specific risk of asymptomatic cardiac abnormalities. Prehypertension apparently increases this risk significantly, while metabolic syndrome determinants do not.*

INTRODUCTION

In western countries, more women than men die of cardiovascular diseases (CVD)[1,2], making CVD in women an important public health issue. In addition to the gender-independent classical risk factors seen in both men and women, the women-specific risk factor pre-eclampsia (PE) is associated with a two-to-seven-fold increased risk of CVD[3].

PE is a pregnancy-related hypertensive syndrome[4], complicating 5–10% of first pregnancies[5,6]. In contrast to the physiological eccentric left ventricular (LV) remodeling seen in healthy pregnancies, pre-eclamptic pregnancies are characterized by the less favorable concentric LV remodeling[7]. The additional increase in LV mass (LVM) in women with PE does not always resolve after delivery[8–10]. In fact, up to 1 year postpartum, 40% of formerly pre-eclamptic patients have structural or functional cardiac abnormalities, consistent with heart failure Stage B (HF-B)[10]. Although using the term 'HF-B' is subject to debate, this definition aids in clustering and identifying asymptomatic structural and cardiac abnormalities in these relatively young women, especially since there is an increasing understanding that CVD are generally progressive disorders that proceed through asymptomatic to symptomatic stages and that the progression from the asymptomatic HF-B to the

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symptomatic HF Stage C (HF-C) increases the risk of mortality five-fold[11]. Because therapeutic interventions during the asymptomatic phase of cardiac impairment can improve the long-term prognosis more effectively than when initiated at a symptomatic stage, identifying this stage in relatively young subpopulations may have major clinical benefit[11,12].

PE is also associated with conventional cardiovascular (CV) risk factors, for example, metabolic syndrome and prehypertension. In this cross-sectional cohort study, we performed CV screening in a group of former PE patients and compared the results with those of a healthy control group in order to determine whether PE, adjusted for conventional CV risk factors, is associated independently with asymptomatic cardiac abnormalities postpartum.

METHODS

The Nijmegen Medical Center Medical Ethics Committee approved the study protocol for this cross-sectional cohort study before patient enrolment (NL32718.091.10). The procedures followed were in accordance with institutional guidelines. Informed consent was obtained before patient enrolment and procedures adhered to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects (revised 13 November 2001, effective 13 December 2001).

In this study, non-pregnant formerly pre-eclamptic women and women with previously uneventful pregnancy (healthy parous controls) were invited for CV risk analysis, 4–10 years postpartum. Formerly pre-eclamptic women ($n = 121$) who had attended previously for postpartum screening were invited by mail to participate in this study. Of these women, 107 former PE patients were enrolled into this follow-up study. Healthy parous controls were recruited by advertisement; 41 eligible women responded and were recruited into the study. As the etiology of PE is considered heterogeneous[13], we included at least two formerly pre-eclamptic women for each healthy parous control.

All included women were Caucasian. Medical history was taken, including family history regarding CVD at age < 60 years in first-line relatives. Obstetric data were collected, including occurrence of intrauterine fetal demise, birth weight and birth-weight centile according to national birth-weight charts[14]. Infants were considered small-for-gestational age when birth weight corrected for gestational age was $< 5^{th}$ centile. PE was diagnosed in the presence of new-onset hypertension (systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg) after 20 weeks of gestation and concomitant proteinuria exceeding 0.3 g/day[15]. Early-onset PE was defined as PE developing before 34 gestational weeks and preterm PE was defined by PE requiring delivery before 37 weeks of gestation. Women were eligible for inclusion in the control group if they had a history of uncomplicated pregnancy; their pregnancy charts were checked to ensure this. In both groups, we excluded women who had, prior to their first pregnancy, chronic hypertension, diabetes or autoimmune disease.

CV risk factor screening (automated BP, body weight, height and laboratory measurements to detect metabolic syndrome) and echocardiographic measurements were performed after an overnight fast. All measurements started at 08:00 h. After 30 min of rest in a sitting position, BP (in mmHg) and heart rate (in bpm) were measured oscillometrically (Dinamap Vital Signs Monitor 1846, Critikon, Tampa, FL, USA), using the cuff size recommended for the patient's arm circumference, at 3-min intervals for 30 min at the right upper arm. We recorded SBP and DBP, mean arterial pressure (MAP) and heart rate, from which we used the median values for analysis. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or the use of antihypertensive medication. Prehypertension was diagnosed as SBP of 120–139 mmHg and/or DBP of 80–89 mmHg.

Height and weight (Seca 888 scale, Hamburg, Germany) were measured and body mass index (BMI) was calculated as: body weight (in kg)/(height (in m))^2.

All participants collected urine in the 24 h preceding the measurements. This 24-h urine sample was assayed for albumin and creatinine to define the (micro) albuminuria corrected for creatinine output (g/mol creatinine) (Aeroset, Abbot Laboratories, IL, USA). Venous blood samples were taken from the antecubital vein and analyzed for glucose, insulin, high-density lipoprotein (HDL) and triglyceride levels (Aeroset, Abbot Laboratories). To estimate insulin resistance, the product of fasting glucose and insulin (homeostasis model assessment index for insulin resistance, $HOMA_{IR}$) was calculated as: insulin (in mU/L) × glucose (in mmol/L)/22.5.

The diagnosis of metabolic syndrome and the cut-off values of its constituents were based on the criteria set by the World Health Organization. It was defined by the concomitant presence of insulin resistance (fasting insulin ≥ 9.2 mU/L or fasting glucose ≥ 6.1 mmol/L or $HOMA_{IR} \geq 2.2$) and two or more of the following factors: hypertension, obesity (BMI ≥ 30 kg/m^2), dyslipidemia (triglycerides ≥ 1.69 mmol/L or HDL ≤ 0.9 mmol/L) and microalbuminuria (urine albumin:creatinine ratio ≥ 2.5 g/mol creatinine).

Cardiographic measurements

Echocardiographic measurements were obtained using a phased-array echocardiographic Doppler ultrasound system (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). The assessments were performed offline using EchoPAC PC SW, GE Vingmed Ultrasound, Version 6.1.2. We performed two-dimensional, M-mode and Doppler echocardiography according to the guidelines of the American Society of Echocardiography (ASE)[16]. Using M-mode in the parasternal long-axis view, we measured LV end-diastolic and end-systolic diameters (LVEDd and LVESd, respectively, in mm), as well as thickness of the interventricular septum (IVST, in mm) and of the posterior

wall (PWT, in mm). LVM (in g) was calculated using the formula $0.8 \times (1.04 \times ((\text{LVEDd} + \text{PWT} + \text{IVST})^3 - \text{LVEDd}^3)) + 0.6$ and indexed for body surface area (LVMi), as recommended by the ASE[17]. The relative wall thickness (RWT) was calculated using the formula $(2 \times \text{PWT})/\text{LVEDd}$ as recommended by the ASE[17]. LV end-diastolic volume (EDV, in mL) and end-systolic volume (ESV, in mL) were estimated using the Teichholz formula[18]. Ejection fraction (EF) was calculated as a percentage by the formula $(\text{EDV} - \text{ESV})/\text{EDV} \times 100$.

The heart rate (in bpm) was obtained by calculating the reciprocal of the mean of five consecutive RR-intervals on the electrocardiogram multiplied by 60. We estimated the mean aortic velocity time integral (VTI) by averaging the outer edge tracings of five consecutive continuous-wave Doppler recordings of the LV outflow tract velocity. By taking the product of VTI and the mid-systolic cross-sectional area at the level of the LV outflow tract in the parasternal long-axis view, we obtained stroke volume (SV, in mL). Cardiac output (CO, in L/min) was obtained by multiplying SV by heart rate. Total peripheral vascular resistance (TPVR in dynes × s/cm^5) was obtained using the formula $\text{TPVR} = 80 \times \text{MAP (in mmHg)})/\text{CO}$.

Outcome measures

The subclinical stages of HF were diagnosed according to the American Heart Association[11]. HF Stage A (HF-A) was defined as the presence of at least one risk factor for HF, including hypertension, atherosclerotic disease, diabetes, obesity, metabolic syndrome, use of cardiotoxins or a family history of cardiomyopathy[11]. HF-B was defined as the presence of previous myocardial infarction, LV concentric remodeling, LV hypertrophy, loss of systolic function or asymptomatic valvular disease[17]. LV remodeling was defined according to ASE guidelines[17] (LV hypertrophy: LVMi > 95 g/m^2; concentric remodeling: RWT > 0.42 and LVMi < 95 g/m^2; or mildly impaired systolic function (EF $< 55\%$)). To define low or preserved EF in this subclinical stage, we used the cut-off value of mildly abnormal EF based on the ASE guidelines[11]; HF-B with preserved EF was defined as HF-B with EF $\geq 55\%$. We defined asymptomatic valvular disease as mild aortic valve insufficiency, mild thickening of mitral valve or central aortic valve insufficiency.

Statistical analysis

Data were analyzed using SPSS version 21 (IBM Corp., Armonk, NY, USA). To analyze differences between women with a history of PE and controls, we used the chi-square for categorical data if there were five or more cases and Fisher's exact test if there were fewer than five cases present in any of the subgroups. We used the independent *t*-test for normally distributed continuous variables and presented data as mean with SD. A two-sided *P*-value < 0.05 was considered statistically significant.

To study the association between metabolic and CV variables with HF-B in the whole population, we used univariate regression analysis to calculate odds ratios (OR). An event was defined as HF-B *vs* no HF-B. To adjust the association of PE with HF-B for possible confounders, we used multivariate analysis and corrected for factors that are known to be significantly associated with HF-B or that were found to be in the univariate analysis. To avoid colinearity we used only one variable if two variables measured the same parameter. We then used univariate regression analysis to test the association of several risk factors with the development of HF-B within the group of former PE patients. A sample-size analysis was performed based on previous findings by Melchiorre *et al.*[10] on the prevalence of altered cardiac geometry 1 year postpartum in former PE patients (28%) compared with controls (6%). The required sample size was calculated with a desired power of 0.95 and a two-sided α-value of 0.05 and it was found that a sample size of at least 34 participants in each group was necessary to detect a significant difference.

RESULTS

In total, 148 women were included in our study, 107 with a history of PE and 41 controls (Figure 1). Baseline characteristics of the PE and control groups are given in Table 1. The PE group was 4 years younger, on average, and had their postpartum measurement 3 years earlier than did the control group. BMI, fasting insulin, HOMA_{IR} and SBP, MAP and heart rate were higher and HDL was lower in formerly pre-eclamptic women compared with controls. Moreover, metabolic syndrome was present in 8% of the PE group and in none of the controls, and hypertension was more prevalent in the PE group (23%) compared with controls (2%).

HF-A and HF-B were both more prevalent in the PE group compared with the control group (Table 2 and Figure 1): 23% *vs* 2% ($P < 0.01$) and 25% *vs* 7% ($P < 0.05$), respectively. Most cases of HF-B had preserved ejection fraction (21/27; 78%). Moreover, if HF-B was diagnosed, it was usually accompanied by concentric remodeling in the former PE group (18/27; 67%) *vs* in one of three (33%) controls. Three women in the former PE group had valve alterations compared with none in the control group. We did not detect previous

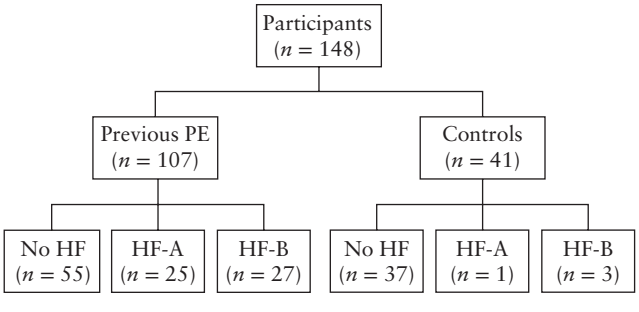

Figure 1 Flowchart summarizing study group of formerly pre-eclamptic women and controls, with respect to classification of heart failure Stage A (HF-A) or B (HF-B). PE, pre-eclampsia.

Table 1 Baseline characteristics 4–10 years postpartum and obstetric history of 107 formerly pre-eclamptic women and 41 controls

Baseline characteristic	*Formerly pre-eclamptic (n = 107)*	*Controls (n = 41)*	P
Patient and obstetric characteristics			
Age (years)	36 ± 4	40 ± 4	< 0.001
Weight (kg)	73 ± 18	68 ± 12	0.10
Smoker	8 (7)	5 (12)	0.36
Family history of CVD	45 (43)	16 (39)	0.85
Postpartum interval (years)	4.8 (4.0–6.3)	7.8 (6.3–9.9)	< 0.001
GA at birth (weeks)	34 ± 4	40 ± 2	< 0.001
Birth weight (g)	1836 ± 950	3344 ± 592	< 0.001
SGA (< 5th centile)	27 (25)	3 (7)	< 0.05
IUFD	9 (8)	0 (0)	NA
Metabolic syndrome	10 (8)	0 (0)	NA
BMI (kg/m^2)	26 ± 6	23 ± 3	< 0.05
Fasting glucose (mmol/L)	4.8 (4.4–5.0)	4.7 (4.5–5.0)	0.76
Fasting insulin (mU/L)	8.0 (5.6–10.6)	6.3 (4.3–7.8)	< 0.01
$HOMA_{IR}$	1.7 (1.2–2.4)	1.4 (0.9–1.7)	< 0.01
HDL (mmol/L)	1.3 ± 0.2	1.6 ± 0.3	< 0.01
LDL (mmol/L)	2.9 ± 0.6	2.9 ± 0.7	0.90
Triglycerides (mmol/L)	0.9 ± 0.4	0.9 ± 0.4	0.58
Total cholesterol (mmol/L)	4.6 ± 0.7	4.9 ± 0.7	0.05
Albumin:creatinine ratio (g/mol)	0.7 (0.3–1.4)	0.5 (0.4–0.8)	0.54
Hemodynamics			
SBP (mmHg)	117 ± 13	109 ± 11	< 0.01
DBP (mmHg)	74 ± 10	71 ± 8	0.18
MAP (mmHg)	86 ± 10	82 ± 9	< 0.02
Heart rate (bpm)	67 ± 11	61 ± 10	< 0.01
TPVR (dynes × s/cm^5)	1372 ± 299	1415 ± 441	0.50
Prehypertension	23 (21)	8 (20)	0.38
Diabetes mellitus	1 (1)	0 (0)	NA
Hypertension	25 (23)	1 (2)	< 0.01

Data are presented as mean ± SD, *n* (%) or median (interquartile range). BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; GA, gestational age; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostatic model assessment index for insulin resistance; IUFD, intrauterine fetal death; LDL, low-density lipoprotein; MAP, mean arterial pressure; NA, not applicable; SBP, systolic blood pressure; SGA, small-for-gestational-age neonate; TPVR, total peripheral vascular resistance.

myocardial infarction in either group. Moreover, the absolute values of LVMi, RWT, IVST, PWT and LVEDd, LVEDV, CO and EF were not different between the groups, although SV was higher in the former PE group compared with the control group ($P = 0.03$).

Table 3 presents the obstetric, cardiometabolic and CV risk factors in relation to HF-B in the studied population of formerly pre-eclamptic women and control group combined. PE in general was associated with HF-B, with an OR of 4.3 (95% CI 1.2–15.0), as were both early-onset and preterm PE. Of the metabolic syndrome variables, only HDL was associated (inversely) with HF-B; BMI, fasting insulin, glucose, low-density lipoprotein, triglycerides, total cholesterol and albumin:creatinine ratio were not. Heart rate and TPVR were also not associated with HF-B, while SBP and DBP were both significantly associated with HF-B (OR, 1.2 (95% CI, 1.0–1.4) and 1.2 (95% CI, 1.0–1.5), respectively, per 5 mmHg increase), as was prehypertension (OR, 5.1 (95% CI, 1.9–13.6)). In the multivariate analysis, we calculated the adjusted OR (aOR) of PE, postpartum interval, HDL and hypertension for HF-B. PE remained as the only independent variable significantly associated with HF-B (aOR, 4.4 (95% CI, 1.0–19.1)).

In the 107 women in the PE group, variables that may increase the risk for HF-B after PE were analyzed (Table 4). Neither age, smoking or a family history of CVD, nor any of the constituents of metabolic syndrome, were significantly associated with HF-B. Among the 27 women with previous PE and HF-B, eight (30%) had hypertension, of whom five (62%) were using antihypertensive medication, including beta-blockers ($n = 2$), angiotensin-converting-enzyme (ACE) inhibitors ($n = 1$), calcium antagonists ($n = 1$) and centrally acting antihypertensive medication ($n = 1$). Among the 80 women with previous PE but no HF-B, 17 (21%) had hypertension, of whom 15 (88%) were using antihypertensive medication, including beta-blockers ($n = 4$), ACE inhibitors ($n = 2$), angiotensin receptor blocker ($n = 6$), calcium antagonists ($n = 2$) and diuretics ($n = 1$). Hypertension did not seem to be associated with HF-B. However, prehypertension was significantly associated with HF-B (occurring in 37% of formerly pre-eclamptic women with HF-B *vs* 16% in those without HF-B ($P < 0.01$) (OR, 4.3 (95% CI, 1.4–12.7)). There was no significant difference between subgroups with respect to a history of early-onset PE, preterm PE or recurrent PE.

Table 2 Prevalence of heart failure Stages A (HF-A) and B (HF-B) and indicators of cardiac function 4–10 years postpartum in 107 formerly pre-eclamptic women and 41 controls

Parameter	*Formerly pre-eclamptic (n = 107)*	*Controls (n = 41)*	P
HF-A	25 (23)	1 (2)	< 0.01
HF-B	27 (25)	3 (7)	< 0.05
Mildly impaired EF	6 (6)	2 (5)	1.00
HFpEF	21 (20)	1 (2)	< 0.01
Concentric remodeling	18 (17)	1 (2)	< 0.05
LVMi > 95 g/m^2	1 (1)	0 (0)	NA
Previous MI	0 (0)	0 (0)	NA
Valve disease	3 (3)	0 (0)	NA
LVMi (g/m^2)	60 ± 13	62 ± 12	0.37
RWT	0.35 ± 0.07	0.33 ± 0.05	0.10
IVST (cm)	0.76 ± 0.16	0.74 ± 0.09	0.47
PWT (cm)	0.78 ± 0.14	0.76 ± 0.11	0.37
LVEDd (cm)	4.5 ± 0.4	4.6 ± 0.4	0.10
LVEDV (mL)	94 ± 23	89 ± 22	0.22
CO (L/min)	5.2 ± 1.1	4.9 ± 1.2	0.20
SV (mL)	81 ± 16	75 ± 17	0.03
EF (%)	63 ± 6	63 ± 6	0.60

Data are presented as *n* (%) or mean ± SD. CO, cardiac output; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; IVST, interventricular septal thickness; LVEDd, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVMi, left ventricular mass index; MI, myocardial infarction; NA, not applicable; PE, pre-eclampsia; PWT, posterior wall thickness; RWT, relative wall thickness; SV, stroke volume.

Table 3 Odds ratios (OR) of obstetric history and cardiovascular and cardiometabolic factors for heart failure Stage B (HF-B) *vs* no HF-B in entire study population of 107 formerly pre-eclamptic women and 41 controls

Parameter	*OR (95% CI) or aOR (95% CI)**
Patient and obstetric characteristics	
Age	0.9 (0.9–1.0)
Smoker	1.9 (0.5–6.5)
Family history of CVD	0.7 (0.3–1.5)
Pre-eclampsia	4.3 (1.2–15.0)†
Early-onset pre-eclampsia	4.7 (1.3–17.1)†
Preterm pre-eclampsia	3.9 (1.1–14.0)†
Recurrent pre-eclampsia	2.0 (0.7–5.2)
Postpartum interval (years)	1.0 (0.9–1.1)
Metabolic syndrome	2.9 (0.7–10.8)
BMI	1.1 (1.0–1.1)
Fasting glucose (mmol/L)	1.2 (0.6–2.6)
Fasting insulin (mU/L)	1.1 (1.0–1.2)
$HOMA_{IR}$	1.3 (0.9–1.8)
HDL (mmol/L)	0.2 (0.0–0.9)†
LDL (mmol/L)	1.1 (0.6–2.1)
Triglycerides (mmol/L)	1.3 (0.5–3.6)
Total cholesterol	1.0 (0.5–1.7)
Albumin:creatinine ratio	1.0 (0.8–1.2)
Hemodynamics	
SBP (per 5 mmHg increase)	1.2 (1.0–1.4)†
DBP (per 5 mmHg increase)	1.2 (1.0–1.5)†
Heart rate (bpm)	1.0 (0.9–1.1)
TPVR (per 200 dynes × s/cm^5)	1.1 (0.8–1.3)
Prehypertension	5.1 (1.9–13.6)†
Hypertension	2.1 (0.8–5.5)
Multivariate analyses	
Pre-eclampsia	4.4 (1.0–19.1)†
Postpartum interval (years)	1.1 (0.6–1.2)
Hypertension (*n* (%))	1.5 (0.6–4.0)
HDL (mmol/L)	0.4 (0.7–2.5)

*Adjusted OR (aOR) for multivariate analyses. †$P < 0.05$. BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostasis model assessment index for insulin resistance; LDL, low-density lipoprotein; SBP, systolic blood pressure; TPVR, total peripheral vascular resistance.

DISCUSSION

In this cross-sectional cohort study, we found that PE was associated independently with a four-fold increased risk for HF-B. Moreover, in formerly pre-eclamptic women, prehypertension was associated with a four-fold increase in the risk for HF-B, while other constitutions of metabolic syndrome were not.

Our findings are in line with those of Melchiorre *et al.*[10], who showed a high prevalence of HF-B up to 1 year after PE. Our study is distinct from earlier studies in its extended postpartum interval (4–10 years) and by the additional statistical correction for other known relevant CV risk factors. It seems that the high prevalence of concentric remodeling and decreased EF after PE is not merely part of a transitional stage of recovering from cardiac remodeling during pregnancy; these factors are also highly prevalent in the remote postpartum years.

Despite advances in the diagnosis and treatment of HF, the number of women dying from this progressive disease increases annually[19]. The progression from the preclinical HF-B to the clinical HF-C is associated with a five-fold increase in related mortality[12,20], decrease in quality-adjusted life years and higher healthcare costs[20]. Early detection, accompanying tailored intervention, of women with HF-B may decrease progression to HF-C, thereby improving clinical outcome and decreasing related mortality[12,20].

This presents clinicians with a challenge. First, HF-B is an asymptomatic stage which does not lead patients to seek medical care. Second, the overall prevalence of HF-B in middle-aged women in the general population is low, so screening programs for the entire female population would probably not be cost-effective; there is a clear need to identify high-risk subpopulations. The clinical impact of our results is potentially substantial, having confirmed the presence of a well-defined former pre-eclamptic population that is at a four-fold increased risk for HF-B compared with the general female population of the same age, especially since progression to the clinical stages of HF is preventable with relatively low-cost intervention, such as administration of easily available medication and life-style adaptation[12].

Interestingly, unlike hypertension, prehypertension increased the risk for HF-B four-fold within the formerly pre-eclamptic group. Prehypertension is known to predispose to later clinical hypertension and is also associated with CV morbidity[21]. Formerly pre-eclamptic women may have higher values of LVM or RWT that may

Table 4 Univariate analysis of obstetric history and metabolic syndrome constituents in 27 formerly pre-eclamptic patients who had heart failure Stage B (HF-B) *vs* those with no HF-B

	HF-B (n = 27)	*No HF-B (n = 80)*	*OR (95% CI)*
Patient and obstetric characteristics			
Age (years)	36 ± 5	36 ± 4	1.0 (0.9–1.1)
Smoker	3 (11)	5 (6)	1.9 (0.4–8.4)
Family history of CVD	9 (33)	36 (45)	0.6 (0.3–1.5)
Early-onset PE	19 (70)	51 (64)	1.4 (0.5–3.5)
Preterm PE	20 (74)	63 (79)	0.8 (0.3–2.2)
Recurrent PE	9 (33)	16 (20)	2.0 (0.7–5.2)
Postpartum interval (years)	4.6 (3.9–5.7)	5.8 (4.3–7.1)	1.2 (1.0–1.4)
Metabolic syndrome	4 (15)	6 (8)	2.1 (0.5–8.2)
Obesity	8 (30)	11 (14)	2.6 (0.9–7.5)
Insulin resistance	11 (41)	32 (40)	1.0 (0.4–2.5)
Dyslipidemia	1 (4)	7 (9)	1.0 (0.6–1.6)
Microalbuminuria	5 (19)	12 (15)	1.3 (0.4–4.1)
Hemodynamics			
Prehypertension	10 (37)	13 (16)	4.3 (1.4–12.7)*
Hypertension	8 (30)	17 (21)	1.6 (0.6–4.4)

Data are presented as mean ± SD, *n* (%) or median (interquartile range). *$P < 0.05$. CVD, cardiovascular disease; OR, odds ratio; PE, pre-eclampsia.

be jeopardized by a mildly increased BP. Previous studies showed that prehypertension accelerates the development of LV hypertrophy and cardiac diastolic dysfunction[21,22]. However, although hypertension is known to be a major risk factor for HF[19,23,24], it did not contribute to the development of HF-B in our study. A possible explanation is that women diagnosed with hypertension are already undergoing treatment with antihypertensive medication, and certain medication (mainly ACE inhibitors and beta-blockers) is known to have a protective and inhibitory effect on adverse cardiac remodeling[11]. We speculate that, in women who have had PE, treatment of prehypertension with BP-lowering medication intervenes in the progressive increase in LVMi and RWT, inhibiting aberrant cardiac remodeling and eventually resulting in a decreased prevalence of HF. However, whether this secondary prevention may result in decreased prevalence of clinical overt HF remains to be elucidated.

In our cohort of seemingly healthy young women, among the components of metabolic syndrome, only low HDL concentration was associated with subclinical HF-B. That we found, in contrast to the findings of previous studies, no other metabolic syndrome variable to be associated with HF-B, may be related to differences in age between our study population and that of previously studied populations and to differences in the HF stages or different phenotypes of HF[25,26].

Phenotypic presentation of HF is currently classified according to whether the EF is reduced (HFrEF) or preserved (HFpEF)[27–29]. Although this terminology is applied to symptomatic HF, specifying different subclinical phenotypes within the HF spectrum may theoretically allow initial stratification prior to clinical diagnosis and enhance preventative clinical approaches to HF. In our population, 78% of the formerly pre-eclamptic women with HF-B presented with preserved EF indicating diastolic rather than systolic loss.

The strength of this study is the prolonged interval after birth, sufficient to allow the assumption that any pregnancy-induced alterations to cardiac structure and function have dissipated. As such, both the effect of pregnancy outcome and underlying risk factors could be weighted reliably. Moreover, this comprehensive long-term study allowed correction for many possible confounders that may affect the development of HF. However, this study also has certain limitations. First, most women who participated in this study were white and of northern European ancestry. Therefore, our findings may not be applicable to other populations. Second, there were some differences in baseline characteristics between controls and cases. However, we corrected for these differences in the multivariate analyses, minimizing the possible confounding effect. Third, the control group was recruited by advertisement, in contrast to the formerly pre-eclamptic group, for which recruitment was hospital-based. The women responding to an advertisement for a CV check may perhaps have a predisposition for CVD, making them question their CV risk. If this is the case, the prevalence of HF-B in the control group may be an overestimation; however, it would still, presumably, be much lower than in our formerly pre-eclamptic group. On the other hand, it is also likely that open advertisement might attract healthier participants than the general population. Another limitation is that SV and CO were derived with continuous-wave Doppler rather than pulsed-wave Doppler. This mode overestimates SV and CO, giving lower values of TPVR compared with those obtained using pulsed-wave Doppler.

Finally, HF-B is a heterogeneous collection of phenotypes; it is unlikely that similar mechanisms can explain each to the same extent. Assessing associations within this group as a whole may overestimate or underestimate relationships based on one component. Therefore, future studies with larger numbers are needed in order to study the associations of different risk factors with different phenotypes of HF-B.

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