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Novel cardiovascular biomarkers in women with a history of early preeclampsia

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ABSTRACT

Objective: Women with a history of preeclampsia are at increased risk for future cardiovascular disease. Determination of cardiovascular biomarkers may be useful to understand the pathophysiological mechanism of cardiovascular disease development in these women.
Methods: We performed an analysis in the Preeclampsia Risk EValuation in FEMales study, a retrospective cohort consisting of 339 women with a history of early preeclampsia and 332 women after normotensive pregnancy. Women attended a follow-up visit ten years after the index pregnancy.
A subset of 8 different cardiovascular biomarkers was investigated, reflecting inflammatory, metabolic, thrombotic and endothelial function markers. Associations between PE and these novel biomarkers were analyzed by linear regression analysis and adjusted for traditional cardiovascular risk factors.
Results: Mean age of 671 women of the PREVFEM cohort was 39 years and women were on average 10 years post index pregnancy. Women post preeclampsia had significantly higher levels of SE-selectin (adjusted difference 4.55, 99%CI 0.37; 8.74) and PAPPA (adjusted difference 19.08; 99%CI 13.18; 24.99), whereas ApoB (adjusted difference −0.23 99%CI −0.32; −0.14) was inversely associated with preeclampsia, compared to women with a previous normotensive pregnancy. Adiponectin, leptin, sICAM-1, sVCAM-1 and PAI-1 were not different between both groups.
Conclusion: We demonstrated an independent association of preeclampsia with SE-selectin and PAPPA (markers of vascular dysfunction), which may contribute to future cardiovascular events in women post preeclampsia. However, ApoB (an apolipoprotein) was significantly lower and could point at a protective mechanism in our PE study women.

1. Introduction

Hypertensive pregnancy disorders (HPD), like gestational hypertension (GH) and preeclampsia (PE), occur in about 10% of pregnancies [1,2]. These syndromes have important consequences for maternal health during pregnancy and the postpartum period, but also for future cardiovascular disease (CVD) risk [3–5]. Dependent on the type of HPD, the risk of future CVD is 1.4–3.0 times higher in women with a history of HPD compared to women with previous normotensive pregnancies [6]. The severity and timing of HPD importantly determines the impact of long-term CVD risk, with early PE as one of the most hazardous conditions [3,7]. The increased CVD risk in women with a history of PE can be partly explained by the increased prevalence of traditional CVD risk factors like hypertension, hypercholesterolemia and the metabolic syndrome (MetS) [8–10]. Although the underlying pathophysiological mechanism of the increased prevalence of cardiovascular risk factors in these women is not completely understood, endothelial dysfunction seems to play an important role, although evidence is not consistent [11,12]. Novel genetic evidence indicates potentially shared mechanisms of both preeclampsia and CVD, in particular for oxidative stress and inflammation [13].

In the last decade(s) several novel biomarkers associated with CVD have been identified [14,15]. Some of these biomarkers, like cytokines (e.g. interleukins); angiogenic factors (endoglin); cell

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adhesion molecules (soluble fms-like tyrosine kinase 1) and coagulation factors (plasminogen activator inhibitor, PAI-1), are upregulated during preeclamptic pregnancies [16–18]. Data of these novel biomarkers in young women with a history of preeclampsia may unravel the pathophysiological mechanisms of the increased CVD risk in these women. However, study data on biomarkers in this subset of women are not consistent. Sattar et al. found increased levels of intercellular adhesion molecule (ICAM) in women post PE, however no differences in lipids, vascular cellular adhesion molecule (VCAM), E-selectin and leptin were reported [11]. In the study of Girouard et al. it was shown that women with a history of PE and GH, have significant differences in lipid profile and several miscellaneous markers (TNF-α, Interleukine-6, leptin, adiponectin and homocysteine) at 8 years post index pregnancy compared with control subjects [19]. Wolf et al. demonstrated increased levels of soluble fms-like tyrosine kinase and insulin resistance in women after PE compared to women with normotensive pregnancies within 18 months postpartum [20]. However, several other studies did not find any differences in biomarker profiles between women with and without a history of HPD [21–23].

In this retrospective cohort study we measured levels of various novel cardiovascular biomarkers in women with and without prior preeclampsia and adjusted the associations for traditional cardiovascular risk markers. Of the many available biomarkers we selected apolipoprotein B (ApoB), a lipid-associated marker, and leptin and adiponectin as cardiometabolic risk markers. We also studied the following endothelial function markers: soluble intercellular adhesion molecule (sICAM-1), soluble vascular adhesion molecule (sVCAM-1), soluble endothelial selectin (SE selectin), and a thrombotic marker, plasminogen activator inhibitor (PAI-1). Next to this we evaluated pregnancy associated plasma protein A (PAPPA), a metalloproteinase, which is associated with vulnerable atherosclerotic plaques [24].

2. Methods

2.1. Population

Since 1991 the obstetric Department of the Isala Klinieken in Zwolle, The Netherlands, register all in-hospital deliveries. We invited consecutively all women registered as having had early-onset preeclampsia, $n = 528$, in the time-period (1991–2007) to participate in the Preeclampsia Risk EValuation in FEMales (PREVFEM) cohort-study. For the reference group we invited an equal number of age-matched females with a non-hypertensive, uncomplicated, pregnancy during the same period. They were selected from the obstetric database after selection based on age and date of delivery, aiming for an equal distribution of these two variables (range ± 2yrs) [10].

The study was initiated to evaluate the presence of cardiovascular risk factors in young women at 10 years post pregnancy complicated by early-onset PE. This was defined as an elevated diastolic blood pressure ≥90 mmHg with proteinuria (≥0.3 g/24 h) between 20 and 32 weeks of gestation. Approval for the study was obtained from the institutional review board of the Isala Klinieken in Zwolle. Participants were included in the study after signing an informed consent form and were invited for a cardiovascular screening program at the department of cardiology. The protocol, definitions of cardiovascular risk factors and baseline data have been described extensively elsewhere [10].

2.2. Biomarker analysis

At the scheduled screening visit an overnight fasting venous blood sample was taken. Blood lipid profile, glucose, CRP and fibrinogen were locally analyzed and the results have been described previously [10]. CRP values > 20 mg/L were excluded to prevent interference of high outliers (mostly of infectious origin) in our analysis.

Assessment of all novel biomarkers was performed at the laboratory of experimental medicine, at the department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands. All markers were analysed with a Luminex assay, a multianalyte technology, based on the principles of flow cytometry [25]. As a consequence of use of a multi-assay kit some samples were out of the detection range, for sICAM-1 the lower detection level was 8 ng/ml ($n = 1$ out of range), for PAPPA the lower limit was 0.69 ng/ml ($n = 28$) and for leptin the lower limit was 0.8 ng/ml ($n = 2$). These values were fixed at the lower detection level.

2.3. Data analysis

Baseline characteristics were expressed as mean (SD) or number (percentage). Differences in variables between women with and without PE for continuous data were analysed by student *T*-test for independent groups and for categorical data with Chi-square or Fisher exact test. Univariate analysis was performed with a two-sided probability value of <0.05.

Biomarker levels were expressed as continuous variables, median with 25 and 75 percentiles, as these variables were not normally distributed. Association between PE and biomarkers was analysed using linear regression analysis and stepwise adjusted according to 4 different models. Model 1 adjusted for age; model 2 for age, years postpartum and smoking; model 3 included the variables of model 2 and presence of hypertension and in model 4 we added the presence of MetS (dichotomous) to the aforementioned variables. Data were expressed as the differences (β) in biomarkers of women with a history of PE compared to the reference women, with 99% confidence interval (99%CI). All *p*-values were two-sided.

As levels of the different biomarkers were not normally distributed (according to the Kolmogorov–Smirnov test), we additionally performed a natural log transformation on the biomarkers and repeated the regression analysis. As the results of these natural log transformed analysis did not differ from the original analysis, we prefer to present the original untransformed data to facilitate interpretation of our data in clinical use.

Data analyses were performed with SPSS software version16.0.

3. Results

A total number of 671 women were included in the PREVFEM-study, 339 in the early-onset PE group and 332 in the reference group. In- and exclusion criteria of our study are demonstrated in Fig. 1 [10]. Mean age of participants in the cohort was 39 years and women were on average 10 years post index-pregnancy. Baseline characteristics of the PREVFEM-cohort have been described elsewhere [10]. Hypertension was more prevalent in women post PE (43%) than in reference women (17%), as was the MetS (18% in PE women versus 9% in reference women). Prevalence of diabetes mellitus, levels of different lipid markers and levels of the inflammatory markers (CRP and fibrinogen) were not different between both groups (Table 1) [10].

Blood samples for biomarker analysis were unavailable for 3 women in the reference group, as a consequence these women were not included in the biomarker analysis. Table 2 shows median