OBSTETRICS

Cardiovascular and thrombogenic risk of decidual vasculopathy in preeclampsia

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OBJECTIVE: Women with a history of preeclampsia (PE) have an increased prevalence of cardiometabolic, cardiovascular, and prothrombotic risk factors. Remotely, these women are at increased risk of developing cardiovascular and thrombotic disease. Decidual vasculopathy (DV) describes vascular lesions in the maternal spiral arteries of the uterus, which are found in approximately 40-60% of women with PE. DV is thought to be related to atherosclerosis because of their morphological similarity. The aim of this study was to investigate the association of cardiovascular and thrombogenic risk factors with DV in women with a history of PE.

STUDY DESIGN: We retrospectively analyzed the cardiovascular and thrombogenic risk of women with a history of PE, comparing cases with DV (n = 95) with cases without the lesions (n = 81) 7 months after the index pregnancy. Data from a cohort of patients with a history of PE were matched with records from our pathology database.

RESULTS: The DV group showed higher diastolic blood pressure (73 vs 70 mm Hg, $P = .031$), lower left ventricular stroke volume (71 vs 76 mL, $P = .032$), higher total peripheral vascular resistance (1546 vs 1385, $P = .009$), and a higher percentage of low plasma volume (34% vs 19%, $P = .030$). DV did not relate to other cardiovascular parameters, urinary protein, body mass index, lipid or glucose metabolism parameters, or thrombophilia.

CONCLUSION: In this study, in women with a history of PE, cases with DV had increased cardiovascular risk, exhibiting circulatory alterations, suggesting reduced venous reserves and elevated arterial tone, without metabolic or thrombophilic disturbances.

Key words: acute atherosis, cardiovascular risk, decidual vasculopathy, preeclampsia

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Preeclampsia (PE) is a major health problem worldwide.[1] It affects 5-8% of all pregnancies and is responsible for approximately 50,000 maternal deaths annualy.[1] PE is defined as new-onset hypertension and the development of proteinuria after 20 weeks' gestational age.[2] The delivery of the placenta is the only known cure of this disorder.[3]

Women with a history of PE have an increased risk of developing venous thrombosis and cardiovascular disease in later life.[4-6] Atherosclerosis and PE share many cardiovascular risk factors, such as endothelial dysfunction, hypertension, obesity, insulin resistance, hyperglycemia, hyperlipidemia, and hypercoagulation (thrombophilia). Many studies have observed significantly elevated hypertension parameters,[7-10] low plasma volume,[9] cardiac dysfunction,[11] dyslipidemia,[9-12] and elevated body mass index[10,13] several years postpartum in women with a history of PE, compared with normotensive controls. Glucose metabolism parameters of insulin[9,14] and homeostasis model assessment of insulin resistance (HOMA-IR)[14] are also elevated in women with a history of PE. Additionally, thrombophilia could be associated with a higher relative risk to develop PE.[15]

Decidual vasculopathy (DV) is a type of vascular lesion in the maternal spiral arteries of the uterus, observed in approximately 40-60% of women with PE.[16,17] The lesions are characterized by the presence of lipid-filled foam cells and vascular fibrinoid necrosis within the vascular wall as well as perivascular infiltration of inflammatory cells.[18] Although nonphysiological remodeling is widely considered the hallmark of PE, the fact that DV is found in a proportion of patients with PE suggests a possible association with a specific subset of patients with the disease.

This is in line with the current tendency to view PE as a heterogenous disease or syndrome, such as maternal and placental PE, although these separate entities are not yet entirely defined. Because of the morphological similarity of the foam cell lesions of DV to atherosclerosis, these lesions are also

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named acute atherosis, although the latter term has also been used to describe the lipid-filled macrophages specifically, with DV, or decidual arteriopathy, being more recent, general terms for spiral artery pathology.[19] It has been suggested that DV and atherosclerosis might have a similar etiological basis.[20] It is unclear whether DV in PE relates to a higher cardiovascular risk in later life.

The aim of this study was to investigate cardiometabolic, cardiovascular, and prothrombotic risk factors in formerly preeclamptic women with and without concomitant DV. We hypothesize that in women with a history of PE, cases with DV will have elevated cardiometabolic, cardiovascular, and prothrombotic risk factors after the index pregnancy, compared with cases without DV.

Materials and Methods

Cardiovascular risk data were obtained between 2004 and 2010 from a retrospective cohort of patients with a history of PE, which was previously approved by the Medical Ethics Committee of the Radboud university medical center on Oct. 25, 2007. Data from the cohort were matched with records from the pathology database at the Radboud university medical center. PE was diagnosed according to established criteria.[2]

Cases were included only if estimated cardiovascular risk measurements and histological placental analysis were performed following the index pregnancy. One hundred ninety-nine women were initially included. Diagnosis of PE of all patients was verified. Women with incomplete records, incomplete placental samples, and multiple pregnancy were excluded (n = 23).

Histological samples

Placental samples (n = 176) had been examined macroscopically and microscopically by experienced pathologists and analyzed according to standard hospital protocol for PE. Placenta samples had been included of 2 or more membrane rolls, the central and peripheral part of the placenta, and macroscopic abnormalities. The percentage of unmodified spiral arteries exhibiting DV changes was not assessed in the study because this requires a different setup with more extensive histological examination of placental basal plate. DV was defined as vascular fibrinoid necrosis and lipid-filled foam cells in the vascular wall of spiral arteries in either the decidua basalis or parietalis (Figures 1 and 2).

Considering the initial analysis was not specifically targeted at DV and not all reports specifically described the presence or absence of the lesions, the research team reanalyzed all placenta specimens to reevaluate the presence of DV. Mismatches (n = 52) were reevaluated a second time with an experienced pathologist (J.B.).

Cardiovascular and thrombogenic risk analysis

Cardiovascular and thrombogenic risk parameters analyzed were cardiovascular function (systolic blood pressure, diastolic blood pressure, mean blood pressure, heart rate, left ventricular stroke volume, left ventricular ejection fraction, mitral E/A ratio, left atrium diameter, total peripheral vascular resistance, uncorrected plasma volume, and abnormal plasma volume corrected for body surface area); proteinuria (total urinary protein per 24 hours); body mass index; glucose metabolism (glucose, insulin, or HOMA-IR); lipid metabolism (total cholesterol, low-density lipoprotein [LDL]-cholesterol, triglyceride and high-density lipoprotein [HDL]-cholesterol); and thrombophilia (low protein C, low protein S, prothrombin mutation, antithrombin deficiency, heterozygous or homozygous factor V Leiden mutation, or hyperhomocysteinemia).

The following protocol was used by the study for the screening procedure for assessing cardiovascular risk. At the time of the examinations, the researchers were unaware of the vasculopathy status of the patients. Additional details are described elsewhere.[9] Arterial blood pressure was recorded in a supine position at 3 minute intervals using a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, FL).

Echocardiography to assess cardiac function was performed in semileft lateral position after 5 minutes of rest, using a cross-sectional, phased-array echocardiographic Doppler system (General Electric Vivid 7; Horten, Norway). Mitral E/A ratio was obtained using pulsed-wave Doppler. Left ventricular ejection fraction was measured using the biplane Simpson's rule. Stroke volume was calculated by multiplying the left ventricular outflow tract velocity time integral and the left ventricular outflow tract. The average left ventricular outflow tract time velocity integral of 5 consecutive ejections was used. Left ventricular outflow tract diameter was measured from the parasternal long axis view using 2-dimensional echocardiography at midsystole. Left atrium diameter was measured at end systole. Total peripheral vascular resistance was calculated by 80 times mean arterial pressure divided by cardiac output (calculated as stroke volume × heart rate).

Plasma volume was measured using the iodine^{125}-human serum albumin indicator dilution method, as described elsewhere,[21] and normalized for body surface area (in milliliters per square meter). A plasma volume less than 1405 mL/m^2 was considered abnormal.

Body mass index was calculated using the following formula: weight in kilograms/(length in meters)^2. A 24-hour urine sample was assayed to calculate total protein level (grams per 24 hours) (Aeroset; Syva Company, San Jose, CA). The insulin resistance estimation was based on the HOMA-IR, using the following formula: (fasting serum insulin [milliunits per liter] × fasting plasma glucose [millimoles per liter])/22.5. Glucose, insulin, total cholesterol, HDL and LDL, and triglycerides were measured with standard automated laboratory techniques (Aeroset).

Factor V Leiden (F5 R506Q) and prothrombin (G20210A) mutation analyses were performed by routine polymerase chain reaction techniques. Plasma was assayed for protein C activity and free protein S and antithrombin activity. Plasma total homocysteine was measured by a high-performance liquid chromatography assay. Thrombophilia was defined as factor V Leiden mutation, prothrombin mutation, protein C activity less than 70%, free protein S less