OBSTETRICS

Preeclampsia in healthy women and endothelial dysfunction 10 years later

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OBJECTIVE: Recent studies have shown that women with a history of preeclampsia have an increased risk of cardiovascular disease. The present study investigated cardiovascular risk factors 10 years after preeclampsia in previously healthy women.

STUDY DESIGN: Based on data from the Medical Birth Registry in Norway, we selected 182 women with and 180 women without preeclampsia in their first pregnancy 9-11 years earlier, excluding women with cardiovascular or renal disease before pregnancy. Flow-mediated dilation of the brachial artery (FMD) and intima-media thickness (IMT) of the carotid artery were measured and blood samples were drawn. Blood samples were analyzed for cardiovascular risk markers and for circulating markers of endothelial function.

RESULTS: A total of 89 women with previous preeclampsia and 69 women without preeclampsia participated, an overall attendance rate of 44%. FMD and IMT were similar between groups. Women with previous preeclampsia more often had urate and soluble fms-like tyrosine kinase values above the 75th percentile (odds ratio [OR], 2.4; $P = .03$, and OR, 2.4; $P = .04$, respectively) and high-density lipoprotein cholesterol values below the 25th percentile (OR, 2.3; $P = .04$). Women with preeclampsia with low birthweight offspring were associated with asymmetric dimethylarginine, L-arginine, and homoarginine above the 75th percentile, whereas the women with preeclampsia with normal-weight offspring were associated with urate and soluble fms-like tyrosine kinase above the 75th percentile.

CONCLUSION: Preeclampsia was not associated with impaired FMD or increased IMT 10 years after pregnancy in previously healthy women, but preeclampsia was associated with changes in circulating markers that might represent early endothelial dysfunction.

Key words: asymmetric dimethylarginine, endothelial dysfunction, flow-mediated dilation of the brachial artery intima-media thickness, preeclampsia, urate

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Several studies have shown that preeclampsia is associated with an increased risk of later cardiovascular disease[1-5] and that women with previous preeclampsia have increased blood pressure, body mass index, insulin resistance, and endothelial dysfunction several years after their preeclamptic pregnancy, as compared with women without preeclampsia.[6-12]

Endothelial dysfunction is regarded as a central factor in the pathophysiology of preeclampsia,[13,14] and recent discoveries have elucidated the process of maternal endothelial damage, in which antiangiogenic factors produced by the placenta seem to play an important role.[15-17] Soluble fms-like tyrosine kinase (sFlt-1) and placental growth factor (PlGF) have been shown to be important, and probably causal, factors in the widespread endothelial dysfunction that accompany preeclampsia.[15,16] Other important factors involved may be urate, shown to be strongly associated with the development of preeclampsia and also a marker of cardiovascular risk,[18-20] and asymmetric dimethylarginine (ADMA),

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an endogenous inhibitor of the nitric oxide pathway and a promising novel cardiovascular risk marker.[21-23]

Endothelial dysfunction is also believed to be involved in the development and progression of atherosclerosis and kidney disease,[24,25] and endothelial dysfunction may be the unifying link between preeclampsia and later cardiovascular and renal disease.[26] Women with previous preeclampsia have been found to have manifestations of endothelial dysfunction several years after their preeclamptic pregnancy,[7,9,27] but several of the previous studies have investigated women with known underlying predisposing conditions and/or severe preeclampsia.[28-30]

In the present population-based study, we wanted to investigate whether preeclampsia in previously healthy women was associated with signs of endothelial dysfunction 10 years after the preeclamptic pregnancy. We chose a variety of markers of endothelial dysfunction, both functional (flow-mediated dilatation [FMD]) and structural measurements (intima-media thickness [IMT]) and different serum biomarkers related to preeclampsia, endothelial function, and inflammation. We also analyzed preeclampsia with and without low birthweight offspring separately because women with severe preeclampsia with low birthweight offspring may have a different pathogenesis than women with preeclampsia with normal-birthweight offspring. Our hypothesis was that preeclampsia would be associated with impaired FMD and increased IMT and with circulating markers of endothelial dysfunction.

Subjects and Methods

Registries

Medical data on all births in Norway are forwarded to the Medical Birth Registry of Norway by compulsory notification.[31] The notification form includes extensive data on the mother and the newborn and is completed by the attending midwife and doctor. The regional ethics committee approved the study.

Study design

The study design has been described in more detail in another paper.[32] We identified women living in the Bergen (Norway) area (population count approximately 325,000) with their first pregnancy in the years 1998-2000. Those diagnosed with diabetes, rheumatic disease, essential hypertension, or renal disease before first pregnancy and those with later preeclamptic pregnancies were excluded. From these, we invited women with and without preeclampsia in their first pregnancy, the latter matched on age, year of first birth, and municipality but otherwise randomly selected as a control group. The number of eligible women for inclusion was 182 in the preeclampsia group and 180 in the control group.

The women who agreed to participate were examined between December 2009 and October 2010. The participants were instructed to be overnight fasting and to abstain from hard exercise and high-fat foods 24 hours before examination, smoking, and intake of caffeine or any medication on the examination day. Women who were menstruating or had acute illness were rescheduled to a later appointment. On the examination day, a questionnaire was completed, body size was measured, and resting blood pressure was measured manually according to European Society of Hypertension—European Society of Cardiology guidelines.[33]

Vascular measurements

The women were examined in a quiet, temperature-controlled room, between 9:00 AM and 5:00 PM. Measurements of endothelial function by postocclusive FMD of the right brachial artery were done according to guidelines by the International Brachial Artery Reactivity Task Force.[34] The blood pressure cuff was placed on the forearm, and the brachial artery was imaged above the antecubital fossa in the longitudinal plane (identical sites of measurements were ensured using anatomical landmarks and pen marks). Images of the artery were recorded continuously for 5 minutes after cuff deflation. After 10 minutes of rest, a single dose (0.4 mg) of nitroglycerin spray was administered sublingually to determine endothelial-independent vasodilation. Measurements were done at the time of maximum dilation. All images were recorded in end diastole. For imaging, we used a GE Vingmed system (GE Vingmed, Vivid 7; GE, Horten, Norway) with a multiple linear array transducer (6-13 MHz).

The same ultrasound equipment was used for IMT measurements. The distal segment of the common carotid artery was identified, and 5 images were recorded on both sides. For the analysis of IMT, Vivid 7 Dimension '05 semi-automatic software for IMT analysis (GE Vingmed, Vivid 7) was used.

The FMD and IMT measurements were obtained by one trained physician (M.K.S.), and all image measurements and analyses were done in a blinded manner after data collection was concluded. Another trained physician (E.L.) also analyzed a random selection of subject measurements ($n = 20$), and the interobserver variability expressed as 1-way random intraclass correlation coefficient (ICC [1,1]) was 0.96 for baseline measurements and 0.78 for FMD. For IMT, the ICC (1,1) was 0.95.

Blood samples and biomarkers

Serum cholesterols (total/high-density lipoprotein [HDL]/low-density lipoprotein [LDL]), serum triglycerides, serum C-reactive protein (CRP), serum glucose, serum insulin, serum urate, blood hemoglobin A1C (HbA1C), and plasma fibrinogen were analyzed at Haukeland University Hospital laboratory. A semi—high-sensitive assay was used for quantification of CRP, with values specified between 1 and 5. Serum samples were frozen immediately after centrifugation (3000 rpm, 15 minutes) and aliquotation and stored at −80°C. These were later analyzed for soluble vascular cell adhesion molecule-1 (VCAM-1), sFlt-1, PlGF, vascular endothelial growth factor (VEGF), and tumor necrosis factor alpha (TNF-α) (high sensitive) using enzyme-linked immunosorbent assay kits (quantikine human immunoassays) from R&D Systems (Minneapolis, MN). ADMA, symmetric dimethylarginine, neopterin, L-arginine, and homoarginine were measured by BEVITAL AS (Bergen, Norway) in serum