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Subclinical signs of vascular damage relate to enhanced platelet responsiveness among nonpregnant formerly preeclamptic women

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Objective: In nonpregnant formerly preeclamptic women, the prevalence of occult cardiovascular abnormalities is increased. These high-risk women mildly benefit from low-dose aspirin in the prevention of recurrent disease. How this effect is mediated, either by affecting platelet or vascular function, is still unsettled. In this study, we tested the hypothesis that in these nonpregnant women, enhanced platelet responsiveness is common and related to microvascular damage.

Study design: At least 6 months' postpartum we evaluated in 66 formerly preeclamptic women platelet count, volume, and in vitro response to low-dose ADP (0.5 μg/mL). Peripheral levels of fibronectin (μg/mL), von Willebrand factor antigen (%), C-reactive protein (high-sensitive CRP, mg/L), urinary albumin, and protein (24-hour collection, g/mol creatinine) served as markers of vascular damage. Hemodynamic function was determined by plasma volume (iodine I 125 HSA indicator dilution method, mL/kg lean body mass), cardiac index (Doppler, mL/min/m^2), blood pressure and heart rate (Dinamap [Critikon, Tampa, FL], mm Hg and beats/min, respectively). Thereafter, we subdivided these 66 women into 2 subgroups either with (n = 10, 15%) or without increased platelet responsiveness (n = 56, 85%). Both groups were compared nonparametrically.

Results: Groups were comparable with respect to age, blood pressure, body mass index, parity, plasma volume, and cardiac index. Women with enhanced platelet responsiveness had higher levels of circulation fibronectin and CRP, and displayed more often albuminuria and proteinuria. In addition, even though platelet count was comparable between groups, the mean platelet volume was higher among women with enhanced platelet responsiveness.

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Conclusion: Fifteen percent of formerly preeclamptic women had enhanced platelet responsiveness, which was associated with elevated levels of various markers for (micro) vascular damage. We speculate that in these women platelets are presensitized on a relatively dysfunctional endothelium. Although this association does not prove causality, these results may indicate a subgroup of women who benefit from low-dose aspirin in the prevention of recurrent disease in a next pregnancy.

About 1 of 10 pregnancies are disturbed by hypertensive complications, disorders still accounting for considerable maternal and associated fetal morbidity and mortality.[1] Substantial evidence supports the hypothesis of pregnancy-related hypertensive disease being superimposed on a preexisting disorder.[2-4] Most of these underlying pathophysiologic phenotypes are either hypertensive (latent or present) or thrombophilic.[4] These disorders share the capacity to jeopardize endothelial and throphoblastic function, either mechanically or biochemically. Moreover, these prepregnant risk factors as determined in an interval between pregnancies relate to subsequent circulatory maladaptation and gestational vascular disorders such as preeclampsia and fetal growth restriction.[5-7]

Although thrombophilia relates to venous thromboembolism, part of the women at risk to develop preeclampsia exhibit platelet activation in both early pregnancy and before pregnancy.[9-11] Platelet activation, which may relate to arterial thrombosis, has been associated with a reduced plasma volume (PV), a condition giving rise to hemodynamic maladaptation and gestational hypertensive disease.[5-8,12] These observations support a role for activated platelets as a preexisting risk condition. Moreover, platelet activation has been associated with numerous other clinical syndromes, including chronic hypertension, myocardial infarction, and stroke, all of these remotely more frequently observed among formerly preeclamptic women.[12-15] In addition, it may also explain the modest role for aspirin in the prevention of gestational vascular complications in women at risk.[16,17] To date, how these effects are mediated, either by affecting platelet or vascular function, is still unsettled.

In this study, we tested the hypothesis that in formerly preeclamptic women, enhanced platelet responsiveness is common and related to microvascular damage. To this end, we evaluated at least 6 months' postpartum in formerly preeclamptic women platelet count and function in relation to the vascular and hemodynamic function. Thereafter, we subdivided these women into 2 subgroups either with or without increased platelet responsiveness.

Methods

Selection of patients

Sixty-six formerly preeclamptic women participated in this study. Data acquisition was initiated at least 6 months' postpartum. Formerly preeclamptic women were recruited from our outpatient clinic at the postpartum follow-up. Preeclampsia and (gestational) hypertension were defined according to the criteria of the National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy.[1] Quantification of the 24-hour urinary sodium output and creatinine of the day before the experiment was performed to estimate average sodium intake and endogenous creatinine clearance. All subjects were instructed to refrain from taking any vitamin supplements at least 2 months before the study. Some women were taking oral anticonceptives at the time of recruitment for this study. They all discontinued this medication at least 1 month before the study. Moreover, participants were instructed not to use nonsteroidal anti-inflammatory drugs in the weeks before measurement. After an overnight fast, participants were tested for hemodynamic and hemostatic function. Participants were requested to refrain from consuming caffeine- or alcohol-containing beverages for at least 10 hours before the experiment. All subjects were white. We excluded women from final analysis who had signs of rhinorrhea or a common cold. The hospital's medical-ethical committee approved the study.

Experimental procedure

Methods

Measurement of platelet-volume, function, and count

The measurement session started at 09:00 AM. During the measurements, subjects were placed in semirecumbent position. Tests were performed after a flawless venapuncture. Blood was collected in glass tubes containing sodium citrate. Platelet count and volume were measured by using a Coulter Gen S hematology cellanalyzer (Beckman Coulter, Fullerton, CA). For the in vitro studies on platelet aggregation, freshly drawn venous blood was collected in 3.2% buffered sodium citrate (1 part citrate and 9 parts blood). Platelet rich plasma (PRP) was obtained by centrifuging this blood for 10 minutes at 200*g* (22°C). For the preparation of platelet poor plasma (PPP), blood was centrifuged at 1600*g* for 10 minutes (22°C). For the aggregation studies, the platelet count of PRP was adjusted to 250,000/μL by dilution with autologous PPP. Platelet aggregation induced by ADP was performed at 37°C by using a