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RESEARCH LETTER

Association of Coronary Endothelial Function and Angiotensin Receptor Autoantibody With Preeclampsia Among Postpartum Women

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Preeclampsia is associated with a 2 to 4 times greater long-term cardiovascular disease (CVD)[1]; however, underlying biological mechanisms are poorly understood. During acute preeclampsia, immune-mediated alterations in angiogenesis and the renin–angiotensin system, mediated partly by circulating autoantibodies to angiotensin II receptor 1 (AT1R-Ab), may impair nitric oxide signaling and contribute to endothelial dysfunction during pregnancy.[1] However, postpartum understanding of these changes and their contribution to increased CVD risk is very limited. While peripheral endothelial function and coronary microvascular function were previously shown to be reduced in individuals with preeclampsia postpartum, to date nitric oxide–mediated coronary endothelial function has not been directly measured in preeclampsia.[2] Coronary endothelial dysfunction strongly predicts and can be targeted to reduce cardiovascular events.[3] We used noninvasive magnetic resonance imaging techniques to measure coronary endothelial function as change in coronary cross-sectional area and blood flow in response to isometric handgrip exercise, an endothelial-dependent stressor.[4] We hypothesized that women with preeclampsia have impaired coronary endothelial function postpartum and that the extent of dysfunction is related to elevated AT1R-Ab, reflecting heightened sensitivity to angiotensin II and oxidative stress.

This study was approved by the Johns Hopkins Institutional Review Board (IRB00219658) and participants provided written, informed consent. Women with and without preeclampsia between 3 and 6 months postpartum were recruited from Johns Hopkins outpatient clinics between 2020 and 2023. Preeclampsia was defined by physician diagnosis per the American College of Obstetrics and Gynecology guidelines. Exclusion criteria included known cardiac disease, pregestational/gestational diabetes, autoimmune disease, and multigestation pregnancies. Participants self-identified as women by gender. To ensure that the postpartum state was not influencing coronary function, we performed additional analyses with a second control group of non-postpartum premenopausal women, that is, no pregnancy in the preceding year, who were previously enrolled as part of a magnetic resonance imaging study.[4] Coronary magnetic resonance

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imaging protocol has previously been described and validated.[4] AT1R-Ab was measured using a novel antigen capture ELISA, previously studied by our group.[5] Data are available on request from the authors.

We used the χ^2 test or nonparametric Mann–Whitney *U* test as appropriate. Linear regression models, adjusted for age, body mass index, and resting systolic blood pressure, were used for the association of preeclampsia with percentage change in coronary cross-sectional area and blood flow. There were no significant differences in race and ethnicity, lipid levels, or smoking/alcohol history between groups, so these were not included in adjustment. We also performed linear regression of AT1R-Ab on percentage change in coronary cross-sectional area and blood flow. Analyses were performed with Stata version 16 (StataCorp, College Station, TX).

Women with preeclampsia (n=29) were 34±6 years old and 21±9 weeks postpartum at the study visit. A total of 34% identified as non-Hispanic Black individuals, and 21% had superimposed preeclampsia. Compared with postpartum controls (n=23), women with preeclampsia had higher systolic blood pressure (134±16 versus 119±16 mm Hg). They had greater impairment in both measures of coronary endothelial function compared with either control group (Figure [A] and [B]). Impairment in percentage change in coronary cross-sectional area (β=−12.2 [95% CI, −17.8 to −6.6]; *P*<0.001) and percentage change in coronary blood flow (β=−24.9 [95% CI, −42.3 to −7.5]; *P*=0.006) remained despite adjustment for potential confounders.

Women with preeclampsia also had higher levels of AT1R-Ab compared with postpartum control women (Figure [C]). AT1R-Ab was significantly inversely associated with stress-induced coronary blood flow change (β −4.2 [95% CI, −8.3 to −0.1]; *P*=0.043), and a trend was observed in inverse association with coronary cross-sectional area (β −1.4 [95% CI, −2.9 to 0.05]; *P*=0.059).

In summary, women with preeclampsia demonstrated both impaired macro- and microvascular coronary endothelial function. Macrovascular function, assessed by cross-sectional area, reflects epicardial (conduit) vessel function, prone to atherosclerosis. Coronary microvascular endothelial function, reflected by changes in blood flow with stress in the absence of obstructive CAD, reflects the response of smaller resistance vessels that regulate blood pressure and flow. Both are separate but synergistic determinants of future CVD, including ischemic heart disease and heart failure. Women with preeclampsia also had higher AT1R-Ab, and levels of AT1R-Ab were inversely associated with coronary endothelial function. Our findings suggest that disruptions in renin–angiotensin system pathways may extend beyond pregnancy and attenuate nitric oxide–mediated endothelial function of the

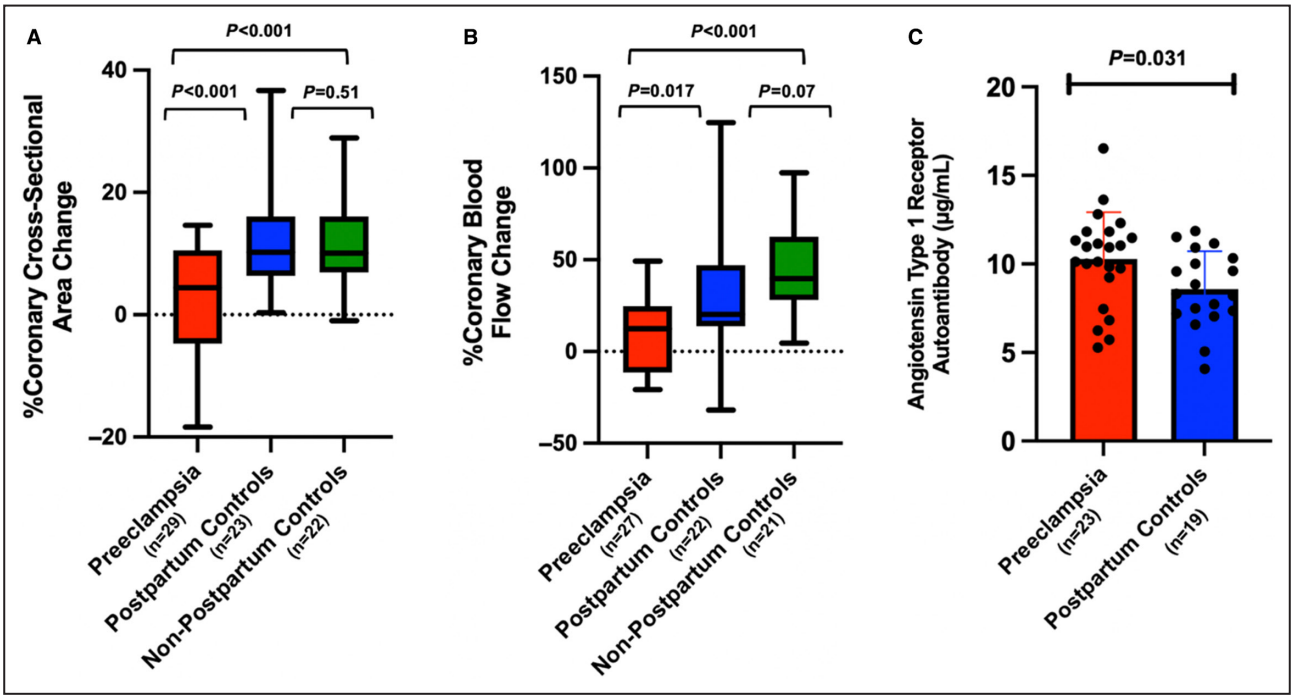

Figure. Comparison of coronary endothelial function and angiotensin type 1 receptor autoantibody among women with preeclampsia and normotensive controls.
Women with preeclampsia have a lower increase in coronary cross-sectional area (**A**) and in coronary blood flow (**B**) compared with normotensive postpartum and non-postpartum controls. Women with preeclampsia have higher levels of angiotensin type 1 receptor autoantibody (AT1R-Ab) compared with normotensive postpartum controls (**C**).

coronary arteries and be a contributor to heightened future CVD risk.

Strengths of this study include prospective enrollment of participants similar in age, race and ethnicity, and cardiovascular risk factors. We also use a noninvasive technique, which can be used in future studies with low maternal and neonatal risk, including among lactating women (no medications or contrast are required). Limitations include small sample size and potential for residual confounding. However, despite this, differences in coronary endothelial function between groups are highly significant. Importantly, these changes are present 3 to 6 months postpartum, when acute pregnancy-related physiologic changes have largely resolved, but early enough postpartum that treatment could reduce future CVD risk. Targeted interventions should be performed to reduce long-term CVD risk among women with a history of preeclampsia.

ARTICLE INFORMATION

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