

RESEARCH LETTER

Association of Angiotensin Receptor Autoantibodies With Cardiovascular Abnormalities in Preeclampsia

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Preeclampsia occurs in 5% to 7% of pregnancies and is defined by hypertension and end organ dysfunction.¹ Preeclampsia can result in acute cardiovascular abnormalities including diastolic dysfunction, pulmonary edema, and adverse myocardial remodeling.² Women with preeclampsia have a 2- to 4-fold increased risk of cardiovascular disease in the long-term, including hypertension, ischemic disease, and heart failure.^{1,3} While the exact pathogenesis is unknown, development of angiotensin II type 1 receptor autoantibodies (AT1R-Ab) in response to maternal inflammation have been implicated.¹ Subtypes of AT1R-Ab bind agonist sites and chronically activate the receptor, causing endothelial cell dysfunction, and possible clinical manifestations of preeclampsia.¹ Elevated AT1R-Ab may also persist postpartum, leading to sustained microvascular dysfunction and risk of cardiovascular disease.

Given the potentially significant role of AT1R-Ab, we compared levels between women with preeclampsia and those with normotensive pregnancies (controls) during late pregnancy and 4 years postpartum. The study groups were derived from a prospective cohort of women with preeclampsia with severe features and controls.² Institutional review board approval was obtained, and all participants provided written consent. Participants were selected antenatally at the time of diagnosis for preeclampsia. Patients in the control group were recruited in the outpatient setting and

matched for age, gestational age, and body mass index. At 4-year follow-up, 21 women with prior preeclampsia and 20 normotensive controls underwent evaluation. There were no significant differences in age or race among those who had initial versus follow-up evaluation. A subset of 12 women with preeclampsia and 12 controls underwent echocardiography 4 years postpartum. All echocardiograms, including diastolic function assessment, were performed in accordance with American Society of Echocardiography guidelines.⁴ The diagnosis of diastolic dysfunction was defined by the presence of >2 of the following abnormal cutoff values for these 4 recommended variables: septal e' velocity <7 cm/s, septal E/e' ratio >15, left atrial volume index >34 mL/m², and peak tricuspid regurgitation jet velocity >2.8 m/s. Diastolic function was classified by the number of these 4 echocardiographic parameters that were normal or abnormal: normal if <50% were abnormal, indeterminate if 50% were abnormal, and diastolic dysfunction if >50% were abnormal.⁴

AT1R-Ab was measured with a novel antigen capture enzyme-linked immunosorbent assay, as described previously.⁵ We performed descriptive statistics for clinical and echocardiographic parameters, conducted between group comparisons using parametric Student *t*-test or non-parametric Mann-Whitney *U* test for normal versus non-normally distributed continuous variables, and performed Chi-squared test for categorical variables. Linear and logistic regressions

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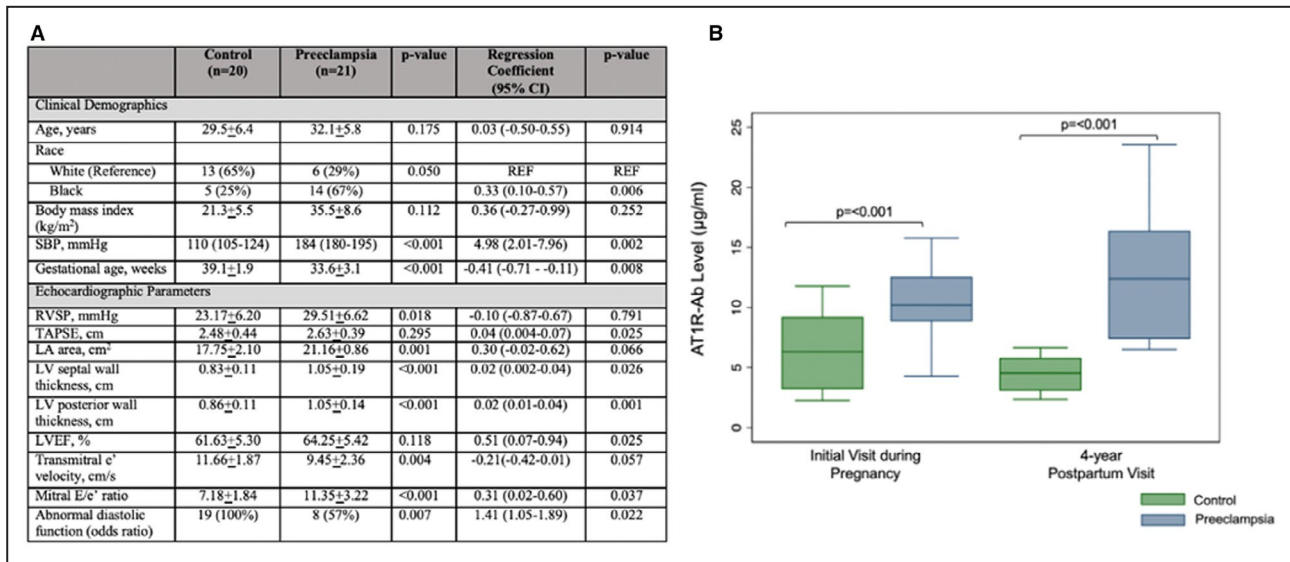


Figure. Angiotensin II type 1 receptor autoantibody in women with preeclampsia during pregnancy and postpartum. **A**, Association of angiotensin II type 1 receptor autoantibody with clinical and echocardiographic variables in preeclampsia. **B**, Comparison of initial and follow-up angiotensin II type 1 receptor autoantibody levels between preeclampsia and controls. AT1R-Ab indicates angiotensin II type 1 receptor autoantibody; LA, left atrial; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure; and TAPSE, tricuspid annular plane systolic excursion.

were performed for association of AT1R-Ab with clinical and echocardiographic parameters.

Mean AT1R-Ab levels during pregnancy were significantly higher in preeclampsia compared with controls (10.21±3.20 versus 6.33±3.40 µg/mL, *P*<0.001) (Figure). Women with preeclampsia were more likely to be Black (67% versus 25%, *P*=0.006) and deliver at an earlier gestational age (33.6 versus 39.1 weeks, *P*<0.001). Additionally, higher AT1R-Ab was associated with earlier gestational age at delivery and higher antepartum systolic blood pressure (Figure [A]). Higher AT1R-Ab was also associated with abnormal echocardiographic parameters during late pregnancy, including increased left ventricular wall thickness, elevated mitral E/e' (a surrogate for left ventricular filling pressure), abnormal diastology (≥ grade 1 dysfunction), higher tricuspid annular plane systolic excursion (a marker of right ventricular function) and higher left ventricular ejection fraction (Figure [A]). Of note, these findings did not remain statistically significant when controlling for race (data not shown), likely because of small sample size and statistical mediation.

At 4 years postpartum, women with preeclampsia also had persistently elevated AT1R-Ab compared with controls (12.76±5.13 versus 4.47±1.49 µg/mL, *P*<0.001) (Figure [B]). Among preeclampsia, women with new incident hypertension at 4 years had higher AT1R-Ab at baseline compared with those without hypertension (10.4±2.1 versus 5.5±2.8, *P*=0.008). There were no associated

echocardiographic abnormalities detected in the small subset of women who had echocardiography 4 years postpartum. Anonymized data and materials have been made publicly available at Mendeley Data and can be accessed at <http://dx.doi.org/10.17632/x5838t5zpw.1>.

In summary, women with preeclampsia have elevated AT1R-Ab during pregnancy and at 4 years postpartum compared with those with normotensive pregnancies. Higher AT1R-Ab is associated with prepartum diastolic dysfunction, adverse remodeling, and hyperdynamic biventricular systolic function. Notably, among women with preeclampsia, initial AT1R-Ab was associated with development of later incident hypertension. Our findings indicate a relationship between AT1R-Ab, echocardiographic indices of diastolic dysfunction, and association with incident hypertension. Our data underscore the need for large cohort studies with racially diverse populations to understand the mechanistic contributions of AT1R-Ab to long-term cardiovascular morbidity in this at-risk population. AT1R-Ab may be useful as a predictive tool for identifying women at risk of developing heart failure, and may provide an avenue for potential targeted treatment with angiotensin II receptor blockers to reduce the risk of cardiovascular disease conferred by AT1R-Ab.

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Disclosures

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