OBSTETRICS

A history of preeclampsia is associated with a risk for coronary artery calcification 3 decades later

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BACKGROUND: A history of preeclampsia is an independent risk factor for cardiac events and stroke. Changes in vasculature structure that contribute to these associations are not well understood.

OBJECTIVE: The aim of this study was to quantify coronary artery calcification (CAC), a known risk factor for cardiac events, in a prospective cohort of women with and without histories of preeclampsia.

STUDY DESIGN: Women without prior cardiovascular events (40 with and 40 without histories of preeclampsia, matched for parity and age at index birth) were recruited from a large population-based cohort of women who were residents of Olmsted County, Minnesota, and who delivered from 1976 through 1982. Computed tomography was performed to measure CAC in Agatston units. All pregnancy histories and covariates were confirmed by review of the medical records. Current clinical variables were assessed at the time of imaging. Differences between women with and without histories of preeclampsia were examined using χ^2 tests and tests; CAC, in particular, was compared as a categorical and ordinal variable, with a χ^2 test and with Wilcoxon 2-sample tests and ordinal logistic regression, as appropriate.

RESULTS: Mean age (SD) at imaging was 59.5 (±4.6) years. Systolic and diastolic blood pressures, hyperlipidemia, and current diabetes status did not differ between women with and without histories of preeclampsia. However, the frequencies of having a current clinical diagnosis of hypertension (60% vs 20%, $P < .001$) and higher body mass index in kg/m^2 (expressed as median [25th-75th percentile], 29.8 [25.9-33.7] vs 25.3 [23.1-32.0], $P = .023$) were both greater in the women with histories of preeclampsia compared to those without. The frequency of a CAC score >50 Agatston units was also greater in the preeclampsia group (23% vs 0%, $P = .001$). Compared to women without preeclampsia, the odds of having a higher CAC score was 3.54 (confidence interval [CI], 1.39—9.02) times greater in women with prior preeclampsia without adjustment, and 2.61 (CI, 0.95—7.14) times greater after adjustment for current hypertension. After adjustment for body mass index alone, the odds of having a higher CAC based on a history of preeclampsia remained significant at 3.20 (CI, 1.21—8.49).

CONCLUSION: In this first prospective cohort study with confirmation of preeclampsia by medical record review, a history of preeclampsia is associated with an increased risk of CAC >30 years after affected pregnancies, even after controlling individually for traditional risk factors. A history of preeclampsia should be considered in risk assessment when initiating primary prevention strategies to reduce cardiovascular disease in women. Among women with histories of preeclampsia, the presence of CAC may be able to identify those at a particularly high cardiovascular risk, and should be the subject of future studies.

Key words: cardiovascular disease, hypertension, preeclampsia, pregnancy

Introduction

Cardiovascular disease (CVD) is the leading cause of death in women. A history of preeclampsia is a sex-specific independent risk factor for cardiac events and stroke.[1-4] The importance of documenting a history of adverse events in pregnancy, such as preeclampsia, is now highlighted in guidelines for the prevention of stroke and coronary artery disease.[5,6]

It is important to understand the pathophysiologic processes linking preeclampsia to subsequent CVD risk, given the strong association between preeclampsia and future adverse cardiovascular outcomes. Conventional risk factors, including obesity and chronic hypertension, are shared by both conditions.[7] Other nontraditional risk factors that are shared by preeclampsia and adverse CVD outcomes include increased levels of C-reactive protein and homocysteine.[8,9]

Coronary artery calcification (CAC), as measured in Agatston units (AU) by computed tomography, is an important biomarker of CVD. The extent of CAC strongly correlates with a higher risk for an adverse cardiac event even in asymptomatic individuals[10]: for a CAC >100, the relative risk for a cardiac event in the next 4 years is >9.[11] The American College of Cardiology/American Heart Association guidelines from both 2010 and 2013 stated that measurement of CAC may help to define risk in those persons at low to intermediate risk based on Framingham scoring.[12] CAC measurement may be beneficial in assessing risk of CVD for women in particular as the Framingham risk score typically underestimates female CVD risk.

A systematic study of the relationship between a history of preeclampsia, as defined by accepted clinical criteria, and CAC quantification in asymptomatic women has not been undertaken. The aim of this study was to quantify and compare CAC in age- and parity-matched women with and without histories of preeclampsia, and to establish whether this association was independent of traditional CVD risk factors. We postulated that CAC would be higher in women with histories of preeclampsia

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and could better stratify cardiovascular risk in these women.

Materials and Methods

The Rochester Epidemiology Project (REP) medical records linkage system was used to identify, from a larger population-based cohort, 40 age- and parity-matched women with and without histories of preeclampsia who then were recruited to undergo imaging, examination, and laboratory assessment.

The REP medical records linkage system was established in 1966 to capture all health care information for the entire population of Olmsted County, Minnesota.[13-15] The REP now encompasses the medical records of a population with an estimated 6.3 million person-years of experience; only 2% of the county residents have denied access to the use of their medical records for research.

Hospital International Classification of Disease Adaptation codes are analogous to *International Classification of Diseases, Ninth Revision* codes. In all, 990 women who delivered from 1976 through 1982 and identified using the REP had Hospital International Classification of Disease Adaptation codes that might be indicative of a possible hypertensive pregnancy disorder (see Supplementary Appendix for specific codes). The medical records of these women were fully abstracted for demographic and clinical information at the time of each pregnancy, including date of birth, ethnicity, race, education, marital status, family history, blood pressure (BP), weight, laboratory values (eg, creatinine, proteinuria, liver enzymes), medications, tobacco, alcohol, pregnancy complications, seizures, persistent headache, epigastric pain, coma, chronic hypertension, diabetes, stroke, cardiac disease, renal disease, hepatic disease, autoimmune disorder, admission to the intensive care unit, postpartum depression, and hyperreflexia.

A potential exposure was confirmed as preeclampsia if a woman had at least 1 preeclamptic pregnancy from 1976 through 1982 and met the standard definition: (1) ≥2 BP readings of a systolic BP (SBP) >140 mm Hg or a diastolic BP (DBP) >90 mm Hg that occur at least 4 hours apart >20 weeks' gestation; and (2) new-onset proteinuria, as defined by a urine dipstick 1+, or proteinuria ≥0.300 g/24 h, or a protein/creatinine ratio equivalent to ≥0.3 g/24 h. Emergency room visits were not included in the assessment.

Inclusion and exclusion criteria

A woman had to be a resident of Olmsted County, Minnesota, when delivering a baby from a pregnancy lasting >20 weeks (live birth or stillbirth) from Jan. 1, 1976, through Dec. 31, 1982 to be eligible for the present study. She also had to be a current resident of Olmsted County, Minnesota; have had a documented clinical visit within the last 2 years; and live within 120 miles of Olmsted County, Minnesota, at the time of the current study to be available for in-person visits. The primary focus of the study was to understand the potential vascular damage and mechanisms that place women with histories of preeclampsia at risk of subsequent CVD. Therefore, all women, regardless of their pregnancy outcomes, were excluded with a medical record–confirmed clinical diagnosis of the following conditions: myocardial infarction, congestive heart failure, stroke, dementia, any cancer (with the exception of nonmelanoma skin cancer), autoimmune disease (eg, multiple sclerosis, lupus), and neurological conditions (eg, epilepsy).

Identification of women with preeclamptic pregnancies for current study

In all, 77 eligible women from the population-based cohort described above with confirmed previous preeclampsia were sent letters describing the study and the contact information for the study coordinator. The study coordinator attempted to contact the woman by telephone if she did not respond within 2 weeks. Of the 77 women contacted with confirmed histories of preeclampsia, 25 (32%) refused, 7 (9%) did not respond (ie, did not respond to the initial letter and we did not contact them further because an eligible woman had been identified), and 5 (6%) were found to be ineligible after screening for additional medical conditions not identified in the medical record. We continued until we identified 40 women with histories of preeclampsia.

Identification of women with normotensive pregnancies

For each woman with a confirmed history of preeclampsia, potential age- and parity-matched women were identified without any of the possible hypertensive pregnancy codes. Women were sequentially contacted and recruited to obtain 1 woman with a history of normotensive pregnancies that was matched for each of the 40 with histories of preeclampsia. Ultimately, 104 women were contacted. Of these, 18 (17%) refused, 8 (8%) did not respond, 5 (5%) wanted to participate but another matched control already had been recruited, and 33 did not respond after the letters, but were not contacted further as a control had already been found. The medical records of these women were fully abstracted for demographic and clinical information, as described previously. All protocols were approved by the Mayo Clinic Institutional Review Board (PR10-005198-05) and all individuals gave written informed consent.

Assessment of outcomes

Contemporary medical record review

The following demographic and clinical data were obtained from review of the medical records and patient interviews at the time of assessment of outcomes: age, body mass index (BMI), SBP, DBP, antihypertensive and-lipid lowering medication use, tobacco use (current, ever, or never), family history of heart disease, and chart-abstracted and physician-confirmed diagnoses of hypertension, hyperlipidemia, and diabetes mellitus.

Assessment of CAC

CAC images were obtained using a 64-detector computed tomography scanner (Siemens Sensation 64, Siemens Medical Solutions, Forchheim, Germany), with a scan configured to cover the heart as described previously.[16,17] Calcium scoring was performed using the Agatston scoring method.[18]