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Uric Acid: A Missing Link Between Hypertensive Pregnancy Disorders and Future Cardiovascular Disease?

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Abstract

Objective: To determine whether women who had a hypertensive pregnancy disorder (HPD) have elevated uric acid concentrations decades after pregnancy as compared with women who had normotensive pregnancies.

Patients and Methods: The Genetic Epidemiology Network of Arteriopathy study measured uric acid concentrations in Hispanic (30%), non-Hispanic white (28%), and non-Hispanic black (42%) women (mean age, 60±10 years). This cross-sectional study was conducted between July 1, 2000, and December 31, 2004. Hispanic participants were recruited from families with high rates of diabetes, whereas non-Hispanic participants were recruited from families with high rates of hypertension. This analysis compared uric acid concentrations in women with a history of normotensive (n=1846) or hypertensive (n=408) pregnancies by logistic regression.

Results: Women who had an HPD had higher uric acid concentrations (median, 5.7 mg/dL vs 5.3 mg/dL; $P<.001$) and were more likely to have uric acid concentrations above 5.5 mg/dL (54.4% vs 42.4%; $P=.001$) than were women who had normotensive pregnancies. These differences persisted after adjusting for traditional cardiovascular risk factors, comorbidities, and other factors that affect uric acid concentrations. A family-based subgroup analysis comparing uric acid concentrations in women who had an HPD (n=308) and their parous sisters who had normotensive pregnancies (n=250) gave similar results (median uric acid concentrations, 5.7 mg/dL vs 5.2 mg/dL, $P=0.02$; proportion of women with uric acid concentrations >5.5 mg/dL, 54.0% vs 40.3%, $P<.001$).

Conclusion: Decades after pregnancy, women who had an HPD have higher uric acid concentrations. This effect does not appear to be explained by a familial predisposition to elevated uric acid concentrations.

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Hypertensive pregnancy disorders (HPDs) complicate 8% of pregnancies and include 4 conditions: gestational hypertension, preeclampsia, chronic hypertension, and chronic hypertension with superimposed preeclampsia.[1] The potential role of elevated uric acid concentrations in the pathophysiology of preeclampsia and other HPDs has been studied for decades.[2] With respect to long-term outcomes, women who have had an HPD are also more likely to develop hypertension,[3,4] cardiovascular disease,[3-5] and chronic kidney disease[6,7] later in life. Uric acid is an established predictor of hypertension[8] and renal disease,[9] especially in women. Some studies suggest that hyperuricemia may also predict cardiovascular disease.[10-12] Less is known about the relationship between uric acid and the increased risk of chronic diseases later in life among women with a history of HPDs.

Some small studies have suggested that uric acid concentrations are increased in women with a history of preeclampsia or other HPDs, compared with women who had normotensive pregnancies.[13,14] Other studies found no differences.[15-19] The limitations of previous studies include small sample sizes, an inability to adjust for confounding

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variables, and focusing on a healthier subset of women with a history of HPDs[13,14,16,19] by excluding those with risk factors or comorbidities. Existing studies have examined younger women,[13-19] whereas cardiovascular disease and chronic kidney disease develop later in life. Finally, the potential role of a familial predisposition to hyperuricemia in women with a history of HPDs has not been investigated. Uric acid concentrations are partially determined by genetic factors and can also be influenced by behavioral or environmental factors that are sometimes shared by siblings.[20-22]

We examined the effect of HPDs on uric acid concentrations measured later in life. Sibships from families with a high prevalence of hypertension or diabetes participated in a study investigating genes that influence hypertension.[23] We hypothesized that several decades after pregnancy, women who had HPDs would have higher uric acid concentrations than would women who had normotensive pregnancies after adjusting for comorbidities, traditional cardiovascular risk factors, and other factors that affect uric acid concentrations. We further posited that women who had HPDs would have elevated uric acid concentrations compared with their sisters who had normotensive pregnancies.

PATIENTS AND METHODS

Participants

This secondary analysis includes 2472 women from 1282 sibships who participated in the cross-sectional Genetic Epidemiology Network of Arteriopathy study. The Genetic Epidemiology Network of Arteriopathy study investigated genes that influence hypertension by enrolling sibships. The Rochester, Minnesota, site enrolled non-Hispanic whites. The Jackson, Mississippi, site recruited non-Hispanic blacks. The Starr County, Texas, site enrolled Hispanics. Non-Hispanic sibships were eligible for the study if at least 2 siblings were diagnosed with hypertension before age 60 years.[23] Due to the high prevalence of diabetes in Hispanics, Hispanic sibships were eligible if at least 2 siblings had diabetes. Each site's institutional review board approved the study. All subjects provided written informed consent before participating. This analysis includes all women who completed the pregnancy history questionnaire and provided a blood sample during the phase 2 (2000-2004) study examination.

Questionnaires

Trained interviewers administered questionnaires concerning personal and family medical history.[23] Women's history of HPDs was assessed using a standardized, previously validated questionnaire.[24] Women were asked, "Have you had at least one pregnancy lasting more than 6 months?" Women who responded "yes" were asked how many pregnancies they had, and whether they developed hypertension in any pregnancy lasting more than 6 months.

Physical Examination

Trained observers performed all measurements using standardized protocols. Blood pressure was measured using an automated oscillometric device. Height was measured with the subject standing with her heels together, without shoes, against a vertically mounted ruler. Weight was measured on a scale. Venipuncture was performed in the morning after an overnight fast ($\geq$8 hours). Serum uric acid concentration was measured with the Hitachi 911 Chemistry Analyzer (Roche Diagnostics) with a standard automated uricase enzymatic assay.[25] Serum triglyceride, total cholesterol, and high-density lipoprotein cholesterol concentrations were measured with the same analyzer. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[26] *Microalbuminuria* was defined as an albumin-creatinine ratio of 25 mg/g or more of creatinine in a spot urine sample.[27] This represents the 95th percentile for women and corresponds to an albumin excretion rate of more than 30 μg/min.

Phase 2 Study Definitions

Women who reported having smoked 100 or more cigarettes during their lifetimes were classified as "ever" smokers. *Hypertension* was defined as hypertension at the study visit (average blood pressures $\geq$140 mm Hg systolic and/or $\geq$90 mm Hg diastolic), or a self-reported physician diagnosis of hypertension with prescription antihypertensive medication use. *A coronary heart disease event* was defined as self-reported myocardial infarction, coronary bypass surgery, coronary angioplasty, balloon dilatation, and/or

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