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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, when compared to 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 (60 ± 10 years of age). 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=1,846) or hypertensive (n=408) pregnancies by logistic regression.

Results—Women who had a HPD had higher uric acid concentrations (Median: 5.7 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 women who had normotensive pregnancies. These differences persisted after adjusting for traditional cardiovascular risk factors, co-morbidities and other factors that affect uric acid concentrations. A family-based subgroup analysis comparing uric acid concentrations in women who had a HPD (n=308) and their parous sisters who had normotensive pregnancies (n=250) gave similar results (Median uric acid concentrations: 5.7 vs. 5.2 mg/dl, $P=0.02$; Proportion of women with uric acid >5.5 mg/dl: 54.0% vs. 40.3%, $P<.001$).

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

Keywords

hypertensive pregnancy disorders; uric acid; hypertension; diabetes; coronary heart disease; chronic kidney disease

Introduction

Hypertensive pregnancy disorders (HPDs) complicate 8% of pregnancies and include four 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 a 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 hypertension⁸ 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 to women who had normotensive pregnancies.^{13,14} Others found no differences.^{15–19} The limitations of previous studies include small sample sizes, the inability to adjust for confounding 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 a HPD would have higher uric acid concentrations than women who had normotensive pregnancies after adjusting for co-morbidities, 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 to their sisters who had normotensive pregnancies.

Methods

Participants

This secondary analysis includes 2,472 women from 1,282 sibships who participated in the cross-sectional Genetic Epidemiology Network of Arteriopathy (GENOA) study. GENOA investigated genes that influence hypertension by enrolling sibships. Rochester, Minnesota enrolled Non-Hispanic whites. Jackson, Mississippi recruited Non-Hispanic blacks. Starr County, Texas site enrolled Hispanics. Non-Hispanics sibships were eligible for the study if at least two siblings were diagnosed with hypertension before 60 years of age.²³ To prevent confounding due to the high prevalence of diabetes in Hispanics, Hispanic sibships were eligible if at least two 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 were 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 (8 hours). Serum uric acid concentration was measured on the Hitachi 911 Chemistry Analyzer (Roche Diagnostics, Indianapolis, Indiana, USA) with a standard automated uricase enzymatic assay.²⁵ Serum triglyceride, total cholesterol and HDL cholesterol concentrations were measured on the same analyzer. The estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation.²⁶ Microalbuminuria was defined as a albumin-creatinine ratio of ≥ 25 mg/g creatinine (Cr) on a spot urine sample.²⁷ This represents the 95th percentile for women and corresponds to an albumin excretion rate of >30 μ g/min.

Phase 2 Study Definitions

Women who reported having smoked ≥ 100 cigarettes during their lifetime were classified as 'ever' smokers. Hypertension was defined as hypertension at the study visit (average blood pressures ≥ 140 mmHg systolic and/or ≥ 90 mmHg 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 stent placement. Dyslipidemia was defined by the use of lipid-lowering drugs, or at least one abnormal lipid measurement at the

study examination (triglycerides 150 mg/dl, total cholesterol 200 mg/dl, or HDL 40 mg/dl). Diabetes was defined by a fasting glucose 126 mg/dL, or the use of oral hypoglycemic medications or insulin, or self-reported diabetes. A decreased eGFR was defined as an eGFR <60 mL/min/1.73m^{2.26} Hypertension in pregnancy and stroke were assessed by self-report. Chronic hypertension in pregnancy was defined as a self-reported first diagnosis of hypertension prior to or during the year of the woman's first hypertensive pregnancy.

Subgroup Analysis of Sisters

This analysis included all parous women from sibships in which there was at least one woman who had a HPD and at least one parous sister who had only normotensive pregnancies. Sibling relationships were confirmed by genetic testing. Only full sisters were included in the analysis.

Statistical Analysis

Quantitative variables are expressed as mean values with standard deviations (for normally distributed data) or as medians with interquartile ranges (for skewed data). Categorical data are presented as absolute numbers with percentages. Wilcoxon rank sum tests and chi-square tests were used to assess pairwise differences in quantitative variables between the pregnancy groups (HPD vs. nulliparous or normotensive pregnancy). A Receiver Operating Characteristics curve was constructed to determine the best cut-off value for modeling the effects of HPDs on uric acid concentrations. The effects of a history of HPDs on increased uric acid concentrations, defined as a categorical measure, were then determined by odds ratios (ORs) presented with 95% confidence intervals (CIs). ORs were derived from logistic regression analysis in models that included age, race, smoking, waist circumference, dyslipidemia, diabetes, hypertension, eGFR, medications that increase uric acid concentrations and medications that decrease uric acid concentrations. Variables were selected into the models based on significance in a univariate logistic regression analysis (data not shown). Models were fit with generalized estimating equations to account for sibling relationships. Statistical analysis was performed using SPSS (SPSS for Windows, version 21.0, SPSS, Chicago, IL). $P < .05$ was considered to be statistically significant.

Results

Participants

Women who had a HPD completed the study 30 ± 12 years after their first hypertensive pregnancy. Although women who had a HPD were significantly younger than women who had normotensive pregnancies (Table 1), they were significantly more likely to have comorbidities (hypertension, diabetes and stroke), cardiovascular disease risk factors (higher BMI, greater prevalence of a family history of hypertension or coronary heart disease) and microalbuminuria. Dyslipidemia and smoking were notable exceptions to this pattern. Women who had a HPD were less likely to have dyslipidemia than nulliparous women, and less likely to have smoked than women who had normotensive pregnancies. Women who had a HPD were more likely to be taking a medication that increased uric acid concentrations than women in the other two groups. The proportion of women who drank

alcohol, used statins, had renal dysfunction, or had experienced a coronary heart disease event did not differ significantly between the pregnancy groups.

Uric Acid

Women who had a HPD had higher serum uric acid concentrations than nulliparous women and women who had normotensive pregnancies (Table 2, $P<.001$). A serum uric acid cut-off of 5.5 mg/dl was used in regression models, as ROC analysis revealed that this cut-off provided the best discrimination between women with HPDs and women in the other two groups (Figure 1S, AUC: 0.560; sensitivity: 55.4%; specificity: 57.1%; $P<.001$). Women who had a HPD were more likely to have uric acid concentrations above 5.5 mg/dl than women who had normotensive pregnancies in univariate comparisons (Table 2, $P<.001$).

Nulliparous women and women who had normotensive pregnancies were pooled for regression analyses. Uric acid concentrations did not differ between these two groups (Table 2) and there were too few nulliparous women to draw conclusions about this group separately. Compared to nulliparous women and women who had normotensive pregnancies, women who had a HPD were more likely to have uric acid concentrations >5.5 mg/dl (OR: 1.49, 95% CI: 1.16–1.91, after adjustment for comorbidities (dyslipidemia, hypertension, diabetes, eGFR), traditional cardiovascular risk factors (age, waist circumference, and ever smoking) and other factors that affected uric acid concentrations (medications that increase uric acid concentrations, medications that decrease uric acid concentrations and race). The effect of HPDs remained significant after excluding nulliparous women (data not shown), women who had a history of coronary heart disease or stroke (Table 3) and women who had a history of coronary heart disease or stroke as well as women who reported chronic hypertension prior to or during the year of their first hypertensive pregnancy.

In addition to a history of HPDs, age, dyslipidemia, hypertension, waist circumference, eGFR and ever smoking and medications that increase uric acid concentration were all associated with higher uric acid concentrations in the model (Table 3). There was a significant interaction between race and diabetes ($P<.001$). Diabetes was associated with higher uric acid concentrations in non-Hispanic women, but not in Hispanic women. Unadjusted uric acid concentrations in non-Hispanic women who had diabetes were higher (Median (IQR): 6.1 (5.0–7.4) mg/dl) than concentrations observed in non-Hispanic women without diabetes (5.4 (4.4–6.5) mg/dl, $P<.001$ by Wilcoxon rank sum test). Among Hispanic women, unadjusted uric acid concentrations did not differ between diabetic (5.0 (4.1–6.0) mg/dl) and non-diabetic women (4.9 (4.1–5.7) mg/dl, $P=.18$ by Wilcoxon rank sum test). As expected, women who were taking medications that lower uric acid concentrations had lower uric acid concentrations than women who were not using these medications.

Characteristics of Sisters

250 women who had HPDs and 308 parous sisters from 208 families were included in this analysis. 42 nulliparous sisters were excluded as there were too few women to draw conclusions about this group. Race, age, education, and the proportion of women who had ever smoked or currently drank alcohol did not differ between women who had HPDs and

their sisters who had normotensive pregnancies (Table 4). There were also no differences in the prevalence of stroke, coronary heart disease, renal dysfunction or the use of medications that decrease uric acid concentrations. Compared to their sisters, women who had a HPD had significantly higher BMIs and were more likely to have diabetes, microalbuminuria and hypertension. Women who had a HPD were also more likely to be taking statins and medications that increase uric acid concentrations.

Pregnancy History and Uric Acid Concentrations in Sisters

Uric acid concentrations (Median (IQR): 5.7 (4.5, 6.9) mg/dl vs. 5.2 (4.3, 6.5) mg/dl, $P=0.02$) and the proportion of women who had a uric acid concentration above 5.5 mg/dl (54.0% vs. 40.3%, $P=.001$) were significantly higher in women who had a HPD compared to their sisters who had normotensive pregnancies. This effect remained significant (OR 1.51, 95% CI 1.01–2.25, $P=0.04$, Table 5) after adjusting for co-morbidities (diabetes, dyslipidemia and eGFR), cardiovascular disease risk factors (age, waist circumference and other factors that affected uric acid concentrations (race, medications that increase uric acid concentrations). There was a significant interaction between Hispanic race and diabetes. Diabetes was associated with higher uric acid concentrations in non-Hispanic women, but not in Hispanic women. Unadjusted uric acid concentrations were 6.3 (5.1–8.0) mg/dl (median (IQR)) among non-Hispanic women who had diabetes, compared to 5.5 (4.4–6.8) mg/dl among non-Hispanic women who did not have diabetes ($P<.001$ by Wilcoxon rank sum test). Among Hispanic women, unadjusted uric acid concentrations were 4.9 (4.2–5.9) mg/dl in women with diabetes and 4.8 (4.0–6.0) mg/dl in women who did not have diabetes ($P=.52$ by Wilcoxon rank sum test). Model results were not different after excluding women with a history of coronary heart disease or stroke, or women with a history of coronary heart disease and stroke as well as women who were first diagnosed with chronic hypertension prior to or during the year of their first hypertensive pregnancy (Table 5).

Discussion

This study demonstrates that when compared to women who had normotensive pregnancies, women with a history of HPDs were more likely to have elevated uric acid concentrations several decades after pregnancy. This difference persisted after adjusting for comorbidities, traditional cardiovascular risk factors and other factors that affect uric acid concentrations. Uric acid concentrations in women with vs. without a HPD and adjusted odds ratios examining the effects of HPDs were very similar in the main analysis and in the subgroup analysis comparing sisters. This suggests that elevated uric acid concentrations in women with a history of HPDs were not explained by an underlying familial predisposition to elevated uric acid concentrations. Elevated uric acid concentrations may reflect an ongoing state of inflammation and oxidative stress in women with a history of HPDs, who are at increased risk for future cardiovascular and renal disease.

The potential role of elevated uric acid in preeclampsia and other HPDs has long been recognized.² Uric acid concentrations decrease during pregnancy; therefore hyperuricaemia has previously been defined as uric acid concentrations that are greater than one standard deviation above normal for gestational age.²⁸ Among pregnant women with hypertension,

hyperuricaemia is associated with earlier delivery, a greater risk of preterm birth and lower birthweight centiles.²⁸ These adverse fetal outcomes are evident in women with and without proteinuria.²⁸ Elevations in uric acid precede maternal disease and are only partially explained by differences in glomerular filtration, assessed by serum creatinine.²⁹ However, the clinical utility of hyperuricemia in predicting preeclampsia remains questionable.³⁰ Researchers have postulated that uric acid may contribute to the pathophysiology of preeclampsia by exacerbating inflammation, oxidative stress and endothelial dysfunction.³¹

The potential role of uric acid in mediating long-term disease risk in women with a history of HPDs has received less attention. Hyperuricemia is an independent predictor of hypertension⁸ and chronic kidney disease.^{9,32} Some studies have suggested that hyperuricemia is also an independent predictor for cardiovascular disease,^{10,11} whereas others have not.³³ Researchers have suggested that hyperuricemia might elevate cardiovascular disease risk indirectly by increasing the risk of hypertension.³⁴ Several studies suggest that hyperuricemia is a stronger predictor of future disease in women, who have lower serum uric acid concentrations than men.^{10,11,35,36} The predictive value of hyperuricemia has traditionally been explained by its ability to identify patients with subclinical renal dysfunction. Uric acid is primarily excreted by the kidney; therefore serum concentrations increase as the glomerular filtration rate falls. However, scientists and clinicians continue to debate whether uric acid also has a pathophysiological role in cardiovascular and renal disease. Animal studies showing that hyperuricemia can cause disease³⁷ and human studies reporting an amelioration of symptoms in patients who receive uric acid lowering medications^{34,38} have reignited this discussion.

Small studies have suggested that uric acid concentrations are increased^{13,14} or not different^{15–19} in women with a history of preeclampsia or other HPDs, compared to women who had normotensive pregnancies. A Swedish study observed elevated uric acid concentrations one-year post-partum in women who had preeclampsia compared to women who had normotensive pregnancies. However, the authors noted that this could have been due to differences in BMI.¹³ Women who had preeclampsia tended to be heavier than those with previous normotensive pregnancies (BMI 25.5 vs. 22.8 kg/m², p=0.08).¹³ Our findings support this interpretation, as higher waist circumference was one factor that contributed to higher uric acid concentrations among women with a history of HPDs in the present study. Furthermore, a study of non-obese, normotensive Chilean women found no differences in uric acid concentrations one to two years post-partum when women who had preeclampsia were compared to those who had normotensive pregnancies.¹⁸ A larger study conducted 10 years post-partum reported increased uric acid concentrations among women who had preeclampsia.¹⁴ In contrast, four additional studies conducted between 5 and 17 years post-partum found no differences in uric acid concentrations between women who had preeclampsia, women who had pregnancy-induced hypertension and women who had normotensive pregnancies.^{15–17,19} Women who had preeclampsia were more likely to have hypertension,¹⁷ microalbuminuria¹⁷ and mild hyperinsulinemia.¹⁵

Several factors could contribute to the differences between the results of the present study and those of previous studies. Women in previous studies were much younger than women in the present study (mean age 27–42 years vs. 60 years^{13–18}). The small sample size (n=20

to 50/group) of most previous studies made it difficult for investigators to adjust for traditional cardiovascular risk factors, comorbidities and other factors that affect uric acid concentrations. The present study includes over 2,000 women, more than 500 of whom were included in the subgroup analysis comparing full sisters. Some previous studies excluded women with hypertension, cardiovascular disease, renal disease, gestational diabetes or other co-morbidities,^{13,16,19} whereas our study enrolled women from families with high rates of hypertension and diabetes. Results were not different after adjustment for hypertension and diabetes, or when women who had experienced a coronary heart disease event or stroke were excluded. The inclusion of hypertensive women is important, as women who had a HPD are twice as likely to develop hypertension as women who had normotensive pregnancies.^{3,4} Elevated uric acid concentrations are an independent predictor of chronic kidney disease, especially in men and women with hypertension.^{9,36} The present study also included women with all forms of HPDs (preeclampsia, gestational hypertension, chronic hypertension and chronic hypertension with superimposed preeclampsia). Previous studies either focused on women with preeclampsia^{13–15,18,19} or included separate groups of women with a history of preeclampsia and women with a history of pregnancy-induced hypertension.^{16,17} The present study included non-Hispanic white, non-Hispanic black and Hispanic women in the United States, whereas previous studies examined Nordic,^{13–16,19} Jordanian¹⁷ or Chilean¹⁸ women.

This study has several limitations. Pregnancy history, coronary heart disease events and stroke were determined by self-report. The pregnancy history questionnaire had an 80% sensitivity and 90% specificity for the determination of preeclampsia among women in Rochester, Minnesota.²⁴ Among previous studies examining uric acid between 1 and 17 years after preeclampsia, some used medical registries^{14,16} or hospital records^{17,19} to assess pregnancy history. Other studies did not report the source used to verify pregnancy history.^{13,15,18} The study targeted sibships with a high prevalence of hypertension or diabetes; therefore the results may not apply to the general population. Despite these limitations, our study extends previous data by reporting elevated uric acid concentrations years after the affected pregnancies in a large cohort of patients while adjusting for traditional CVD risk factors, co-morbidities, and factors that influence uric acid concentrations (e.g. medications). The subgroup analysis compares full sisters to isolate the effect of HPDs after adjusting for a potential familial predisposition to elevated uric acid concentrations. A previous analysis among non-Hispanic men and women in the cohort used for the present study reported adjusted uric acid heritability estimates of 0.48 in non-Hispanic whites and 0.51 in non-Hispanic blacks.²⁰ Women who develop HPDs could have a stronger genetic predisposition to elevated uric acid concentrations or other behavioral risk factors, compared to their sisters who have had normotensive pregnancies. However, the familial predisposition to elevated uric acid concentrations will still be more similar in sisters than in women who are not related.

Conclusions

Compared to women who had normotensive pregnancies, women with a history of HPDs had elevated uric acid concentrations several decades after pregnancy, even after adjusting for traditional cardiovascular risk factors. Elevated uric acid concentrations in women with a

history of HPDs could not be fully explained by an underlying familial predisposition to elevated uric acid concentrations. Future studies should examine the time course of changes in uric acid after a pregnancy complicated by a HPD. Studies should also determine whether uric acid contributes to the pathophysiology of cardiovascular and renal disease in women with a history of HPDs. Identifying the mechanisms that increase future disease risk will help researchers and clinicians to develop effective post-partum prevention programs for women who have had HPDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

HPD hypertensive pregnancy disorder

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Table 1

Demographic Characteristics

Variable	n	Nulliparous (n = 218)	Normotensive Pregnancy (n = 1,846)	Hypertensive Pregnancy (n = 408)
Race	2,472			
Non-Hispanic White		83 (38.1%)	507 (27.5%)	112 (27.5%)
Hispanic		70 (32.1%)	546 (29.6%)	116 (28.4%)
Non-Hispanic Black		65 (29.8%)	793 (42.9%)	180 (44.1%)
Age (years)	2,472	57.2 ± 12.5	60.6 ± 10.1 ^c	57.5 ± 10.7 ^d
Body mass index (kg/m ²)	2,465	32.7 ± 8.0	31.7 ± 6.7 ^c	34.5 ± 7.1 ^{c,d}
Waist circumference (cm)	2,459	104.0±18.8	102.4±16.2	107.7±16.8 ^{c,d}
Education	2,472			
Less than high school (< 8 years)		41 (18.8%)	461 (25.0%)	88 (21.6%)
Partial high school (9–11 years)		14 (6.4%)	212 (11.5%)	62 (15.2%)
High school graduate/GED (12 years)		51 (23.4%)	547 (29.6%)	117 (28.7%)
Post high school (>12 years)		112 (51.4%)	626 (33.9%)	141 (34.6%)
Ever smoked	2,472	70 (32.1%)	578 (31.3%)	107 (26.2%) ^d
Alcohol use	2,472	51 (23.4%)	369 (20.0%)	95 (23.3%)
Estimated GFR < 60 ml/min/1.73 m ²	2,472	19 (8.7%)	148 (8.0%)	38 (9.3%)
Microalbuminuria>25mg/g	2,419	34 (15.7%)	263 (14.6%)	79 (19.8%) ^d
Diabetes	2,471	65 (29.8%)	607 (32.9%)	156 (38.2%) ^{c,d}
Hypertension	2,468	154 (70.6%)	1259 (68.3%)	335 (82.5%) ^{c,d}
Dyslipidemia	2,472	178 (81.7%)	1434 (77.7%)	303 (74.3%) ^c
Statins	2,472	41 (18.8%)	409 (22.2%)	93 (22.8%)
Medications that increase uric acid ^a	2,472	106 (48.6%)	969 (52.5%)	238 (58.3%) ^{c,d}
Medications that decrease uric acid ^b	2,471	63 (28.9%)	514 (27.9%)	118 (28.9%)
Coronary heart disease event	2,471	16 (7.3%)	139 (7.5%)	34 (8.3%)
Stroke	2,472	9 (4.1%)	68 (3.7%)	26 (6.4%) ^d
Family history of hypertension or coronary heart disease	2,472	189 (86.7%)	1478 (80.1%) ^c	358 (87.7%) ^d

Values shown are mean ± standard deviation or n (%). Abbreviations: GED, general educational development; GFR, glomerular filtration rate.

Women were considered positive if they were taking one or more medication that

^a increases uric acid (diuretics, regular aspirin use or warfarin) or

^b decreases uric acid (the anti-gout medications allopurinol or probenecid; losartan, fenofibrate or estrogen replacement therapy).

Significant difference ($P < .05$) from:

^c Nulliparous,

^d Normotensive pregnancy.

Table 2

Uric Acid According to Pregnancy Outcome

Variable	Nulliparous (n =218)	Normotensive Pregnancy (n = 1,846)	HPD (n = 408)
Uric acid (mg/dL)	5.5 (4.4, 6.4)	5.3 (4.4, 6.4)	5.7 (4.6, 6.9) <i>a,b</i>
Uric acid > 5.5 mg/dl	103 (47.2%)	782 (42.4%)	222 (54.4%) <i>b</i>

Values shown are median (interquartile range) or n (%).

Significant difference ($P<.05$) from:

^aNulliparous women,

^bWomen who had normotensive pregnancies.

Table 3

Factors Associated with Uric Acid Concentrations > 5.5mg/dl

Variable	All Women		Excluding women with a history of CHD or stroke ^e		Excluding women with a chronic hypertension in pregnancy and/or a history of CHD or stroke ^f	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
History of HPDs ^a	1.49 (1.16–1.91)	.002	1.51 (1.16–1.97)	.002	1.43 (1.06–1.93)	.02
Age, per 10 years	1.09 (1.04–1.15)	<.001	1.10 (1.04–1.16)	.001	1.08 (1.02–1.14)	.005
Waist circumference, per 5cm	1.15 (1.12–1.19)	<.001	1.16 (1.12–1.20)	<.001	1.16 (1.12–1.20)	<.001
Ever smoked	1.31 (1.07–1.60)	.008	1.36 (1.10–1.68)	.005	1.37 (1.10–1.70)	.005
Race*diabetes ^b	1.54 (1.32–1.80)	<.001	1.44 (1.21–1.71)	<.001	1.45 (1.22–1.73)	<.001
Dyslipidemia	1.29 (1.03–1.62)	.02	1.35 (1.07–1.71)	.01	1.33 (1.05–1.69)	.02
Hypertension	1.57 (1.24–1.99)	<.001	1.57 (1.23–2.01)	<.001	1.58 (1.23–2.03)	<.001
eGFR (<60 ml/min/1.73 m ²)	6.45 (4.15–10.02)	<.001	6.66 (4.03–11.01)	<.001	6.58 (3.97–10.91)	<.001
Medications that increase uric acid ^c	1.71 (1.39–2.11)	<.001	1.84 (1.48–2.29)	<.001	1.87 (1.50–2.35)	<.001
Medications that decrease uric acid ^d	0.72 (0.59–0.88)	.002	0.72 (0.58–0.89)	.003	0.72 (0.58–0.90)	.004

Abbreviations: CHD, coronary heart disease; OR, odds ratio; CI, confidence interval.

^aHPD vs. nulliparous women or women who had normotensive pregnancies. Results were not different when nulliparous women were excluded (HPD vs. normotensive pregnancy: OR 1.57; 95% CI 1.21–2.02; p=0.001).^bSee results for explanation^cDiuretics, regular aspirin use, warfarin^dThe anti-gout medications allopurinol or probenecid; losartan, fenofibrate or estrogen replacement therapy^e274 women with a history of coronary heart disease or stroke were excluded^f360 women with chronic hypertension in pregnancy and/or a history of coronary heart disease or stroke were excluded (86 women with chronic hypertension in pregnancy; 248 women with a history of coronary heart disease or stroke; 26 women with both)

Table 4

Demographic Characteristics in Sisters According to Pregnancy Outcome

Variable	n	Women who had a HPD (n = 250)	Sisters who had a Normotensive Pregnancy (n = 308)
Race	558		
Non-Hispanic White		63 (25.2%)	77 (25.0%)
Hispanic		86 (34.4%)	103 (33.4%)
Non-Hispanic Black		101 (40.4%)	128 (41.6%)
Age (years)	558	56.5 ± 10.6	57.2 ± 10.8
Body mass index (kg/m ²)	557	34.4 ± 7.0	32.3 ± 6.8 ^c
Waist circumference (cm)	556	107.4 ± 16.7	102.6 ± 16.6 ^c
Education	558		
Less than high school (< 8 years)		52 (20.8%)	76 (24.7%)
Partial high school (9–11 years)		39 (15.6%)	35 (11.4%)
High school graduate/GED (12 years)		70 (28.0%)	84 (27.3%)
Post high school (>12 years)		89 (35.6%)	113 (36.7%)
Ever smoked	558	60 (24.0%)	83 (26.9%)
Alcohol use	558	56 (22.4%)	58 (18.8%)
Estimated GFR < 60 ml/min/1.73 m ²	558	27 (10.8%)	24 (7.8%)
Microalbuminuria>25mg/g	541	44 (18.0%)	31 (10.4%) ^c
Diabetes	558	96 (38.4%)	91 (29.5%) ^c
Hypertension	556	201 (80.7%)	187 (60.9%) ^c
Dyslipidemia	558	194 (77.6%)	223 (72.4%)
Statins	558	54 (21.6%)	45 (14.6%) ^c
Medications that increase uric acid ^a	558	139 (55.6%)	140 (45.5%) ^c
Medications that decrease uric acid ^b	558	68 (27.2%)	76 (24.7%)
Coronary heart disease event	558	20 (8.0%)	15 (4.9%)
Stroke	558	15 (6.0%)	9 (2.9%)
Family history of coronary heart disease	558	223 (89.2%)	262 (85.1%)

Values shown are mean ± standard deviation or n (%). Abbreviations: GED, general educational development; GFR, glomerular filtration rate.

Women were considered positive if they were taking one or more medication that

^a increases uric acid (diuretics, regular aspirin use or warfarin) or

^b decreases uric acid (the anti-gout medications allopurinol or probenecid; losartan, fenofibrate or estrogen replacement therapy).

Significant difference ($P < .05$) from:

^c Women who had a HPD.

Table 5

Factors Associated with Uric Acid Concentrations > 5.5mg/dl in Women who Have had an HPD, and their Sisters who had Normotensive Pregnancies

Variable	All Women		Excluding women with a history of CHD or stroke ^d		Excluding women with a chronic hypertension in pregnancy and/or history of CHD or stroke ^e	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
History of HPDs ^a	1.51 (1.01–2.25)	.04	1.83 (1.20–2.79)	.005	1.64 (1.03–2.60)	.04
Age, per 10 years	1.14 (1.02–1.27)	.02	1.20 (1.07–1.34)	.001	1.16 (1.03–1.30)	.01
Waist circumference, per 5cm	1.18 (1.11–1.27)	<.001	1.17 (1.09–1.25)	<.001	1.17 (1.08–1.26)	<.001
Race*diabetes ^b	1.58 (1.12–2.23)	.009	not included		not included	
Dyslipidemia	1.85 (1.16–2.96)	.01	1.85 (1.13–3.02)	.01	1.74 (1.04–2.90)	.03
eGFR (<60 ml/min/1.73 m ²)	5.67 (2.35–13.65)	<.001	6.67 (2.40–18.55)	<.001	6.37 (2.23–18.18)	.001
Medications increasing uric acid ^c	1.94 (1.27–2.97)	.002	2.34 (1.51–3.62)	<.001	2.75 (1.73–4.38)	<.001

Abbreviations: CHD, coronary heart disease; OR, odds ratio; CI, confidence interval.

^aHPD vs. parous sisters who did not have a HPD.

^bSee results for description

^cDiuretics, regular aspirin use, warfarin

^d55 women with a history of coronary heart disease or stroke were excluded

^e114 women with chronic hypertension in pregnancy and/or a history of coronary heart disease or stroke were excluded (38 women with chronic hypertension in pregnancy; 59 women with a history of coronary heart disease or stroke were excluded; 17 women with both)