Hypertension in Pregnancy Is a Risk Factor for Microalbuminuria Later in Life

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The authors aimed to compare renal function by estimated glomerular filtration rate and albuminuria in 3 groups of women: nulliparous women, women with a history of normotensive pregnancies, and women with a history of at least one hypertensive pregnancy. Women who participated in the second Family Blood Pressure Program Study visit (2000–2004) and had serum creatinine and urine albumin measurements (n=3015) were categorized as having had no pregnancy lasting >6 months (n=341), having had only normotensive pregnancies (n=2199), or having had at least 1 pregnancy with hypertension (n=475) based on a standardized questionnaire. Women who reported having had at least one pregnancy with hypertension were significantly more likely to be hypertensive (75.6% vs 59.4%, P<.001), diabetic (34.2% vs 27.3%, P ≤ .001), and have higher body mass index (32.8 vs 30.5, P<.001) than those who reported normotensive pregnancies. There was a significantly greater risk of microalbuminuria (urine albumin-creatinine ratio >25 mg/g) in those who reported at least one pregnancy with hypertension (odds ratio, 1.37; confidence interval, 1.02–1.85; P=.04) than in those with normotensive pregnancies, after adjusting for risk factors for chronic kidney and cardiovascular disease. Hypertension in pregnancy is associated with an increased risk of future microalbuminuria. *J Clin Hypertens (Greenwich).* 2013;15:617–623. ©2013 Wiley Periodicals, Inc.

Hypertensive pregnancy disorders affect 5% to 10% of pregnancies and encompass a spectrum of disease phenotypes, including preeclampsia, a form of hypertension unique to pregnancy.[1] Preeclampsia can occur either de novo or superimposed on chronic hypertension after 20 weeks of gestation, and is characterized by a new-onset or worsening of preexisting proteinuria.[2,3] Preeclampsia and its convulsive form eclampsia, remain one of the major causes of maternal and fetal morbidity and mortality. Chronic hypertension that persists during pregnancy and gestational hypertension, defined as hypertension occurring for the first time during the second half of pregnancy in the absence of proteinuria, usually have more benign courses. These disorders likely reflect a spectrum of disease marked by endothelial dysfunction initiated by both maternal and uteroplacental factors.[4,5]

To date, case-control and registry-based cohort studies have suggested that women with histories of hypertensive pregnancy disorders, and preeclampsia, in particular, are at risk for future cardiovascular disease (CVD).[6,7] Recent data have also suggested that women with preeclampsia may be at risk for chronic kidney disease (CKD). Several cohort studies have demonstrated that a history of preeclampsia is associated with an increased risk of microalbuminuria,[8,9] which is an important risk factor for both cardiovascular mortality,[10] and the initiation and progression of CKD.[11,12] A meta-analysis published in 2010 of the 7 largest cohort studies of preeclamptic mothers found an increased relative risk of increased albumin excretion in women with a history of preeclampsia vs those with no history of hypertension in pregnancy.[13] The current available studies are limited by small sample size, phenotypic heterogeneity, and few adjust for the presence of major risk factors for CKD, including diabetes mellitus or preexisting hypertension.

In this study, our goal was to assess evidence of CKD among women in the large, multiracial cohort of the Family Blood Pressure Program (FBPP) study based on their reported history of hypertension in pregnancy. We wanted to examine whether a history of hypertension in pregnancy is an independent risk factor for kidney dysfunction as evaluated by the estimated glomerular filtration rate (eGFR) and spot urine albumin-creatinine ratio (UACR), after controlling for traditional risk factors for CKD and CVD.

METHODS

Participants

This study included 3015 patients from 1600 sibships who participated in the FBPP study's second examination conducted between 2000 and 2004. The FBPP study was established in 1995 by the National Heart, Lung, and Blood Institute (NHLBI) to identify genetic factors that contribute to hypertension by recruiting sibships of various ethnic backgrounds, including

non-Hispanic whites, African Americans, Mexican Americans, and Asian Americans of both Japanese and Chinese descent. It comprises 4 separate networks: GenNet, Genetic Epidemiology Network of Atherosclerosis (GENOA), Hypertension Genetic Epidemiology Network (HyperGen), and Stanford Asian Pacific Program in Hypertension and Insulin Resistance (SAPPHIRe). There were 13 field centers throughout the United States. The recruitment strategies and characteristics of each cohort have been described previously.[14] This study included patients from GENOA, HyperGen, and SAPPHIRe for whom urinary albumin and creatinine (Cr) measurements were available. Briefly, GENOA recruited sibships with at least two individuals with hypertension diagnosed before age 60 and included 3 field centers: Jackson, MI; Starr County, TX; and Rochester, MN, which recruited African Americans, Mexican Americans, and non-Hispanic whites, respectively. HyperGen recruited hypertensive sibships and, if available, their parents and ≥ 1 untreated adult offspring from 5 field centers: Birmingham, AL; Forsyth County, NC; Framingham, MA; Minneapolis, MN; and Salt Lake City, UT. Lastly, SAPPHIRe recruited sibships from Asian Pacific populations and included two types of sibship pairs: concordant (both siblings with hypertension) and discordant (one sibling with and one without hypertension).

The phase II study examination included a questionnaire regarding participants' personal and family medical histories, medication history, and history of menopause and hormone replacement therapy from female participants. The study visit occurred any time between December 2000 and November 2004 for the patients in this study. In addition, the questionnaire included questions regarding pregnancy and hypertension (described below).

Study Visits
All participants gave informed consent and the institutional review board at each clinic site approved all protocols. The questionnaires were administered via personal interviews with trained examiners. They underwent a standard physical examination and blood and urine tests. The height was measured while the patient was standing against a vertically mounted ruler without shoes on, and weight was measured on a balance scale. Body mass index (BMI) was calculated as weight (kg)/height (m).[2] All patients had their systolic and diastolic blood pressures (BPs) measured using an automatic oscillometric BP measurement device. Three measurements of BP and heart rate were made for each patient.

At the phase II examination visit, the diagnosis of hypertension was confirmed if the average systolic BP or diastolic BP was >140 mm Hg or 90 mm Hg, respectively, or if there was a prior diagnosis of hypertension and use of prescription antihypertensive medication was reported. The diagnosis of diabetes was determined by self-report and an "ever smoked" status was defined as

having smoked >100 cigarettes at any point in the patient's lifetime. The diagnosis of CVD was established by self-report of myocardial infarction, coronary bypass surgery, coronary angioplasty, balloon dilatation, or stent placement. The highest grade of completed education was assessed, as was the use of prescription medications in the last month.

The eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation, and a decreased GFR was defined by an eGFR <60 mL/min/1.73 m^2.[15] Microalbuminuria was defined as a UACR ≥ 25 mg/g creatinine (Cr) on a spot urine sample, which represents the 95th percentile for women, and corresponds to an albumin excretion rate of >30 μg/min.[16] Proteinuria was defined as UACR ≥ 300 mg/g Cr on a spot urine sample. Elevated C-reactive protein (CRP) levels were defined as >0.3 mg/dL[17] and were only available for GENOA patients.

Pregnancy Questionnaire
A questionnaire regarding hypertension and pregnancy that has been previously validated[18] was administered to all networks. In brief, female patients were queried as to whether they had a pregnancy lasting >6 months and whether they had developed hypertension during any of their pregnancies. The participants were asked whether they had a history of preeclampsia or protein in the urine during any hypertensive pregnancy.

Laboratory Methods
Blood was drawn by venipuncture and urine was collected after an overnight fast of at least 8 hours. Serum and urine Cr were measured using the Jaffe assay, and urine albumin was determined using an immunoturbidity method implemented on an automated chemistry analyzer (Hitachi 911; Roche Diagnostics, Indianapolis, IN). Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were all measured by standard methodology, also using the Hitachi 911 Chemistry Analyzer. Low-density lipoprotein (LDL) was calculated using the Friedewald equation when the triglyceride concentration was >400 mg/dL. CRP was measured by a highly sensitive latex particle-enhanced immunoturbidimetric assay.[19]

Statistical Analysis
We used Wilcoxon-rank sum tests to assess pairwise differences in age between the pregnancy groups and chi-square tests for network, race, and education variables. Because of differing recruitment strategies among the networks, all analyses were adjusted for age, race, and network before assessing differences in other measures between pregnancy groups. We used linear regression models for continuous measures and logistic regression models for categorical measures, to adjust for age, race, and network, and reported adjusted mean±standard deviation or adjusted percentages within each pregnancy group. These models were fit

with generalized estimating equations to account for sibling relationships. Quantitative variables with skewed distributions were log-transformed for the models. We also fit additional models for the quantitative and categorical measures of CKD that were adjusted for education, smoking, hypertension, use of hormone replacement therapy, diabetes, BMI, family history of hypertension or CVD, use of antihypertensive medications, and use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), in addition to age, race, and network. The use of antihypertensive medications, ACE inhibitors, and ARBs, were only available in the GENOA network and were coded as 0 for patients in other networks.

RESULTS
A total of 3015 women from 3 of the 4 networks (GENOA, HyperGen, and SAPPHIRe) participated in the second study visit and had UACR and Cr values measured. Of the available patients, 2674 (89%) women reported having at least one pregnancy lasting >6 months and 475 (16%) women reported having hypertension in at least 1 pregnancy. In women with a history of hypertensive pregnancy, the median (interquartile range) time from the first pregnancy with hypertension until the visit when UACR was measured was 27 (19–37) years. In those who reported having hypertension in pregnancy, 144 (31%) reported preeclampsia. Nulliparous women were more likely to have completed higher levels of education than women with at least one pregnancy (P<.001). Non-Hispanic whites made up a larger proportion of those who were nulliparous (42%) compared with both the normotensive and hypertensive pregnancy groups (30% for both, P<.001). Alhough there were only 146 Japanese patients total, the proportion of Japanese patients in the nullip-

arous group was significantly higher (8%) than in the normotensive (5%, P=.01) and hypertensive (3%, P=.002) pregnancy groups. The other demographic characteristics of the patients divided by hypertension-in-pregnancy status are shown in Table I.

After adjusting for age, race, and network, compared with women with a history of normotensive pregnancy, those with hypertensive pregnancies had a significantly higher prevalence of hypertension (75.6% vs 59.4%, P<.001), use of antihypertensive medications (80.8% vs 61.3%, P<.001), use of ACE inhibitors/ARBs (49.9% vs 33.0%, P<.001), diabetes (34.2% vs 27.3%, P<.001), and had a higher BMI (32.8 vs 30.5, P<.001) (Table II). Compared with women with a history of normotensive pregnancy, nulliparous women had a higher prevalence of hypertension (67.4% vs 59.4%, P=.001) and use of antihypertensive medications (68.5% vs 61.3%, P=.037). Estimated GFR was lower in nulliparous women compared with those with normotensive pregnancies (88.4 vs 90.7 mL/min/1.73 m^2, P=.01), but not significantly different in normotensive pregnancies compared with those with hypertensive pregnancies. The mean eGFR was >60 mL/min/1.73 m^2 in all 3 groups of women. UACR was significantly higher in women with a hypertensive pregnancy compared with both normotensive and nulliparous women (7.1 vs 5.4 mg/g Cr for normotensive and nulliparous women, P=.003 and P=.029, respectively). There was also a significant increase in the prevalence of microalbuminuria (19% vs 12.8%, P<.001) and proteinuria (5.4% vs 2.9%, P=.008) in patients with hypertensive vs normotensive pregnancies.

Renal Outcomes
We performed linear regression models on the following continuous measures of CKD—log(UACR), log(Cr),

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TABLE I. Age, Race, Network, and Education Differences by Pregnancy Status

Variable	No.	Nulliparous (n=341)	Normotensive Pregnancy (n=2199)	Hypertensive Pregnancy (n=475)	Normotensive vs Nulliparous P Value	Hypertensive vs Nulliparous P Value	Hypertensive vs Normotensive P Value
Age	3015	51 (40–63)	59 (50–66)	56 (46–64)	<.001	<.001	<.001
Race							
Non-Hispanic white	3015	144 (42)	664 (30)	142 (30)	<.001	<.001	.46
Hispanic		68 (20)	531 (24)	114 (24)			
Non-Hispanic black		102 (30)	900 (41)	204 (43)			
Japanese		27 (8)	104 (5)	15 (3)			
Network							
GENOA	3015	216 (63)	1806 (82)	400 (84)	<.001	<.001	.29
HyperGEN		98 (29)	289 (13)	60 (13)			
SAPPHIRe		27 (8)	104 (5)	15 (3)			
Education							
Less than high school education (≤8 y)	3015	40 (12)	454 (21)	87 (18)	<.001	<.001	.27
Partial high school education (9–11 y)		15 (4)	227 (10)	62 (13)			
High school graduate or GED (12 y)		82 (24)	617 (28)	129 (27)			
Post–high school education (>12 y)		204 (60)	901 (41)	197 (41)			

Abbreviations: GENOA, Genetic Epidemiology Network of Atherosclerosis; HyperGen, Hypertension Genetic Epidemiology Network; SAPPHIRe, Stanford Asian Pacific Program in Hypertension and Insulin Resistance.

TABLE II. Age, Race, and Network-Adjusted Mean±Standard Deviations or Percentages by Pregnancy Status

Variable	No.	Nulliparous (n=341)	Normotensive Pregnancy (n=2199)	Hypertensive Pregnancy (n=475)	Normotensive vs Nulliparous P Value	Hypertensive vs Nulliparous P Value	Hypertensive vs Normotensive P Value
Ever smoked	3015	30.1	31.1	27.4	.73	.40	.11
Current hypertension	3011	67.4	59.4	75.6	.001	<.001	<.001
Antihypertensive medications	2422	68.5	61.3	80.8	.037	<.001	<.001
ACE inhibitors/ARBs	2422	36.9	33.0	49.9	.28	.002	<.001
Diabetes	3014	26.7	27.3	34.2	.84	.027	<.001
Log(BMI)	3009	3.44±0.24	3.42±0.20	3.49±0.21	.10	<.001	<.001
BMI[a]		31.1	30.5	32.8			
Hormone replacement therapy	3010	23.0	23.4	21.9	.87	.70	.47
Birth control	2995	3.3	3.1	2.8	.79	.62	.73
Log(total cholesterol)	3015	5.29±0.21	5.28±0.19	5.26±0.21	.43	.09	.14
Total cholesterol, mg/dL[a]		198.0	196.0	193.0			
Log(triglycerides)	3015	4.84±0.51	4.82±0.51	4.85±0.49	.47	.68	.13
Triglycerides, mg/dL[a]		125.2	122.5	127.1			
Log(LDL cholesterol)	2947	4.74±0.34	4.74±0.31	4.71±0.35	.75	.14	.09
LDL cholesterol, mg/dL[a]		114.6	113.9	110.6			
HDL cholesterol, mg/dL	3015	56.2±16.0	55.5±15.4	54.6±15.9	.40	.14	.28
Log(Cr)	3015	0.58±0.13	0.56±0.13	0.57±0.17	.005	.50	.07
Creatinine, mg/dL[a]		0.79	0.75	0.77			
Estimated GFR (CKD-EPI), mL/min/1.73 m²	3015	88.4±16.4	90.7±16.4	89.7±19.3	.014	.32	.24
Log(UACR)	3015	1.85±1.38	1.85±1.43	2.09±1.61	.96	.029	.003
UACR, mg/g Cr[a]		5.4	5.4	7.1			
Elevated UACR (≥25)	3015	14.3	12.8	19.0	.48	.10	<.001
Elevated UACR (>300)	3015	3.8	2.9	5.4	.50	.38	.008
Family history of hypertension	3015	77.6	74.8	80.9	.28	.22	.001
Family history of CVD	3015	40.1	41.3	44.7	.60	.10	.07

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Cr, creatinine; CVD, cardiovascular disease; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; UACR, spot urine albumin-creatinine ratio.

[a]Variables were log-transformed for the linear models used to estimate the adjusted means in each pregnancy group. Adjusted mean±standard deviations are shown on the log-scale, but for ease of interpretation, the adjusted means are also shown after being un-transformed.

and eGFR—adjusted for education status, smoking status, current hypertension, use of antihypertensives and ACE inhibitors/ARBs (GENOA patients only), use of hormone replacement therapy, diabetes mellitus, log (BMI), and family history of hypertension and CVD (Table III), in addition to age, race, and network. Those with a normotensive pregnancy had a significantly lower predicted serum Cr (*P*=.01) and higher predicted eGFR (*P*=.02) than the nulliparous patients. There was no significant difference in predicted UACR between the

normotensive and nulliparous groups. There was no significant difference in predicted log(UACR), log(Cr), or eGFR between those with hypertensive pregnancies, as compared with normotensive or nulliparous patients.

In the logistic regression model (Table IV), we assessed the effect of a history of hypertensive pregnancy vs normotensive pregnancy and history of normotensive pregnancy vs nulliparous state on the risk of microalbuminuria (UACR >25 mg/g Cr) as a categorical variable. The logistic regression models were

TABLE III. Estimated Mean Difference in Renal Outcomes for Pregnancy Groups

Renal Parameter	Normotensive vs Nulliparous Difference	P Value	Hypertensive vs Nulliparous Difference	P Value	Hypertensive vs Normotensive Difference	P Value
Log(UACR)	0.0229	.78	0.1402	.18	0.1173	.13
Log(Cr)	−0.0194	.011	−0.0134	.20	0.0060	.46
eGFR (CKD-EPI)	2.133	.022	1.900	.13	−0.2337	.81

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Cr, creatinine; eGFR, estimated glomerular filtration rate; UACR, spot urine albumin-creatinine ratio.

TABLE IV. Logistic Regression Model Predicting UACR >25 mg/g Cr by Pregnancy Groups

Parameter	OR (95% CI)	P Value
Hypertensive pregnancy (vs normotensive)	1.37 (1.02–1.85)	.038
Normotensive pregnancy (vs nulliparous)	0.85 (0.58–1.25)	.413
Network		.001
HyperGen	reference	
GENOA	0.95 (0.51, 1.78)	.875
SAPPHIRe	4.88 (2.06, 11.53)	<.001
Race		<.001
Non-Hispanic white	reference	
Hispanic	2.37 (1.44–3.89)	<.001
Non-Hispanic black	3.36 (2.25–5.00)	<.001
Age, per 10 y	1.06 (0.92–1.21)	.434
Education level		.032
High school graduate or GED (12 y)	reference	
Less than high school education (≤8 y)	0.99 (0.68, 1.46)	.977
Partial high school education (9–11 y)	1.17 (0.80–1.70)	.426
Post–high school education (>12 y)	0.69 (0.51–0.94)	.018
Ever smoked	0.93 (0.72–1.19)	.555
Current hypertension	2.29 (1.53–3.43)	<.001
Hormone replacement therapy	0.68 (0.50–0.92)	.013
Antihypertensive medications (GENOA only)	1.30 (0.86–1.96)	.220
ACE inhibitors/ARBs (GENOA only)	0.74 (0.55–0.98)	.036
Diabetes	4.19 (3.19–5.52)	<.001
Log(BMI)	0.86 (0.49–1.54)	.620
Family history of hypertension	1.07 (0.81–1.42)	.641
Family history of CVD	0.97 (0.75–1.24)	.800

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; GENOA, Genetic Epidemiology Network of Atherosclerosis; HyperGen, Hypertension Genetic Epidemiology Network; OR, odds ratio; SAPPHIRe, Stanford Asian Pacific Program in Hypertension and Insulin Resistance; UACR, spot urine albumin-creatinine ratio.

adjusted for the same potential confounders as the linear regression models. There was a significant increase in the risk of microalbuminuria in those with a history of hypertensive pregnancy (odds ratio [OR], 1.37; 95% confidence interval [CI], 1.02–1.85; P=.04) vs those with a normotensive pregnancy. There was no significant difference in the predicted risk of microalbuminuria in those with normotensive pregnancies vs nulliparous patients (OR, 0.85; CI, 0.58–1.25; P=.41) or those with hypertensive pregnancies vs nulliparous patients (OR, 1.17; CI 0.74–1.84; P=.50). We evaluated our models to see if there was any difference in the above outcomes—log(UACR), log(Cr), eGFR, and UACR >25 mg/g Cr—between those with a reported history of preeclampsia vs those with a history of hypertensive pregnancy alone and there were no significant differences.

We have previously reported elevated CRP levels in patients with hypertensive pregnancies vs those with normotensive pregnancies in GENOA patients[6] (presented as abstract, article in press). CRP was only available in the GENOA patients in this study but in subset analyses among the GENOA patients, we found no significant interaction between hypertensive pregnancy and the presence of elevated CRP levels on the development of microalbuminuria (P=.16 for log (UACR) as the outcome and P=.12 for UACR >25 mg/g Cr as the outcome). In addition, adjusting for elevated CRP only minimally changed the estimated differences in microalbuminuria among the pregnancy groups.

DISCUSSION

In this study, we present evidence that women with a history of hypertension in pregnancy are at significantly increased risk for microalbuminuria later in life compared with women with normotensive pregnancies. This relationship remained significant after adjustment for significant risk factors for both CKD and CVD.

Studies on the long-term effects of hypertensive pregnancy on the kidney have shown differing results. Several previous cohort and case-control studies have suggested that there is an increased risk for microalbuminuria after hypertensive pregnancy[8,9,20] and this has been confirmed in a recent meta-analysis.[13] At least two other studies have suggested no increased risk for microalbuminuria.[21,22] One small study of 10 women with HELLP syndrome (a particularly severe form of preeclampsia, characterized by hemolysis, elevated liver enzymes, and low platelet count) showed no difference in UACR at 5 years of follow-up between cases and controls;[21] however, this was a small study and HELLP syndrome is not typically characterized by significant albuminuria. Another study by Lampinen and colleagues[22] assessed the 5-year outcomes after index pregnancy in 30 cases and 21 controls, and excluded patients with chronic hypertension, renal disease, diabetes, or gestational diabetes. They did not find an increased incidence of microalbuminuria, but their inclusion criteria may have been too strict. The strength of our study is that this cohort has well-characterized data on comorbidities with known associations to microalbuminuria. This population included approximately 3000 patients, giving it sufficient power to detect the expected association between microalbuminuria and the relevant comorbidities, such as diabetes and hypertension, as is seen in the logistic regression model shown in Table IV.

Epidemiologic studies have shown that microalbuminuria is an important risk factor for CKD and CVD. Several studies have shown that patients with microalbuminuria, both in diabetics and the general population, are at an increased risk for progression of CKD.[11,23–25] In addition, it has long been considered a marker of general endothelial dysfunction, as first described in type 1 diabetic patients and referred to as the Steno

hypothesis.[26] This has been validated more recently in physiologic studies showing impaired endothelium-dependent, endothelium-independent, and flow-mediated vasodilation of the brachial artery in diabetic patients with microalbuminuria.[27,28] Microalbuminuria is a significant independent risk factor for CVD in both diabetics and nondiabetics.[29,30] Taken together with our other studies from this same cohort of patients showing increased risk for CVD and elevated C-reactive protein[6,7] in patients with a history of hypertensive pregnancy, this study lends further evidence to the hypothesis that a hypertensive pregnancy may inflict long-term, clinically significant vascular changes in the kidney that manifests as microalbuminuria up to 3 decades later.[1] This may in part be due to systemic inflammatory mediators, but in our subset analysis of GENOA patients alone, there was no significant interaction between hypertensive pregnancy and elevated CRP levels on the development of microalbuminuria, and the ORs for those with hypertensive vs normotensive pregnancies were only minimally changed when adjusting for elevated CRP. This suggests that inflammation alone cannot account for the relationship between hypertension in pregnancy and microalbuminuria. Further study into other inflammatory markers, such as lipoprotein(a) and homocysteine, followed prospectively after a hypertensive pregnancy as compared with a normotensive pregnancy, may help elucidate this relationship.

We did not find a statistically significant difference in serum Cr or eGFR in patients with a hypertensive pregnancy vs those with a normotensive pregnancy. This may in part be due to the fact that serum Cr is an indicator of impaired renal function, whereas microalbuminuria may be a marker of renal damage that can be present prior to the decline in function. We also did not detect a difference in log(UACR) between hypertensive and normotensive or nulliparous patients when viewed as a continuous variable, but did see a difference when microalbuminuria was dichotomized as greater than or less than 25 mg/g Cr. This may be due to the fact that the majority of women in all groups had values within the normal range of UACR and thus the relationship with hypertensive pregnancy was masked.

We did observe a slightly decreased serum Cr and higher eGFR in those with normotensive pregnancies vs nulliparous women. While it is a well-established phenomenon that GFR increases and serum Cr decreases during normal pregnancy,[31] there are few data on the long-term renal function after normal pregnancy. Our data would either suggest that this hyperfiltration persists post-delivery or that normotensive pregnancy is in some way protective against a decline in GFR. We do not have information on the reasons that a woman may have remained nulliparous, although these reasons may contain potential confounders unaccounted for in our models. It has been shown that hyperfiltration, even in the early stages of hypertension, is associated with the development of microal-

buminuria. In the Hypertension and Ambulatory Recording Venetia Study (HARVEST), 502 never-treated patients with stage I hypertension (systolic BP 140–159 mm Hg, diastolic BP 90–99 mm Hg) were followed prospectively for approximately 8 years. It was shown that patients with hyperfiltration, defined as a Cr clearance >150 mL/min/1.73 m^2, had an increased risk for the development of microalbuminuria (adjusted hazard ratio, 4.0; 95% CI, 2.1–9.2; $P<.001$) vs patients with normal filtration.[32] To analyze whether hyperfiltration was in part responsible for the risk of microalbuminuria observed in our study, we fit the log(Cr) and eGFR regression models with an additional adjustment for log(UACR), and the log(UACR) and UACR >25 mg/g Cr regression models with and additional adjustment for log(Cr). Even after the additional adjustment, the relationships between hypertensive pregnancy and the renal outcomes remained similar.

STUDY LIMITATIONS

Our study has several limitations. The majority of this cohort was recruited on the basis of a diagnosis of hypertension and therefore has a higher incidence of hypertension than the general population. The medical history and exposure status were ascertained via survey, which introduces the potential for recall bias. In order to minimize the influence of recall bias, standardized protocols and questionnaires were used. Women have been shown to have reasonable recall of pregnancy-related complications.[33] The survey regarding hypertension in pregnancy used in this particular study has been validated previously in patients with a history of preeclampsia >20 years in the past and was found to have 80% sensitivity and 96% specificity.[18] This indicates that patients would be more likely to under-report rather than over-report their exposure, which would result in an underestimation of the true risk of microalbuminuria.

Despite these limitations, our study shows that hypertensive pregnancy is an independent risk factor for microalbuminuria after controlling for known risk factors for CKD and CVD. In the most recent guidelines from the American Heart Association in 2011, preeclampsia was formally identified as a major risk factor for CVD in women.[34] The question remains, what tools should we use to identify women at the highest risk for CVD? Testing for microalbuminuria is simple, inexpensive, and noninvasive and has been shown to be cost-effective when used to prevent renal and cardiovascular outcomes.[35,36] Women with a hypertensive pregnancy have been shown to be at an increased risk for renal and CVD, and therefore routine screening for microalbuminuria may be a way to monitor and intervene early in this population. Another unanswered question is whether intervention with medications, such as ACE inhibitors, in the postpartum period after a mother has finished breastfeeding, can prevent the development of microalbuminuria and lower subsequent CVD risk.

CONCLUSIONS

Hypertension in pregnancy is associated with an increased risk of microalbuminuria independent of traditional risk factors for CKD and CVD. The body of evidence that this is a population at risk for significant cardiovascular and renal disease continues to grow and may eventually lead to standardized guidelines for the long-term follow-up of women with a hypertensive pregnancy.

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