

Uric Acid Is as Important as Proteinuria in Identifying Fetal Risk in Women With Gestational Hypertension

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Abstract—Gestational hypertension is differentiated into higher and lower risk by the presence or absence of proteinuria. We asked if hyperuricemia, a common finding in pregnancy hypertension, might also be an indicator of increased risk. We examined fetal outcome data from 972 pregnancies collected from 1997 to 2002 in a nested case-control study. Participants were nulliparous with no known medical complications. The frequency of preterm birth, the duration of pregnancy, frequency of small-for-gestational-age infants, and birth weight centile were determined for pregnancies assigned to 8 categories by the presence or absence of combinations of hypertension, hyperuricemia, and proteinuria. In women with gestational hypertension, hyperuricemia was associated with shorter gestations and smaller birth weight centiles and increased risk of preterm birth and small-for-gestational-age infants. Hyperuricemia increased the risk of these outcomes in the presence or absence of proteinuria. Risk was also increased in a small group of women with hyperuricemia and proteinuria without hypertension. Women with only hypertension and hyperuricemia have similar or greater risk as women with only hypertension and proteinuria. Those with hypertension, proteinuria, and hyperuricemia have greater risk than those with hypertension and proteinuria alone. The risk of these outcomes increased with increasing uric acid. Hyperuricemia is at least as effective as proteinuria at identifying gestational hypertensive pregnancies at increased risk. Uric acid should be reexamined for clinical and research utility. (*Hypertension*. 2005; 46:1263-1269.)

Key Words: gestational hypertension ■ preeclampsia ■ pregnancy ■ uric acid ■ intrauterine growth restriction ■ preterm birth ■ risk assessment

Hypertensive disorders during pregnancy increase maternal and infant risk. The greatest impact is associated with the pregnancy-specific syndrome, preeclampsia.¹ Preeclampsia, conventionally diagnosed by the gestational onset of hypertension and proteinuria, increases perinatal mortality 5-fold¹ and kills 50,000 women yearly worldwide.² Its management, delivery to halt the progression of the pathophysiology, is responsible for 15% of preterm births in developed countries.³ Gestational hypertension without proteinuria has much less of an adverse effect on maternal or fetal outcome, whereas the major risk from hypertension that antedates pregnancy is the superimposition of preeclampsia.⁴ The importance of differentiating these conditions is reflected in several classification schemes in which gestational hypertension with proteinuria is separated from gestational hypertension without proteinuria and hypertension that antedates pregnancy.⁴⁻⁶

These diagnostic criteria currently used to discriminate high-risk from lower risk women with gestational hypertension are arbitrary. The term “preeclampsia” was coined in the early 20th century when it was recognized that hypertension

and proteinuria could be precursors to a pregnancy-specific seizure disorder, eclampsia, which had been recognized for 2000 years. It soon became evident that the combination of hypertension and proteinuria identified high-risk women and infants.⁷ These important findings identified preeclampsia as an important entity to increase maternal and infant risk. However, it has never been established that, of the myriad of other signs, symptoms, or biochemical abnormalities associated with preeclampsia, hypertension and proteinuria are the best indicators of outcome.

Elevated uric acid is another component of the preeclampsia syndrome that was recognized many years ago.⁷ It is one of the most consistent and earliest detectable changes in preeclampsia and has been cited as a better predictor of fetal risk than blood pressure.^{8,9} Despite these findings, uric acid assessment in the evaluation of gestational hypertension has fallen into disfavor. A recent publication stated “. . . the utility of measuring serum uric acid levels in hypertensive diseases of pregnancy is limited.”¹⁰

In the current study, we used a research database in which preeclampsia had been rigidly diagnosed to ask whether the

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inclusion of uric acid in the diagnosis of preeclampsia would be an indicator of outcome. We focused primarily on fetal outcomes, gestational age at delivery, and birth weight centiles, because these adverse outcomes occur more frequently than severe maternal morbidities. We also assessed measures of maternal disease severity as indicated by the presence of severe preeclampsia and the degree of blood pressure elevation in labor.

Methods

We evaluated data acquired from 1997 to 2002 as part of an ongoing study of preeclampsia approved by the Magee-Womens Hospital Institutional Review Board. Eligibility criteria were nulliparous women with singleton gestations and no obstetric or medical problems. Socio-demographic and clinical data were ascertained by an interview at entry to the study and medical chart abstraction after delivery.

We studied all of the nulliparous women in the database who had gestational hypertension and/or proteinuria and delivered a live birth ($n=437$), as well as a random sample of 628 nulliparous women who had neither gestational hypertension nor proteinuria and delivered a live birth. Plasma uric acid concentration was measured in the hospital on samples collected on admission for delivery on 92% of the 437 women with gestational hypertension and/or proteinuria and on 9% of the 628 women with neither gestational hypertension nor proteinuria. We measured serum uric acid concentrations on samples collected at admission for labor and delivery for the remaining women. Of the 1065 women available, 80 with either gestational hypertension and/or proteinuria and 13 with neither gestational hypertension nor proteinuria had missing data on 1 of the confounders and were excluded from the final analysis. Compared with the sample of 1065 women, the final sample of 972 was less likely to have hypertension, proteinuria, and hyperuricemia (14.5% versus 17.3%), to deliver before 37 weeks (14.7% versus 17.4%), and to have an infant born at <5th centile (5.5% versus 6.1%). There were no meaningful differences in maternal race, smoking, or age.

Preeclampsia was defined by the research criteria recommended by the National High Blood Pressure Education Program⁴: gestational hypertension, proteinuria, and return of all abnormalities to normal by 12 weeks postpartum. Gestational hypertension was defined as diastolic blood pressure persistently ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic for the first time after 20 weeks of gestation. In this study, we determined blood pressure as the average of the last 5 blood pressures obtained in semi-Fowlers position after hospital admission for delivery but before medications or clinical perturbations that would alter blood pressure. Proteinuria was the excretion of >300 mg of protein in 24 hours, a random sample of 2 plus, a catheterized sample of 1 plus, or a protein creatinine ratio of >0.3 . Hyperuricemia was defined as serum or plasma uric acid concentrations ≥ 1 SD above normal for gestational age,¹¹ a value that corresponds with what is considered hyperuricemia at term in most studies.^{8,12,13} We chose 1 SD rather than a fixed value as abnormal, because uric acid increases strikingly¹¹ with advancing gestation. For the same reason, the analysis of uric acid as a continuous variable is presented as z scores to account for gestation-specific changes in uric acid.

Plasma uric acid was measured by autoanalyzer in the Magee-Womens Hospital clinical laboratories or in a blinded fashion on stored specimens from our database by a diagnostic kit (Pointe Scientific). In preliminary studies, we found uric acid to be extremely stable. Values for serum uric acid concentration performed in our laboratory using the diagnostic kit on samples stored from 6 to 72 months at -70°C agreed with values obtained in the clinical laboratory ($r^2=0.8$). The intra-assay variation in our laboratory assays of uric acid was 8.8%. Severe disease was defined as including any of the following: systolic blood pressure ≥ 160 , diastolic blood pressure ≥ 110 , platelets $\leq 100,000$, proteinuria ≥ 5 g on a 24-hour collection, or elevated liver enzymes.

Preterm birth was defined as ≤ 37 completed weeks of gestation. Gestational age-specific birth weight centile was based on data from Magee-Womens Hospital adjusted for sex and race. Small-for-

gestational age (SGA) was defined as birth weight ≤ 10 th centile and ≤ 5 th centile.

Maternal race and smoking status were self-reported at enrollment. Prepregnancy body mass index [weight (kg)/height (m)²] was based on measured height and maternal self-report of prepregnancy weight at the initial visit.

Statistical Analysis

The χ^2 test for homogeneity and 1-way ANOVA were used to test for differences in categorical and continuous maternal characteristics, respectively, by diagnostic criteria. Multivariable log-binomial regression was used to calculate risk ratios associated with the independent effect of diagnostic criteria on the risk of preterm birth and SGA infants. Multivariable linear regression was used to assess the independent effect of diagnostic criteria on gestational age at delivery and birth weight centile. Covariates entered into the full models were maternal age (continuous), race [white or other (98% African-American)], education (<12 , 12, or >12 years), marital status (married, nonmarried, or marriage-like), prepregnancy body mass index (<18.5 , 18.5–24.9, 25.0–29.9, or ≥ 30.0 kg/m²),¹⁴ gravidity (1 or ≥ 2), and smoking status (smoker or nonsmoker). Full models were reduced using backward elimination, where confounding was defined as a change of $>10\%$ in a comparison of the unadjusted and adjusted estimates for the association between diagnostic criteria and the outcome.

Interactions among the 3 diagnostic criteria (gestational hypertension, proteinuria, and hyperuricemia) were statistically significant for all of the models except for preterm birth but were maintained in this model for consistency. Because of the interaction among diagnostic criteria, we categorized each woman into 1 of 8 groups: gestational hypertension, proteinuria, and hyperuricemia (HPU); gestational hypertension and proteinuria only (HP); gestational hypertension and hyperuricemia only (HU); proteinuria and hyperuricemia only (PU); gestational hypertension only (H); proteinuria only (P); hyperuricemia only (U); and normal values of blood pressure, urinary protein, and serum or plasma uric acid (NNN).

We examined the relation between uric acid z score¹¹ and odds of preterm birth and SGA infants ≤ 10 th centile using logistic regression (Figure). Because of the interactions between hypertension and proteinuria, we studied this relation within 3 strata: (1) women with neither hypertension nor proteinuria; (2) women with hypertension but without proteinuria; and (3) women with hypertension and proteinuria. Nonparametric smoothing with locally weighted regression¹⁵ was used to determine the appropriate specification of uric acid z score in each model. Differences were considered significantly if $P<0.05$.

Results

HP Versus HPU

We asked if the addition of hyperuricemia (HPU) to the standard diagnosis of preeclampsia (HP) identified a subset of women with a more severe form of preeclampsia. Neither blood pressure before 20-weeks gestation nor any of the maternal characteristics was different in the 2 groups (Table 1). HPU defined a more severe disorder. Diastolic and systolic blood pressures at labor were higher ($P<0.003$), and severe preeclampsia and hemolysis, low platelets, and elevated liver enzymes were diagnosed in 19.9% and 2.8%, respectively, of women with HPU and in 16.7% and 0%, respectively, of women with HP. We also examined the impact of the inclusion of hyperuricemia on the duration of pregnancy and fetal growth (Tables 2–4). Compared with pregnancies with HP, pregnancies with HPU delivered an average of 3.6 weeks earlier (Table 4) and were nearly 7 times as likely to deliver preterm (Table 2). As expected, the majority of early deliveries were induced as treatment of preeclampsia, [indicated preterm births (HP, 3 of 4, and HPU, 71 of 81)].

TABLE 1. Maternal Characteristics by Diagnostic Criteria

Characteristic	NNN (n=431)	H (n=83)	P (n=21)	U (n=184)	HP (n=48)	HU (n=52)	PU (n=12)	HPU (n=141)	P Value
Race (%)									<0.001
White	65.7	62.7	71.4	76.6	72.9	75.0	83.3	78.7	
Other	34.3	37.4	28.6	23.4	27.1	25.0	16.7	21.3	
Age, y (%)									<0.001
<18	10.0	8.5	9.5	7.1	6.3	5.8	8.3	5.7	
19–21	42.9	48.2	38.1	31.5	27.1	23.1	16.7	17.0	
22–24	15.5	15.7	9.5	19.0	10.4	9.6	25.0	18.4	
25–29	16.2	10.8	23.8	20.7	25.0	38.5	41.7	27.7	
30–34	11.8	13.3	14.3	16.3	18.8	19.2	8.3	20.6	
≥35	3.5	3.6	4.8	5.4	12.5	3.9	0.0	10.6	
Smoking status (%)									0.06
Nonsmoker	68.7	78.3	81.0	69.0	72.9	76.9	91.7	80.1	
Smoker	31.3	21.7	19.0	31.0	27.1	23.1	8.3	19.9	
Prepregnancy BMI (kg/m ²) (%)									<0.001
<18.5	7.4	1.2	0.0	6.0	2.1	0.0	0.0	3.6	
18.5–<25	57.8	36.1	52.4	46.7	41.7	42.3	50.0	39.0	
25–<30	20.4	37.4	28.6	26.1	29.2	26.9	25.0	30.5	
≥30	14.4	25.3	19.1	21.2	27.1	30.8	25.0	27.0	
Education, y (%)									<0.001
<12	22.7	18.1	19.1	32.1	16.7	7.7	8.3	7.1	
12	26.9	27.7	19.1	25.5	29.2	30.8	58.3	29.8	
>12	50.4	54.2	61.9	42.4	54.2	61.5	33.3	63.1	
Marital status (%)									<0.001
Married	25.3	24.1	28.6	34.2	45.8	50.0	50.0	47.5	
Not married	58.7	61.5	66.7	50.0	52.1	36.5	50.0	48.9	
Marriage-like relationship	16.0	14.5	4.86	15.8	2.1	13.5	0.0	3.6	
Systolic BP <20 weeks, mean (SD)	112 (7.6)	117 (7.9)	114 (7.2)	113 (7.7)	117 (8.6)	119 (9.0)	117 (8.3)	117 (10.1)	<0.001
Diastolic BP <20 weeks, mean (SD)	69 (5.5)	71 (6.5)	69 (5.9)	68 (5.8)	72 (7.0)	72 (6.0)	73 (6.1)	72 (7.2)	0.002
Systolic BP at labor, mean (SD)	118 (9.2)	148 (10.4)	126 (10.7)	121 (10.1)	154 (11.6)	148 (11.4)	133 (7.5)	160 (14.9)	<0.001
Diastolic BP at labor, mean (SD)	71.6 (6.9)	86.3 (7.5)	73.5 (8.5)	73.0 (6.9)	90.1 (8.7)	88.1 (7.4)	76.6 (4.8)	94.0 (10.6)	<0.001
Uric acid z score, mean (SD)	−0.15 (0.81)	−0.18 (0.94)	−0.24 (0.80)	2.0 (0.83)	0.02 (0.71)	1.9 (0.90)	2.0 (1.6)	2.8 (1.5)	<0.001
Severe disease (%)	0	2.2	0	0.5	16.7	5.4	6.7	19.9	<0.001
HELLP syndrome (%)	0	0	0	0	0	0	0	2.8	<0.001
Labor type and route of delivery									<0.001
Spontaneous vaginal at term	63.8	54.2	38.1	54.9	27.1	34.6	25.0	7.8	
Induced vaginal delivery at term	15.6	20.5	23.8	16.3	37.5	26.9	16.7	18.4	
Cesarean at term	14.4	20.5	28.6	21.7	27.1	19.2	41.7	16.3	
Spontaneous vaginal preterm	4.4	2.4	4.8	4.4	2.1	5.8	0	7.1	
Induced vaginal delivery preterm	0.7	1.2	4.8	1.6	4.2	7.7	16.7	22.7	
Cesarean preterm	1.2	1.2	0	1.1	2.1	5.8	0	27.7	

BMI indicates body mass index; BP, blood pressure; P value indicates significance of χ^2 test for homogeneity or F-test for a 1-way ANOVA; severe disease includes at least one of: systolic blood pressure ≥ 160 , diastolic blood pressure ≥ 110 , platelets $\leq 100\ 000$, proteinuria ≥ 5 grams on a 24-hour collection, or elevated liver enzymes.

We examined fetal growth adjusted for gestational age in the HP and HPU compared with NNN pregnancies and with each other. After adjusting for confounders, the risk of an infant having a birth weight ≤ 10 th or ≤ 5 th centile was significantly higher in the HPU group compared with NNN women, but there was no difference between pregnancies with HP and NNN (Table 3). Although the mean birth weight centile was smaller for infants born to HP and HPU women than for infants of women in the NNN group, the adjusted

mean birth weight centile was significantly lower for the HPU group than for the HP women (Table 4).

HP Versus HU

We identified women with gestational hypertension who did not achieve the diagnostic increase of both increased protein and uric acid (negative data were present on all of the women). We asked whether HU had implications for the severity of the disease or impact on fetal outcome and if

TABLE 2. Association Between Diagnostic Criteria and Risk of Preterm Birth <37 Weeks Gestation (n=972)

Diagnostic Group	Unadjusted Prevalence of Preterm Birth (%)	Adjusted* RR† (95% CI)	P Value
NNN	6.3	1.0 (referent)	—
H	4.8	0.8 (0.3, 2.7)	0.69
P	9.5	1.7 (0.4, 6.6)	0.45
U	7.1	1.1 (0.6, 2.2)	0.69
HP	8.3	1.4 (0.5, 3.8)	0.51
HU	19.2	3.3 (1.7, 6.4)	<0.001
PU	16.7	3.0 (0.8, 11.1)	0.10
HPU	57.5	9.7 (6.5, 14.3)	<0.001

RR indicates risk ratio.

*Adjusted for prepregnancy body mass index and smoking.

†Other contrasts of interest are as follows [RR (95% CI)]: HPU vs HP: 6.9 (2.7–17.9), $P<0.001$; HU vs HP: 2.4 (0.8–7.0), $P=0.12$; HU vs H: 4.0 (1.3–12.2), $P=0.01$.

the maternal characteristics were similar to women with HP. Aside from HP women being more likely to be unmarried (Table 1; $P=0.04$), there were no differences in maternal characteristics. Severe disease was diagnosed in 16.7% of women with HP and in 5.4% of women with HU ($P>0.05$). Blood pressure elevation in labor was similar (Table 1). The adjusted risk of preterm birth among women with HU was 3.3 times that of NNN women (Table 2), but the risk was not significantly elevated for women with HP. Of the HU preterm births, 7 of 10 were indicated deliveries. HU women were also >10 times as likely as HP women to have an SGA infant less than the 10th or 5th centile, although estimates were imprecise (Table 3). The adjusted gestational age at delivery and birth weight centile were decreased among women in both HU and HP groups compared with NNN women (Table 4), but the difference was significantly greater in the HU than HP group.

H Versus HU

The current diagnosis of transient hypertension of pregnancy is based on diagnostic gestational hypertension without proteinuria.⁴ This diagnosis includes women with and without hyperuricemia. Two women (2.2%) with H alone had severe disease because of high blood pressure. By contrast, 3 women (5.4%) with HU had severe disease with 2 of the 3 having the diagnosis based on elevated liver enzymes and low platelets, as well as high blood pressure. As is evident from the data presented above, the HU women are a group with shorter pregnancies and lower birth weight centiles than NNN women. This was not the case for H women, who had no increase in risk of preterm birth, SGA or reduced length of gestation, or birth weight centile compared with NNN women (Tables 2–4). This was despite blood pressures in labor being similar in both the HU and H groups (Table 1). Maternal characteristics were different between the H and HU women. Women in the HU group were older ($P<0.04$ for ages <34 years) and more likely to be white ($P=0.03$), to have >12 years of education ($P=0.02$), and to be married ($P=0.001$).

Other Relationships

Pregnancy outcomes for the other combinations of variables showed no significant difference in outcomes from NNN pregnancy with the exception of the PU group. Despite small sample size ($n=12$), this group had significantly greater incidence of SGA both at the 5th and 10th centile and a lower mean gestational age at delivery and birth weight centile than NNN pregnancies (Tables 3 and 4).

Preterm Labor and SGA Diagnosis in Relation to Uric Acid Concentration

Among the women without hypertension and without proteinuria ($n=615$), there was no relation between the uric acid concentration z score and the odds of either preterm birth or SGA (data not shown). By contrast, among those with hypertension but without proteinuria ($n=135$), there was a

TABLE 3. Association Between Diagnostic Criteria and SGA (n=972)

Diagnostic Group	SGA <10th Centile			SGA <5th Centile		
	Unadjusted Prevalence (%)	Adjusted* RR† (95% CI)	P Value	Unadjusted Prevalence (%)	Adjusted† RR‡ (95% CI)	P Value
NNN	8.5	1.0 (referent)	—	4.6	1.0 (referent)	—
H	2.2	0.3 (0.1, 1.2)	0.09	1.1	0.3 (0.1, 2.1)	0.21
P	4.2	0.7 (0.1, 4.5)	0.66	4.2	1.2 (0.2, 8.7)	0.83
U	7.4	0.9 (0.5, 1.7)	0.77	2.1	0.5 (0.2, 1.4)	0.16
HP	12.3	1.3 (0.5, 3.2)	0.53	4.6	0.9 (0.2, 3.9)	0.93
HU	22.4	3.5 (2.0, 5.9)	<0.001	15.5	4.6 (2.2, 9.7)	<0.001
PU	33.3	6.1 (3.0, 12.7)	<0.001	20.0	7.4 (2.4, 22.1)	<0.001
HPU	23.9	2.6 (1.7, 4.1)	<0.001	12.5	2.2 (1.2, 4.5)	0.02

RR indicates risk ratio.

*Adjusted for race, smoking, and marital status.

†Adjusted for prepregnancy body mass index, smoking, and marital status.

‡Other contrasts of interest are as follows [RR (95% CI)]: HPU vs HP: 2.0 (0.8–4.8), $P=0.13$; HU vs HP: 11.4 (2.7–48.1), $P=0.001$; HU vs H: 2.6 (1.1–6.6), $P=0.04$.

§Other contrasts of interest are as follows [RR (95% CI)]: HPU vs HP: 2.4 (0.6–10.0), $P=0.24$; HU vs HP: 16.4 (2.2–125.1), $P=0.007$; HU vs H: 4.9 (1.1–21.3), $P=0.03$.

TABLE 4. Relation Between Diagnostic Criteria and Length of Gestation and Birth Weight Centile (n=972)

Diagnostic Group	Gestational Age at Delivery			Birth Weight Centile		
	Unadjusted Gestational Age at Delivery (weeks)*	Adjusted† Coefficient‡,§ (95% CI)	P Value	Unadjusted Birth Weight Centile*	Adjusted Coefficient‡,¶ (95% CI)	P Value
NNN	39.5 (1.9)	0.0 (referent)	—	50.0 (28.0)	0.0 (referent)	—
H	39.4 (1.5)	-0.12 (-0.66, 0.42)	0.67	50.2 (28.1)	-3.4 (-10.0, 3.1)	0.31
P	38.6 (4.2)	-0.95 (-1.94, 0.05)	0.06	55.9 (28.6)	3.1 (-9.0, 15.2)	0.61
U	39.5 (1.8)	0.03 (-0.37, 0.42)	0.90	51.7 (29.0)	-0.21 (-4.6, 5.0)	0.93
HP	39.0 (1.5)	-0.53 (-1.21, 0.15)	0.13	42.8 (28.7)	-11.7 (-19.0, -2.4)	0.01
HU	38.7 (2.0)	-0.89 (-1.55, -0.23)	0.008	38.9 (31.8)	-14.8 (-22.9, -6.8)	<0.001
PU	38.0 (2.1)	-1.62 (-2.93, -0.31)	0.02	33.3 (31.1)	-21.3 (-37.2, -5.4)	0.01
HPU	35.4 (3.7)	-4.15 (-4.59, -3.71)	<0.001	33.7 (26.5)	-20.5 (-25.9, -15.11)	<0.001

*Mean (SD).

†Adjusted for prepregnancy body mass index, smoking, and education.

‡Each coefficient represents the change in the gestational age at delivery (weeks) or birth weight centile associated with having gestational hypertension, proteinuria, and/or hyperuricemia compared with normal women.

§Adjusted for prepregnancy body mass index, smoking, and marital status.

||Other contrasts of interest are as follows [coefficient (95% CI), P value]: HPU vs HP: -3.63 (-4.37 to -2.88), P<0.001; HU vs HP: -0.78 (-1.57 to 0.01), P=0.05; HU vs H=-0.37 (-1.23 to 0.52), P=0.42.

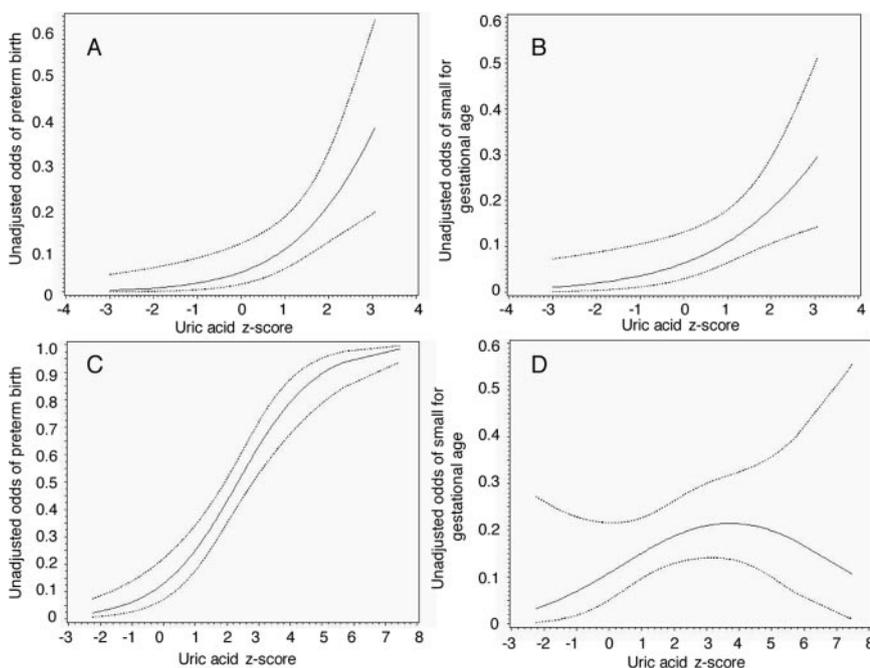
¶||Other contrasts of interest are as follows [coefficient (95% CI), P value]: HPU vs HP: -9.8 (-18.8 to -0.79), P=0.03; HU vs HP: -11.4 (-21.0 to -1.79), P=0.02; HU vs H=-4.2 (-15.0 to 6.68), P=0.45.

striking positive relationship between uric acid z score and the odds of preterm birth and SGA (Figure 1 a and b). Every 1-unit increase in uric acid z score increased the odds of preterm birth by 2.3-fold (odds ratio, 2.3; 95% CI, 1.4–3.7) and SGA by 1.8-fold (odds ratio, 1.8; 95% CI, 1.2–2.7). The results for women with both hypertension and proteinuria (n=189) also showed an increase in the odds of preterm birth with increasing uric acid (Figure 1c). Every 1-unit increase in uric acid z score increased the odds of preterm birth by 2.3-fold (odds ratio, 2.3; 95% CI, 1.7–2.9). The SGA relationship was not as clear. The odds of SGA increased with uric acid concentration to a z score of 4. However, as shown

in Figure 1d, estimates were imprecise beyond z scores of 4 because of sparse data. Adjusting for aforementioned covariates had no effect on these relationships.

Discussion

The data presented indicate that in women with gestational hypertension with or without proteinuria, elevated uric acid concentration identifies a group of pregnancies at increased risk for SGA and preterm delivery compared with each condition in the absence of hyperuricemia. The increased incidence of preterm delivery in this study in most instances reflects the severity of disease rather than natural history



Association between uric acid z score and odds of preterm birth and SGA <10th centile. (a and b) these relations among women who had gestational hypertension but no proteinuria (n=135); (c and d) these relations among women who had both gestational hypertension and proteinuria (n=189). Solid lines indicate the point estimate; dotted lines indicate the upper and lower 95% confidence bands.

because most early deliveries with hypertension and proteinuria were medically indicated preterm inductions and births.

The relationship of uric acid to gestational age and birth weight centile in women with gestational hypertension is concentration dependent. In the presence of hypertension with or without proteinuria, the incidence of preterm delivery increased as uric acid increased. A similar linear trend was seen for the incidence of SGA among women with hypertension and no proteinuria.

In our study, HU and H women were substantially different, despite the fact that, in all of the classification schemes, these groups would be combined. HU women were more likely to be white, older, more educated, and married. More importantly, they had an increased risk of early delivery and SGA that was not present in women with gestational hypertension alone. Data from the PU women indicating increased SGA and shortened pregnancies is intriguing and supports preeclampsia as a syndrome in which perhaps any 2 pathophysiological abnormalities will identify a pregnancy at increased risk.

There are obvious limitations to this study. Twenty-four-hour urine collections for the determination of proteinuria were performed on only a small percentage of women. It is well recognized that with the hectic protein excretion of preeclampsia, random urines with negative findings can be associated with increased protein excretion.¹⁶ This could have led us to conclude that women with HU did not have proteinuria. However, twenty-four-hour urines were done in a fairly similar proportion of HU (15%) and HP (25%) women, although 35% of HPU women had this determination. In addition, if uric acid did influence delivery decisions, this would account for the increased frequency of indicated preterm birth. However, like most U.S. institutions, uric acid is not considered in management decisions at our institution. This is supported by the similar frequency of indicated delivery in women with HP or HPU. Additionally, this potential bias would not explain the excess of SGA infants with increased maternal uric acid concentration. Although the women in this sample are racially and socioeconomically diverse, data comes from a single center, which may limit generalizability.

Despite the fact that hyperuricemia is not a conventionally used diagnostic criterion for preeclampsia and not typically considered a useful aid to management, several observations have suggested that the presence of hyperuricemia may identify a form of pregnancy hypertension with increased risk. Redman⁸ 25 years ago demonstrated an increased risk of fetal death in preeclampsia with elevated uric acid. Likewise, in another study, there was an increase in SGA among gestationally hypertensive women with proteinuric and non-proteinuric hyperuricemia.¹⁷ Elevated uric acid has been related to eclamptic seizures.¹⁸ The duration of hypertension after a hypertensive pregnancy was similar in women with hypertension and either hyperuricemia or proteinuria and longer than in women with gestational hypertension alone.¹⁹ There seems to be a special interrelationship between the renal lesion of preeclampsia and hyperuricemia. In a study of 62 pregnant women with gestational hypertension without proteinuria, the characteristic preeclamptic renal lesion,

termed glomeruloendotheliosis, was only present in women with hyperuricemia.²⁰

Is it biologically plausible that increased uric acid could be associated with adverse outcome? The hyperuricemia of preeclampsia has been variably suggested to be associated with lactic acidosis, altered renal function, or oxidative stress. The currently favored concept is that increased circulating uric acid is secondary to reduced renal urate clearance, as can be seen with hypovolemia. Uric acid is the end product of purine catabolism catalyzed by the enzyme xanthine oxidase/dehydrogenase. This bifunctional enzyme in its dehydrogenase form produces uric acid and reduced nicotinamide-adenine dinucleotide and, in the oxidase form, produces uric acid and superoxide. The enzyme is upregulated, and the expression of the oxidase form increased proportionally with hypoxia. Thus, increased uric acid production occurs in a setting of hypoxia, local acidosis, or increased tissue breakdown or with reduced renal function and can increase oxidative stress—all of which would indicate more severe preeclampsia. Recently, an additional possibility has been suggested, that uric acid might itself be causally related to hypertension.^{21,22} In animal experiments, rats rendered minimally hyperuricemic by inhibiting uricase had increased blood pressure that could be reversed by lowering uric acid.²³ It has been suggested that, in humans, uric acid might increase hypertension by increasing salt sensitivity and vascular smooth muscle proliferation.²⁴

Perspectives

What are the clinical implications of these findings? Based on the limitations of our design, it is important that the relationships we observed are examined prospectively and tests performed to determine whether management based on this additional information positively and cost effectively affects outcome. It is quite likely based on prior studies that uric acid will add little to the armamentarium used in the complex decision making for delivery, the cornerstone of management in women with preeclampsia.²⁵ It does appear, however, that plasma or serum uric acid—a simple, inexpensive and readily available test—should be additionally evaluated. Our data suggest that uric acid is at least as important as proteinuria in identifying pregnancies with gestational hypertension with at-risk infants. Although currently available data support the concept that gestational hypertension without proteinuria has an outcome far better than when the hypertension is accompanied by proteinuria, there is still evidence of increased risk.²⁶ An important question to resolve is whether, as is suggested by our data, the adverse outcomes are only present with concomitantly increased uric acid. Finally, this finding encourages a reevaluation of the current classification of pregnancy hypertension using different markers of pathophysiology.

The research implications are more direct. Including uric acid in the research diagnosis of preeclampsia identifies a more severe group that is likely to have a more homogeneous pathophysiology than when this marker is not included. Certainly in the evaluation of gestational hypertension without proteinuria as a “control” for preeclampsia, the absence of hyperuricemia identifies a lower risk group.

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Uric Acid Is as Important as Proteinuria in Identifying Fetal Risk in Women With Gestational Hypertension

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