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Uric acid concentrations are associated with insulin resistance and birthweight in normotensive pregnant women

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Abstract

OBJECTIVE—To investigate whether uric acid concentrations are increased in pregnant women with insulin resistance and to correlate both with fetal growth.

STUDY DESIGN—Uric acid, glucose and insulin were measured in plasma at 20.4 ($\pm$ 2.0) weeks gestation in 263 women. The association between uric acid and insulin resistance as estimated using the homeostasis model assessment (HOMA) was analyzed and related to birthweights.

RESULTS—In 212 (80.6%) women who remained normotensive throughout pregnancy, HOMA increased 1.23 units per 1 mg/dl increase in uric acid [(95%CI: 1.07,1.42), $p=0.003$]. Infants born to normotensive women in the upper quartile of uric acid and lowest HOMA quartile weighed 435.6 grams less than infants of women with highest uric acid and HOMA quartiles ($p < 0.005$).

CONCLUSION—Increasing uric acid concentrations were associated with insulin resistance in mid-pregnancy. Hyperuricemia was associated with lower birthweight in normotensive women, and this effect was attenuated by insulin resistance.

Keywords

uric acid; hyperuricemia; insulin resistance; birthweight

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Condensation

In normotensive women, uric acid was associated with insulin resistance in mid-pregnancy, and in the absence of insulin resistance, hyperuricemia was related to reduced birthweight.

INTRODUCTION

An estimated 66% of adults in the United States are either overweight or obese.¹ The obesity epidemic is associated with an increase in the frequency of the metabolic syndrome, now present in 6% of women in the United States aged 20-29. The prevalence doubles to 13% among women aged 30-39.^{2, 3} Both obesity and metabolic syndrome are associated with increased risk for adverse pregnancy outcomes including gestational diabetes, gestational hypertension, preeclampsia, stillbirth, accelerated fetal growth and cesarean section.⁴⁻⁶

Metabolic syndrome is associated with hyperuricemia as well as insulin resistance.^{2, 7} In pregnancy, elevated serum uric acid in hypertensive pregnant patients is associated with poor perinatal outcomes including small for gestational age (SGA) infants and preterm birth (PTB).^{8, 9} Insulin resistance, however, is a component of gestational diabetes and increasing risk for excessive fetal growth, as well as gestational hypertension and preeclampsia.¹⁰⁻¹² Thus, although both uric acid and insulin resistance are associated with metabolic syndrome, these conditions could have opposing or perhaps synergistic effects on maternal and fetal health. Only one small study in pregnancy investigated the association between third trimester serum uric acid concentrations and insulin resistance.¹³ Insulin resistance was correlated with elevated serum uric acid in women with gestational hypertension ($r=0.92$; $p=0.0026$), but not in women with preeclampsia ($r=0.16$; $p=0.72$) or controls ($r=-0.16$; $p=0.67$). Neonatal outcomes were not assessed for any group.

In this study, we related insulin resistance and uric acid concentrations at mid-gestation among normotensive and hypertensive women. We hypothesized that uric acid concentrations would be increased in pregnant women with insulin resistance, regardless of hypertensive status. Additionally, we postulated that elevated uric acid concentrations in normotensive women would be associated with decreased fetal growth, and that this effect would be mediated by insulin resistance.

MATERIALS AND METHODS

We used banked plasma samples from specimens drawn at 18-21 weeks gestation from fasting subjects enrolled in the Pregnancy Exposures and Preeclampsia Prevention Study. This was a prospective study of pregnant women ($n = 2812$) enrolled at <21 weeks gestation from 1997-2006 and followed to the post partum visit. Fasting samples were collected beginning in 2002. Of 706 nulliparous women in the longitudinal study that were invited to give a fasting sample, 272 plasma samples were available from women with no history of pre-pregnancy diabetes or chronic hypertension. This subset of women was about one year older (24.4 versus 23.3 years, $p = 0.01$) and slightly more likely to have a high school education (89.4% versus 85.6%, $p = 0.01$) than the other women in the longitudinal study. They did not differ, however, regarding race or gestational age at delivery.

Baseline demographic information and medical history were collected via a structured interview. Pregnancy outcomes were also recorded from the medical record as part of the original study and were available for analysis.

Gestational hypertension included patients with new-onset elevated blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic after 20 weeks of gestation. Preeclampsia was characterized as elevated blood pressure with proteinuria as defined by ≥ 300 mg in a timed 24 hour urine collection, $> 2+$ on a voided or $>1+$ on a catheterized random urine specimen, or a spot urine protein to creatinine ratio ≥ 0.3 . In prior studies we have demonstrated that preeclamptic women with hyperuricemia (HPU) defines a more severe form of preeclampsia while gestational hypertension without proteinuria but with elevated uric acid (HU) results in adverse fetal outcomes similar to those of women with hypertension and proteinuria (HP).⁹

Therefore, in women with hypertensive disease, we differentiated between women with and without hyperuricemia defined as 1 standard deviation above the mean value for gestational age at the time of diagnosis. Normotensive patients were those without blood pressure elevations.

Neonatal outcomes assessed included birthweight and birthweight percentile, adjusted for race, sex and gestational age at delivery from a reference population of over 10,000 births at Magee-Womens Hospital. Small for gestational age (SGA) was defined as birthweight < 10th percentile. These outcomes were analyzed in all groups but only reported for normotensive women due to small numbers.

Covariates included education, maternal race, pre-pregnancy body mass index (BMI, kg/m²), and gestational age and maternal age at time of plasma collection. Education was categorized as less than high school (12 years), or at least a high school level (≥ 12 years). Maternal race was either non-black or black. Gestational age was determined by best obstetrical assessment, using early ultrasound where available.

Plasma samples

Banked plasma samples were stored at -70°C until assayed. Insulin was measured by an ELISA kit from LINCO Research. This was a sandwich ELISA using monoclonal mouse anti-human insulin coated to the plate, and a second biotinylated monoclonal mouse anti-human antibody to capture the insulin. The interassay variation was 12.4%. Glucose was measured using a colorimetric assay from Pointe Scientific, Inc. Kit G7519 using glucose oxidase and a Quinoneimine dye. The coefficient of variance was 13.0%. Homeostasis model assessment (HOMA) was calculated as described by Matthews et al. using the formula: insulin resistance = $\text{insulin} / (22.5e^{-\ln\text{glucose}})$.¹⁴ Uric acid was measured using a colorimetric assay from Pointe Scientific, Inc. Kit U7581-120 using Uricase. The coefficient of variance was 7.5%.

Analysis

Uric acid, glucose, insulin and HOMA were evaluated as continuous variables and were summarized by means and standard deviations or medians and interquartile ranges, depending on the distribution.

Linear regression was performed to investigate the association between uric acid and HOMA. HOMA values were log-transformed (resulting in a normal distribution) prior to analysis. All models were adjusted for race a priori. Other covariates considered included education, sample age, BMI, smoking and maternal age. Only BMI and maternal age significantly contributed to the final model. The model fit was improved when maternal age was transformed to the inverse of age squared. BMI was included as a continuous variable. Results did not change when potential outliers, influential and leverage points were dropped from the model, so they were retained.

Mean birthweights and birthweight percentiles were evaluated for each group and by HOMA and uric acid quartiles. Student's T-test was performed to assess for differences in mean birthweights and birthweight percentiles where appropriate. Logistic regression was performed to investigate the association between uric acid and SGA, adjusting for education, maternal race, HOMA, BMI, maternal age and smoking. A two-tailed p-value of < 0.05 was considered statistically significant. Analyses were performed with Stata software, version 10.0 for Windows.

RESULTS

Of the 272 available plasma samples, 263 women had complete data and met study criteria. The mean gestational age at collection was 20.4 (± 2.0) weeks. Overall, 212 women remained normotensive (80.6%) while 23 women developed gestational hypertension without hyperuricemia (8.7%), 8 developed gestational hypertension with hyperuricemia (3.0%), 10 developed preeclampsia with hyperuricemia (3.8%) and 10 became preeclamptic without hyperuricemia. The demographic and neonatal characteristics are shown in Table I. These demographics did not differ between hypertensive groups, except that BMI was higher in women who developed preeclampsia (HP and HPU) compared to women who remained normotensive (28.1 ± 7.0 in all preeclampsia compared to 24.8 ± 5.7 in normotensive women, $p < 0.05$). Pre-pregnancy BMI was weakly correlated to uric acid concentration, with an $r^2 = 0.08$ ($p < 0.005$).

Insulin Resistance and Uric Acid

Overall, insulin resistance was associated with uric acid with an r^2 of 0.18 ($p < 0.001$). When divided by hypertensive status, this correlation held true for women who remained normotensive ($r^2 = 0.17$, $p = 0.003$, Figure 1) and women who developed the less severe form of preeclampsia (HP, $r^2 = 0.86$, $p = 0.02$), but not for women who developed either form of gestational hypertension (H, HU) or hyperuricemic preeclampsia (HPU).

For all women, the HOMA concentration increased by 1.40 units [95%CI: 1.24, 1.58], $p < 0.001$] for every 1 mg/dl increase in uric acid. When stratified by BMI, the relationship between HOMA and uric acid was apparent among normal weight ($\text{BMI} < 25 \text{ kg/m}^2$) women [1.20 (95%CI: 1.27, 1.40), $p = 0.02$], and there was an even stronger association among overweight ($\text{BMI} \geq 25 \text{ kg/m}^2$) women [1.45 (95%CI: 1.16, 1.81), $p = 0.001$].

In women who remained normotensive, the mean uric acid concentration at 20 weeks gestation was 3.5 (± 0.8) mg/dl, mean glucose 79.4 (± 11.5) mg/dl, median insulin 6.9 (IQR 8.4) and calculated HOMA 1.3 (IQR 1.8). The HOMA increased per 1 mg/dl rise in uric acid concentration in normotensive women [1.23 (95%CI: 1.07, 1.42), $p = 0.003$], however remained significant only in overweight women [$\text{BMI} < 25 \text{ kg/m}^2$ ($n = 136$): 1.14 (95%CI: 0.95, 1.34), $p = 0.17$ and $\text{BMI} \geq 25 \text{ kg/m}^2$ ($n = 76$): 1.32 (95%CI: 1.03, 1.70), $p = 0.03$].

Fetal Growth in Normotensive Women

SGA occurred in 30.8% of pregnancies in normotensive women with uric acid in the highest quartile (uric acid > 4.1 mg/dl) compared to only 3.4% of normotensive women with uric acid in the lowest quartile (uric acid ≤ 2.9 mg/dl, $p < 0.001$). Uric acid concentrations as a continuous measure were associated with SGA in normotensive women after adjusting for maternal pre-pregnancy BMI and race (OR= 1.06, 95%CI: 1.01, 1.12, $p = 0.02$). When additionally adjusted for smoking, the magnitude of the association was unaffected, but precision was compromised (OR= 1.05, 95%CI: 0.99, 1.10, $p = 0.09$). Uric acid was weakly correlated with smoking ($r = 0.14$, $p = 0.03$).

When combining the effects of uric acid in the highest quartile and insulin resistance in normotensive women, 33.3% had SGA infants when the HOMA was in the lowest quartile, compared to 15% when HOMA was in the upper quartile. Infants born to normotensive women in the upper quartile for uric acid and lowest HOMA quartile weighed, on average, 435.6 grams less compared to infants born to women with the highest uric acid and HOMA quartiles ($p < 0.005$, Table 2). Similarly, infants born to women with high uric acid but low HOMA trended towards having infants that were close to the bottom quartile of weight for gestational age; infants born to women with similar uric acid concentrations but high HOMA were average

weight for gestational age ($p=0.06$ for birth weight percentile). The average gestational age at delivery for these two groups did not differ ($p=0.58$).

COMMENT

We found an association between uric acid and insulin resistance in mid-pregnancy. HOMA increased significantly for every 1 mg/dl increase in uric acid even among women with a normal BMI, although the magnitude of association was greater among obese women. When only women who remained normotensive were examined the association between insulin resistance and hyperuricemia persisted. It trended towards significance in normal weight women, but was more pronounced in overweight normotensive women.

The strength of our study was the ability to study the association of uric acid concentration and insulin sensitivity in a large number of women with well characterized outcomes. However, it is limited by our inability to investigate the association of insulin resistance, uric acid and birth weight in women who developed hypertensive disease due to low numbers of these specific outcomes. We also did not measure creatinine in order to adjust for glomerular filtration rate (GFR), and GFR can significantly affect uric acid concentration. However, our colleagues have previously demonstrated that adjusting for serum creatinine did not change uric acid concentration throughout pregnancy for controls or women who did not develop severe preeclampsia.¹⁵ A decreased GFR may contribute to an increased uric acid, but this likely occurs later in pregnancy closer to the time of preeclampsia diagnosis. Our samples are in mid-pregnancy, so adjusting for creatinine likely would not change our findings. We also did not adjust for alcohol consumption which is a known cause of hyperuricemia. Alcohol consumption was very low in our population, with only 28 women (10.6%) reporting using any alcohol since becoming pregnant and only 2 women (0.01%) reporting regular weekly consumption, so this should not have been a major confounder. However, alcohol consumption was not validated in this cohort, and pregnant women may be likely to under-report actual use.

Our findings are consistent with the well-established association between uric acid and insulin resistance in non-pregnant adults. In a study of 83 women with insulin resistance, serum insulin was linearly associated with serum uric acid concentrations at all levels of glucose tolerance, even after controlling for other causes of hyperuricemia and hyperinsulinemia.¹⁶ Increasing metabolic score, which incorporated markers of metabolic syndrome including increased waist circumference, elevated BP, elevated triglycerides, lower HDL cholesterol and elevated fasting glucose, or overt diabetes, was also associated with higher mean serum uric acid levels in 1107 subjects from the Genetic Epidemiology Network of Arteriopathy (GENOA) study.¹⁷ Finally, increasing concentrations of serum uric acid were significantly associated with higher prevalence of metabolic syndrome in subjects from the Third National Health and Nutrition Examination Survey (NHANES III).⁷ The link between elevated uric acid concentration and metabolic syndrome in the absence of hypertension may be explained in part by elevated insulin levels reducing urinary excretion of uric acid.¹⁸⁻²⁰ However, uric acid may also be an independent risk factor for the development of insulin resistance and subsequent diabetes, as elevated uric acid predates the development of type 2 diabetes in non-pregnant adults.²¹

Uric acid and insulin resistance were not associated in women who developed gestational hypertension with or without hyperuricemia or hyperuricemic preeclampsia in our study, although the numbers are small. There was an association in women who later developed preeclampsia without hyperuricemia. These findings contrast with those of Weisz et. al who found that insulin resistance correlated with elevated serum uric acid at 32-35 weeks gestation in women with gestational hypertension, but not in women with preeclampsia or controls.¹³ Our samples were collected, on average, more than 10 weeks earlier in gestation. Also, their study had only 23 patients compromising the precision of the results. The lack of association

between uric acid and insulin resistance in women who developed gestational hypertension or hyperuricemic preeclampsia in our study may be explained in part by the observation that uric acid can be independently associated with development of hypertension (i.e. in the absence of insulin resistance) as has been shown in non-pregnant adults.²² Elevated uric acid along with other markers of metabolic syndrome at 28 weeks gestation was associated with higher risk for pregnant women to develop preeclampsia.²³ Even in the absence of developing hypertensive disease, however, our data supports the possibility that uric acid is an important component of the metabolic syndrome in pregnancy, and may be an independent marker for maternal as well as fetal health.

The combined effects of second trimester insulin resistance and hyperuricemia without hypertension on fetal growth are striking. In this study, for normotensive women with uric acid in the highest quartile but without insulin resistance, there was a higher incidence of SGA, and overall birth weight was significantly decreased, compared to women with combined elevated uric acid and insulin resistance. We only examined the relationship of uric acid and insulin resistance to birthweight in women who remained normotensive due to the small numbers of women with hypertensive disease. Whether these findings prevail in women with hypertensive disease is unknown. Our early data suggests that this may not be the case.

The association between uric acid and decreased birth weight was diminished by the presence of insulin resistance. It is unknown whether hyperuricemia directly causes impaired fetal growth or is just a biomarker for SGA. Uric acid in vitro causes endothelial damage, which could contribute to hypertension as well as lead to placental vasculature damage.²⁴ Women with hyperuricemia early in pregnancy may also have abnormal placentation due to suboptimal trophoblast invasion.²⁵ In rats, hyperuricemia caused by blocking uricase leads to systemic and glomerular hypertension as well as arteriolar damage, and these effects can be reversed by a selective inhibitor of uric acid synthesis.²⁶ Uric acid is relevant to oxidative stress, and is a prominent anti-oxidant.²⁷ However, uric acid is a co-product of an equation that results in production of superoxide, and can itself act as a free radical in setting of low antioxidants.^{28, 29} We have also demonstrated that in an in vitro system, uric acid reduces the placental uptake of amino acids by the Sytem A amino acid transporter.³⁰ The mechanism by which insulin resistance might attenuate these effects is unclear. Insulin resistance increases substrate availability for the fetus. Perhaps the effects of hyperuricemia are overcome to an extent in the setting of excess glucose.

Uric acid was associated with insulin resistance in mid-pregnancy, even among normal weight women and those who remained normotensive throughout pregnancy. The relationship between uric acid and birthweight was mediated by the presence of insulin resistance. In the absence of insulin resistance, hyperuricemia was associated with an increased risk for reduced fetal growth among women who remained normotensive.

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Figure 1.

Association of uric acid to the log HOMA in normotensive pregnant women. Associations were adjusted for age, race and body mass index. HOMA = Homeostasis model assessment.¹⁴

Table 1

Characteristics of the women and their newborns [means (SD) or numbers (%)] according to hypertensive status.

Characteristics	Normotensive n = 212	Gestational Hypertension n = 31	Preeclampsia n = 20	p-value
Maternal age (years)	24.5 (5.4)	24.0 (5.2)	23.2 (5.8)	0.36
BMI (kg/m ²)	24.8 (5.7)	25.5 (6.5)	28.1 (7.0)	<0.05*
< 25	136 (65.1%)	19 (61.3%)	8 (40.0%)	
≥ 25	73 (34.9%)	12 (38.7%)	12 (60.0%)	
Sample age	20.2 (1.9)	20.5 (2.1)	20.9 (2.2)	0.22
Maternal Race				0.19
Non-black	156 (73.6%)	21 (67.7%)	11 (55%)	
Black	56 (26.4%)	10 (32.3%)	9 (45%)	
Smokers	46 (21.7%)	9 (29.0%)	5 (25.0%)	0.64
Education				0.22
< 12 years	26 (12.3%)	1 (3.2%)	1 (5.0%)	
≥ 12 years	186 (87.7%)	30 (96.8%)	19 (95.0%)	
GA at delivery (weeks)	38.8 (2.1)	39.0 (1.4)	37.8 (3.0)	0.24
Birthweight (g)	3308 (580)	2993 (770)	3265 (514)	0.07
Percentile	54.1 (29.1)	48.1 (28.4)	47.4 (29.1)	0.38
SGA				
≤10 th percentile	20 (9.4)	4 (12.9)	2 (10.0)	0.73
≤5 th percentile	10 (4.7)	1 (3.2)	2 (10.0)	0.47

BMI = body mass index; GA= gestational age; SGA= small for gestational age and is adjusted for race, sex and gestational age

* There was a statistically significant difference between BMI in the women with preeclampsia compared to controls (p=0.05).

Table 2

Birthweights, birth percentiles (adjusted for gestational age, sex and race), maternal pre-pregnancy BMI and number (n) by uric acid and HOMA quartiles for women who remain normotensive throughout pregnancy.

Birth weights in grams (SD) Percentile (SD) Maternal pre-pregnancy BMI (SD) (n)	HOMA Quartiles		
	Lowest	Mid	Upper
Uric Acid Quartiles			
Lowest	3327.3 (523.8)	3484.3 (535.7)	3144.1 (686.3)
1.5 to $\leq$ 2.9 mg/dl	66.0 (20.8)	57.7 (29.0)	53.6 (33.3)
	22.3 (3.3)	22.2 (4.0)	23.1 (4.3)
	(19)	(27)	(12)
Mid	3251.5 (664.9)	3374.7 (576.9)	3397.5 (672.1)
3.0 to $\leq$ 4.1 mg/dl	49.1 (31.1)	56.4 (30.1)	61.8 (29.0)
	23.0 (5.0)	25.9 (6.0)	26.9 (7.0)
	(31)	(50)	(23)
Upper	2731.7 (245.8)*	3289.6 (443.5)	3167.3 (516.2)*
4.2 to 6.4 mg/dl	26.9 (22.7)**	45.7 (27.6)	49.7 (25.3)**
	25.6 (5.3)	26.6 (6.9)	26.5 (4.8)
	(6)	(24)	(20)

The birthweight and birthweight percentiles for those patients in the upper quartile for uric acid and lowest HOMA quartile were *lower* than those in patients with highest uric acid and HOMA quartiles (p=0.009* and p=0.06**).