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Elevated first-trimester uric acid concentrations are associated with the development of gestational diabetes

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Abstract

Objective: To demonstrate that elevated first trimester uric acid is associated with development of gestational diabetes mellitus (GDM).

Study Design: Uric acid was measured in 1570 plasma samples collected at mean gestational age of 8.9 ± 2.5 weeks. The primary outcome was GDM, diagnosed by three hour glucose tolerance test using Carpenter and Coustan criteria or by a one hour value of ≥ 200 mg/dl. Logistic regression was performed, adjusting for relevant covariates.

Results: Almost half (46.6%) of the women with GDM had first trimester uric acid concentrations in the highest quartile (>3.57 - 8.30 mg/dl). Women with uric acid in the highest quartile had a 3.25-fold increased risk (95%CI: 1.35, 7.83) of developing GDM after adjustment for BMI and age. This effect was concentration dependent as risk increased with increasing uric acid quartiles ($p=0.003$).

Conclusion: First trimester hyperuricemia is associated with an increased risk of developing GDM, independent of BMI.

Keywords

gestational diabetes; hyperuricemia; uric acid

INTRODUCTION

Uric acid is associated with insulin resistance in non-pregnant women.¹ Outside of pregnancy, hyperuricemia is also associated with the markers of metabolic syndrome, including obesity and dyslipidemia.²⁻⁵ Uric acid is an independent risk factor for developing type 2 diabetes within 10 years in non-pregnant adults, an association that was stronger in women compared to men.⁶

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In pregnancy, uric acid is correlated with insulin resistance in women with gestational hypertension.⁷ Serum uric acid is higher at 24-28 weeks gestation in women diagnosed with gestational diabetes compared to women without diabetes.⁸ Uric acid is also higher in non-pregnant women with a history of gestational diabetes, independent of body mass index.⁹ Since uric acid is associated with insulin resistance and predates development of type 2 diabetes in non-pregnant adults, we hypothesized that higher uric acid in the first trimester would be associated with the development of gestational diabetes.

MATERIALS AND METHODS

We used banked plasma samples from specimens drawn at < 15 weeks gestation from subjects enrolled in the Pregnancy Exposures and Preeclampsia Prevention Study (PEPP). PEPP is an ongoing study of preeclampsia approved by the Magee-Womens Hospital Institutional Review Boards. We investigated women in the longitudinal study from 1997-2002 who were enrolled at <21 weeks gestation and followed to the post partum visit (total pregnancies n=2215). 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. Of the 2215 women in the original cohort, 1612 had samples available < 15 weeks. Of these, 20 had chronic hypertension, 11 had pregestational diabetes, 8 had two samples taken and we used only the earlier gestational age, and 3 did not have complete data in the database, leaving a total n=1570. This subset of women did not differ from the larger cohort as far as maternal entry age (25.2 versus 25.2 years, p=0.88), pre-pregnancy BMI (25.5 versus 25.5 kg/m², p=0.9), or high school education (81.4% versus 80.2%, p=0.36).

Gestational diabetes was diagnosed between 24 and 28 weeks gestation with a three hour glucose challenge test using Carpenter and Coustan criteria or a one hour 50 g value of ≥ 200 mg/dl.^{10, 11} Covariates included maternal age at entry to the study, parity, pre-pregnancy body mass index (BMI, kg/m²), maternal race, education, and gestational age at which the uric acid sample was obtained. Maternal race was classified as either non-black or black because of the low frequencies of non-white, non-black participants (n = 8 Hispanic, 16 Asian/Pacific Islander, 1 Native American and 12 other). The baseline characteristics of the non-white, non-black participants were comparable to white participants, and therefore we elected to combine these groups. Education was categorized as less than high school (12 years), or at least a high school level (≥ 12 years). Gestational age was determined by best obstetrical assessment, using early ultrasound data where available.

Plasma samples

Banked plasma samples were stored at -70° C until assayed. Our lab has previously performed internal analyses and demonstrated that uric acid concentrations are stable with prolonged storage and freeze thaws. Uric acid was measured using a colorimetric assay from Pointe Scientific, Inc. Kit U7581-120 with a detection limit of 10 mg/dl. The coefficient of variance was 9.0%.

Analysis

Demographic data were summarized by uric acid quartiles, as means and standard deviations or numbers and percents, and test for trend was performed using linear or logistic regression. Logistic regression was performed to investigate the association between first trimester uric acid concentrations and gestational diabetes. Uric acid was evaluated as both a continuous and a categorical variable. We ultimately decided to use uric acid quartiles in order to balance sufficient numbers in each category to enhance the discriminatory power of uric acid early in gestation, and to be able to compare our results to other studies. Covariates that were considered

included maternal age, parity, pre-pregnancy body mass index, maternal race, education and gestational age of sample. Only maternal age and BMI significantly contributed to the final model with p -values < 0.1 . However, we also adjusted for gestational age of the sample since the samples collected from women with uric acid in the highest quartile were collected on average about one week earlier in gestation. For the overall model, an α level of < 0.05 was considered statistically significant. An interaction between uric acid and BMI was tested and was not significant ($p=0.47$).

We explored the ability for first trimester uric acid to predict the development of gestational diabetes. Positive and negative predictive values were calculated, as well as a receiver operating characteristic curve. We also explored the ability for first trimester uric acid to predict the development of gestational diabetes specifically in non-obese women, since obesity is a known risk factor for developing gestational diabetes and these women would already be screened early. Analyses were performed with Stata software, version 10.0 for Windows.

RESULTS

A total of 1570 samples were available for analysis with a mean gestational age at sampling of 8.9 ± 2.5 weeks and uric acid concentration of $3.08 (\pm 0.85)$ mg/dl. Gestational diabetes mellitus complicated 73 (4.6%) of the pregnancies. The demographic and neonatal characteristics according to increasing uric acid quartiles are shown in Table 1. The mean maternal age and gestational age at sampling decreased slightly with increasing uric acid quartile. Maternal pre-pregnancy BMI increased linearly with increasing uric acid quartile ($p<0.01$ for trend) and was associated with uric acid with an r^2 of 0.16 ($p<0.001$).

The adjusted odds of gestational diabetes increased with increasing first trimester uric acid quartile ($p=0.003$ for trend, Table 2). Women with early pregnancy uric acid concentrations in the highest (4th) quartile had a three-fold increased risk for developing GDM compared to those in the lowest quartile. Of the 73 women who developed gestational diabetes mellitus, 34 (46.6%) had uric acid in the 4th quartile and 39 (53.4%) had a BMI <30 kg/m². Among these 39 non-obese women, 18 (46.2%) had first trimester uric acid concentrations in the highest quartile.

First trimester uric acid concentrations ≥ 3.6 mg/dl, (the highest quartile) were associated with a trend towards increased risk of developing gestational diabetes (adjusted OR=1.21; 95% CI: 0.75, 1.96) compared to women with concentrations below this concentration (lower three quartiles), after adjusting for BMI. Using a cut point of 3.6 mg/dl yielded a positive predictive value (PPV) of 9.0% and negative predictive value (NPV) of 96.7% for development of GDM. The area under the receiver operator curve was 0.7 (Fig. 1). When restricted to non-obese women (BMI < 30 kg/m², $n = 1027$), a first trimester uric acid concentration ≥ 3.6 mg/dl was not associated with an increased risk of gestational diabetes (adjusted OR=1.16, 95% CI: 0.13, 3.07). If a first trimester uric acid cutoff of 3.6 mg/dl was used, 18 cases of gestational diabetes occurred out of 138 non-obese women, with a PPV of 6.7% and NPV of 97.8%.

COMMENT

First trimester hyperuricemia was associated with an increased risk of developing gestational diabetes mellitus. The risk of developing gestational diabetes was 3.25-fold higher if first trimester uric acid was in the 4th quartile. Although uric acid was strongly associated with body mass index, the risk of gestational diabetes was increased among women with elevated first trimester uric acid independent of BMI.

Uric acid increases with increased protein intake, alcohol consumption, decreased excretion, or increased endogenous production. Our present study did not assess the role of diet on uric

acid and GDM, although this would be an interesting future investigation. Reported alcohol consumption was very low in our population with <1% of women reporting regular (defined as at least weekly) intake, so we did not adjust for it. We did not measure creatinine in order to adjust for glomerular filtration rate (GFR), but the majority of women would be expected to have normal excretion since we excluded women with prior diabetes, hypertension, kidney disease or major medical problems. In addition, our colleagues previously demonstrated that adjusting for serum creatinine did not change the relationship of elevated uric acid in early pregnancy to later pregnancy hyperuricemia.¹² We were unable to directly test for increased endogenous production, but this warrants future investigation. Our study is also limited because we were unable to investigate the important association between uric acid concentration, GDM and race since our reference population is not diverse.

Our findings are consistent with the association of uric acid with insulin resistance in the non-pregnant population.¹ In a large cross-sectional study of 53,477 non-pregnant adults, serum uric acid was positively correlated with fasting serum glucose and insulin resistance, as well as features of the metabolic syndrome, including waist circumference, low HDL cholesterol, hypertriglyceridemia, hypertension and fasting glucose ≥ 110 mg/dl.¹³ Hyperuricemia has also been demonstrated to be a risk factor for developing type 2 diabetes.^{6, 14} In our study, we found that uric acid ≥ 3.6 mg/dl early in pregnancy is associated with a 3-fold increased risk of developing gestational diabetes. The early pregnancy uric acid concentrations in our study were similar to those reported by others; however, to our knowledge there are no prior reports of the association between first trimester uric acid and GDM among low risk women.¹⁵

Uric acid in the first trimester likely approximates pre-conception uric acid, and elevated uric acid may identify women who are predisposed to metabolic syndrome with an increased risk of developing GDM, independent of obesity. Alternatively, uric acid decreases early in pregnancy, so perhaps women with elevated uric acid have a poor adaptation to pregnancy (i.e. abnormal placentation), putting them at risk for adverse pregnancy outcomes such as GDM.

It is possible that the association of uric acid with insulin resistance is causal. Two mechanisms have been hypothesized by which uric acid can cause insulin resistance.¹⁶ Nakagawa et al. proposed that uric acid causes endothelial dysfunction and decreases nitric oxide production by the endothelial cell.² In animals, insulin's action on glucose uptake into cells in the skeletal muscle and adipose tissue is dependent on nitric oxide.^{17, 18} Thus, decreases in nitric oxide lead to decreased glucose uptake and the development of insulin resistance. Another mechanism by which uric acid may induce insulin resistance may be that uric acid causes inflammation and oxidative stress in adipocytes, which is a contributor to the development of metabolic syndrome in mice.^{19, 20}

While our study demonstrates a striking association between first trimester uric acid and risk of developing gestational diabetes, only half of the women with uric acid in the highest quartile actually developed the disease. This finding may be due to different pathways of development of gestational diabetes. Women who have a pregnancy complicated by gestational diabetes have up to a 50% chance of developing type 2 diabetes in their lifetime. It would be interesting to know whether these were the women with elevated uric acid in the first trimester. This possibility is supported by a study by Di Cianni et al. in which serum uric acid was measured at a median of 16 months postpartum in women who had pregnancies complicated by gestational diabetes.²¹ Uric acid was significantly higher in women with metabolic syndrome (4.8 ± 1.2 mg/dl) versus women without metabolic syndrome (4.1 ± 0.8 , $p < 0.01$), independent of BMI, and metabolic syndrome is a known risk factor for developing type 2 diabetes.

Our findings do not support assessing uric acid concentration in pregnant women in the first trimester to predict the development of GDM. The area under the ROC curve was 0.7 for first

trimester uric as a predictor of GDM. This value is not sufficiently robust for elevated uric acid to be a clinically relevant predictor of GDM, which had a prevalence of only 4.6% (PPV = 9.0% for a uric acid cutoff of 3.6 mg/dl). However, the relationship of uric acid elevation in early pregnancy does indicate that metabolic state may affect adverse pregnancy outcomes. With the increase in both metabolic syndrome and obesity, more women are entering pregnancy with these conditions. It is possible that of the women who develop GDM, those with elevated first trimester uric acid are the women who are at risk to develop type 2 diabetes, and this warrants future investigation.

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Figure 1. Receiver operator curve adjusted for maternal age, prepregnancy BMI (kg/m^2) and gestational age of sample. First trimester uric acid concentration and risk of developing gestational diabetes mellitus

Table 1

Characteristics of the women and their newborns for the cohort of 1570 women.

Characteristics	1 st (0.9-2.5)	2 nd (2.5-3.0)	3 rd (3.0-3.6)	4 th (3.6-8.3)	p - value for trend
First Trimester Uric Acid Quartile (range, mg/dl)					
Maternal age (years)	25.7 (6.2)	25.3 (5.9)	24.6 (5.6)	24.9 (5.7)	0.02
Nulliparous	221 (56.2%)	244 (62.2%)	242 (61.7%)	232 (59.0%)	0.98
BMI (kg/m ²)	23.0 (4.2)	24.1 (5.1)	26.0 (6.4)	29.0 (7.5)	<0.01
<30	365 (23.2%)	345 (22.0%)	308 (19.6%)	249 (15.9%)	<0.01
>30	28 (1.8%)	47 (3.0%)	(5.4%)	144 (9.2%)	<0.01
Gestational age at sample	9.3 (2.5)	9.0 (2.3)	8.8 (2.5)	8.7 (2.6)	<0.01
Maternal Race					0.74
Non-black	243 (15.5%)	277 (17.6%)	240 (15.3%)	260 (16.5%)	
Black	150 (9.6%)	115 (7.3%)	152 (9.7%)	133 (8.5%)	
Smokers	98 (6.2%)	140 (8.9%)	132 (8.4%)	107 (6.8%)	0.61
Education					0.98
< 12 years	73 (4.6%)	70 (4.5%)	78 (5.0%)	70 (4.5%)	
> 12 years	320 (20.4%)	322 (20.5%)	314 (20.0%)	323 (20.6%)	
GA at delivery (weeks)	39.1 (2.1)	39.4 (1.5)	39.0 (2.6)	39.2 (2.2)	0.86

Data are presented as means (±SD) or numbers (%); BMI = pre-pregnancy body mass index (kg/m²); GA= gestational age

Table 2

Risk of gestational diabetes by first trimester uric acid quartile.

Uric acid quartile (mean mg/dl)	GDM n (%)	Adjusted OR* (95% CI)
1 st (2.1)	7 (0.5)	ref
2 nd (2.7)	12 (0.8)	1.62 (0.63-4.22)
3 rd (3.2)	20 (1.3)	2.35 (0.96-5.78)
4 th (4.2)	34 (2.2)	3.25 (1.35-7.83)

* The model was adjusted for maternal entry age, pre-pregnancy BMI (kg/m²), and gestational age of sample (p=0.003 for trend).