ARE INCREASED URIC ACID LEVELS IN PREGNANCY COMPLICATED BY GESTATIONAL DIABETES MELLITUS LINKED TO IMPAIRED GLUCOSE TOLERANCE?

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Introduction

Uric acid (UA) is a terminal metabolite of purine metabolism but from a large part reabsorbed (by 90%). Recent evidence shows that UA is an important risk factor of several diseases and increased UA levels were associated with obesity, hypertension, hyperinsulinaemia and insulin resistance. However the role of UA levels in pregnancy complicated by gestational diabetes mellitus (GDM) is less established. Serum UA levels show substantial genetic component influenced by SNPs in genes encoding its transporters.

We hypothesize that increased UA levels in pregnany can serve as a marker of more severe insulin resistance leading to high-risk GDM and, hypothetically, to diabetes development soon after delivery. Our aims were (i) to assess mid-gestational and early *postpartum* UA levels in a group of pregnant women with GDM and healthy pregnant counterparts, (ii) to associate them with a severity of carbohydrate abnormalities in the 2nd trimester (i.e. respective values of oral glucose tolerance test (oGTT) or need for insulin therapy), and (iii) to study possible genotype-phenotype relationship between UA levels and SNPs in its transporters (*ABCG2* rs2231142 and *SLC2A9* rs1014290, rs12498742 and rs16890979).

Materials and Methods

A total of 143 women were included in the case-control study (of those 109 with GDM diagnosed according to WHO criteria). Characteristics of both groups are summarized in Table 1. All subjects underwent oGTT with 75g of glucose between 24-30th week of pregnancy (timing of the 1st blood sample). Women with diagnosed GDM underwent *postpartum* oGTT 6 weeks or later after delivery (timing of the 2nd blood sample) Plasma UA levels were determined by reversed-phase HPLC-UV. Selected SNPs in UA transporters were genotyped using commercial PCR-based assays (TaqMan®). Non-parametric statistical tests were used (Mann-Whitney, Wilcoxon, Spearman correlation coefficient).

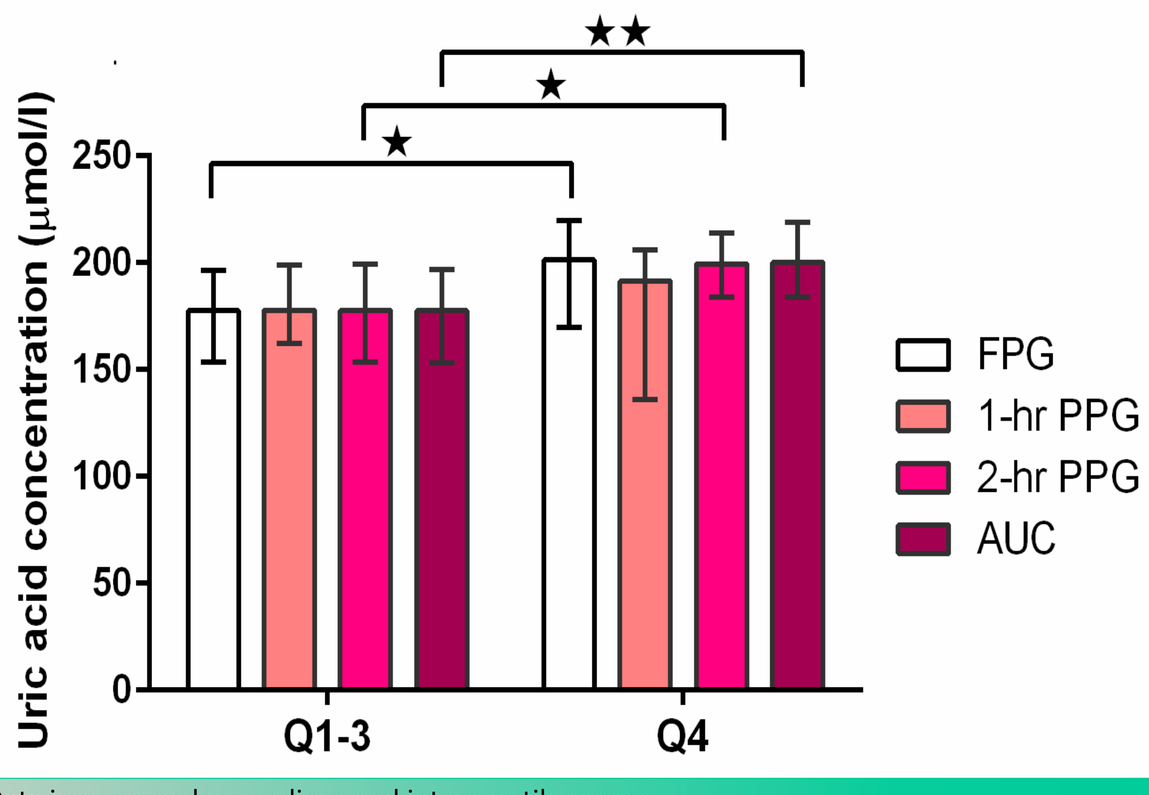
Results

UA levels did not differ between GDM and control group. A sub-group of patients treated with insulin had significantly higher UA levels compared to those on diet only in mid-trimester and *postpartum* (P = 0.041 and P = 0.049). A sub-group of GDM-women with pre-gestational BMI > 30 had higher UA levels in mid-trimester and *postpartum* (P = 0.002 and P = 0.013). UA levels were higher in GDM defined as high-risk (need for insulin in GDM therapy, abnormal foetal growth, pre-gestational BMI > 30, weight gain during pregnancy > 20 kg or hypertension) during pregnancy (P=0.02). Mid-gestational UA levels did not differ between subjects with GDM history and persistent *postpartum* glucose intolerance and those with normal glucose tolerance after delivery. UA levels raised in both groups *postpartum* (both $P < 1 * 10^{-6}$ for GDM and both P < 0.001 for control group).

Additionally, strong correlations of UA levels with respective parameters of oGTT were found, we divided study participants into quartiles (Q) according to their glycaemia levels. We have found significant differences in UA levels between women in the highest quartile (GDM women only) of respective parameters of oGTT and the rest of studied women (Figure 1).

Neither genotype nor allele distributions of studied SNPs differed between GDM women and controls (all P = NS, Chi-square). Furthermore, genotype-phenotype relationships were analysed for all studied SNPs. UA levels differed significantly between carriers of genotypes in rs1014290 and rs12498742 in GLUT9 *postpartum* and rs16890979 in GLUT9 during pregnancy and *postpartum* (P = 0.006, P = 0.003, P = 0.01 and P = 0.009, respectively, Kruskal-Wallis ANOVA). Allele G in rs1014290 and rs12498742 and allele T in rs16890979 in GLUT9 were associated with lower UA levels (Figure 2).

Figure 1 –UA levels according to quartiles of oGTT



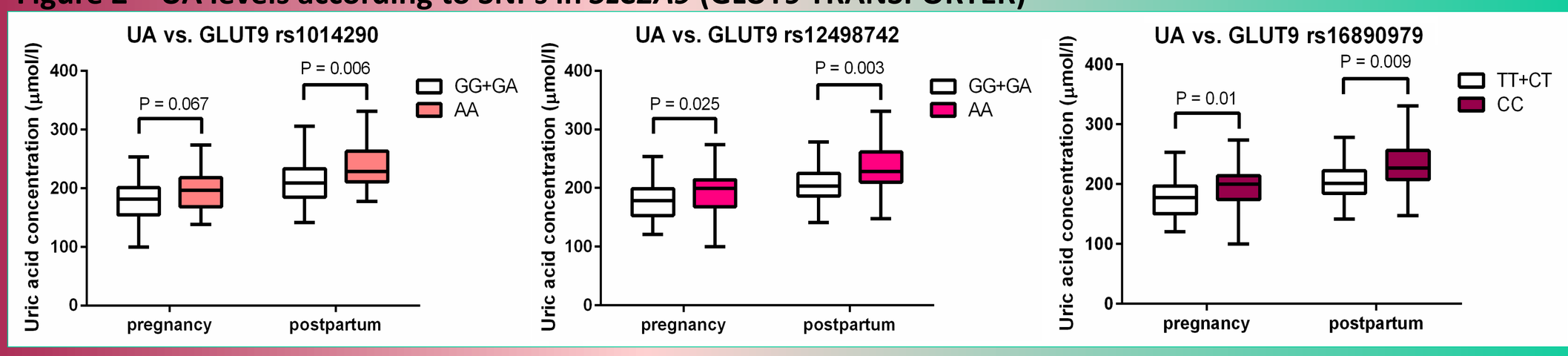
Data is expressed as medians and interquartile ranges.
* P < 0.001, ** P = 0.011, t-test

Table 1 – Characteristics of study subjects

Parameters	GDM (n = 109)	Controls (n = 34)	P
Pre-gestational parameters			
Age	33 [30 – 35]	31 [28 – 33]	**0.040**
BMI [kg m^{-2}]	24.6 [21.2 – 28.7]	22.5 [20.6 – 27.0]	NS
Mid-gestational parameters			
Insulin treatment	37.8 %	-	-
High-risk GDM	48.6 %	-	-
UA [µM]	183 [154 – 205]	178 [168 – 190]	NS
***Postpartum* parameters**			
Weight gain during pregnancy [kg]	8 [5 – 10]	13 [10 – 17]	**< 1*10^{-6}**
Offspring birth weight [g]	3120 [2790 - 3500]	3355 [3070 – 3700]	**0.032**
UA [µM]	221[195 – 249]	213 [190 – 248]	NS

Data is expressed as medians and interquartile ranges.

Figure 2 – UA levels according to SNPs in *SLC2A9* (GLUT9 TRANSPORTER)



Box and Whisker plots were constructed as medians, minimum and maximum values and interquartile ranges.

Conclusions

Our data support a possible link between obesity, increased UA levels and the risk of GDM development. UA metabolism might be disturbed in a sub-group of GDM patients within upper quartile of FPG, 2-hr PPG and AUC and those who require insulin treatment during pregnancy. UA levels were significantly higher among women with high-risk GDM potentially indicating risk of *postpartum* glucose abnormality (study ongoing).

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