

## Hyperuricemia in the Pregnancy and Gestational Diabetes

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### Abstract

This review aims to determine the metabolic effect of hyperuricemia in pregnant woman, especially those with gestational diabetes mellitus (GDM). In women, the serum uric acid level is lower compared to men of similar age. The value is related to higher estrogen concentration to increase uric acid clearance. Hyperuricemia already established as independent risk factors for metabolic syndrome and cardiovascular disease (CVD) as well as type 2 Diabetes Mellitus (DM). Asymptomatic hyperuricemia in non-pregnant adult women will increase insulin resistance due to oxidative stress, and production of inflammatory cytokine (tumor necrosis factor- $\alpha$ ), which inevitably increases blood sugar level. Uric acid level and serum creatinine is lower in normal pregnancy due to increased renal clearance and the uricosuric effect of estrogen. Hyperuricemia is one of the contributing factors associated with insulin resistance among pregnancy instead direct effect of placental hormones. Earlier in the first trimester of pregnancy, the risk for GDM is increased. However, the causal effect of uric acid levels on DM still requires further study .

**Key words:** Hyperuricemia, Gestational DM, type 2 Diabetes Mellitus.

### *Hiperurisemia pada Kehamilan dan Diabetes Gestasional*

#### **Abstrak**

*Tulisan ini bertujuan untuk mengetahui efek metabolik hiperurisemia pada wanita hamil, khususnya pada populasi gestational diabetes mellitus (GDM). Kadar asam urat serum pada wanita lebih rendah jika dibandingkan dengan pria dengan usia yang sama. Hal ini terkait dengan konsentrasi hormon estrogen yang lebih tinggi yang dapat meningkatkan bersihan asam urat. Seperti yang diketahui, hiperurisemia merupakan faktor risiko independen sindrom metabolik dan penyakit kardiovaskular (CVD) maupun diabetes mellitus (DM). Hiperurisemia asimtomatik pada orang dewasa yang tidak hamil akan meningkatkan resistensi insulin akibat peningkatan stres oksidatif, dan produksi sitokin inflamasi (tumor necrosis factor- $\alpha$ ), yang pada akhirnya meningkatkan kadar gula darah. Kadar asam urat dan kreatinin serum lebih rendah pada kehamilan normal karena terjadi peningkatan pembersihan ginjal dan efek urikosurik dari hormon estrogen. Hiperurisemia merupakan salah satu faktor yang berkorelasi dengan terjadinya resistensi insulin selama kehamilan, alih alih efek langsung dari hormon plasenta. Pada awal trimester pertama kehamilan, risiko GDM meningkat. Meskipun demikian, efek kausal dari kadar asam urat pada DM membutuhkan penelitian lebih lanjut.*

**Kata Kunci:** Hiperurisemia, Diabetes Gestasional, diabetes mellitus tipe 2

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## Introduction

Hyperuricemia in Asian populations is currently increasing, most likely related with the nature of diet and environment.<sup>1</sup> Elevated serum uric acid can be caused by either an increase in uric acid production, or impaired renal excretion, and/or a combination of both factors.<sup>2</sup> Oversaturation of serum uric acid, approximately at > 6.8 mg/dL, can manifest from asymptomatic hyperuricemia to chronic monosodium urate (MSU) crystal deposition in several target organs, mainly the musculoskeletal tissue (cartilages, tendons, soft tissue, bony process, and ligaments), and kidneys.<sup>3</sup>

In women, the serum uric acid level is lower compared to in men of a similar age (normal value: < 6.0 mg/dL).<sup>4</sup> On the other hand, the concentration of uric acid remains stable at 4.0 ± 2.0 mg/dL until menopause.<sup>4</sup> This lower value is known to be related possibly with higher estrogen concentrations that leads to increased uric acid clearance.<sup>4,5</sup> However, even in low-risk pregnancy (primigravida and no concurrent hypertension or other comorbidities), a study by Jayanthi et al reported that the incidence of hyperuricemia was found around 47% of patients.<sup>4</sup>

In non-pregnant populations, chronic inflammatory event caused by asymptomatic hyperuricemia associates with several clinical consequences.<sup>5</sup> Some findings already established the correlation of hyperuricemia as independent risk factors for non-emerging diseases especially metabolic syndrome and cardiovascular disease (CVD).<sup>6</sup> The increment of 1 mg/dl serum uric acid will notably increase the risk of diabetes mellitus (DM) type 2 to 17%.<sup>7</sup> However, the postulates of hyperuricemia causing either hyperglycemia or hyperinsulinemia in both direction remain controversies.<sup>8</sup> A meta-analysis done in an Asian population by Choi et al reported that hyperuricemia was a strong independent predictor of the incidence of new-onset type 2 DM (HR: 1.78, 95% CI: 1.12 to 2.8) after 5 years follow up.<sup>9</sup> The risk is especially increased in females, old age (≥ 55 years), mild obesity (body mass index (BMI) 24-30 kg/m<sup>2</sup>), coronary artery disease (CAD), metabolic syndrome, smoking, alcohol intake, in patients without hypertension, hyperlipidemia, and stroke.<sup>9</sup>

Yet some reports also reported an association between hyperuricemia as a risk factor in increasing insulin resistance, and gestational diabetes. This review aims to determine the metabolic effect of hyperuricemia in pregnant women, especially women with GDM.

## Uric Acid Metabolism in Non-Pregnant Adult

Uric acid production and metabolism depend on various factors that regulate hepatic production, as well as renal and gut excretion of uric acid.<sup>10</sup> Serum uric acid pool may result from the end product of an exogenous pool of purine and endogenous purine metabolism.<sup>10</sup> The purine pool varies significantly with diet, especially animal protein.<sup>10</sup> High fructose diet and high sodium intake are also contributory factors in the increase of uric acid level and production.<sup>8</sup> On the other hand, endogenous production uric acid is mainly from the liver, intestines and other tissues like muscles, kidneys and vascular endothelium.<sup>10</sup> Up to now, there are 28 single-nucleotide polymorphisms (SNPs) known to affect uric acid level.<sup>11</sup> The gene encodes SLC2A9 that also encodes glucose transporter 9 (GLUT9) and ATP-binding cassette G2 (ABCG2) mainly influential to hyperuricemia.<sup>11</sup> The variation in SLC2A9 may be responsible for 3.5% variation, particularly in women.<sup>11</sup> On the other hand, non-synonymous SNP in ABCD decreases urate efflux by 53%.<sup>11</sup>

Asymptomatic increase of serum uric acid metabolism may affect several target organs in addition to the joints and kidneys. The generation of uric acid from hypoxanthine and xanthine by xanthine oxidase (XO) enzyme pathway may induce the production of reactive oxygen species (ROS) which contributory to cardiac dysfunction to failing myocardium.<sup>1</sup> The study by Barbieri, et. al. concludes a strong association between higher uric acid concentration and the prevalence of severe coronary artery disease (CAD) particularly in women.<sup>12</sup>

Asymptomatic hyperuricemia in non-pregnant adults increases insulin resistance due to oxidative stress and production of inflammatory cytokine (tumor necrosis factor- $\alpha$ ), which ultimately increases blood sugar level.<sup>15,21</sup> For decades, the evidence remains debatable in assuming that hyperuricemia as the consequences of insulin resistance or precursor. However, in a recent study, the hyperuricemia is a predictor for insulin resistance, and independent risk factor to develop type 2 DM within 10 years especially in women.<sup>8,13,14</sup>

## Uric Acid Metabolism, Hyperuricemia, and Insulin Resistance During Pregnancy

The uric acid level and serum creatinine should be lower in normal pregnancy due to increased renal clearance and the uricosuric effect

of estrogen.<sup>15</sup> The elevation of serum uric acid level has been associated with several adverse pregnancy outcomes. This may result in the collaborative addition of oxidative stress, renal dysfunction, tissue injury, and cardiovascular disease, which commonly seen in severe preeclampsia.<sup>16</sup> However, even maternal hyperuricemia in normotensive women was associated with preterm birth ( $p=0.0001$ ), small for gestational age (SGA) delivery ( $p=0.02$ ), development of neonatal intraventricular hemorrhage (IVH) ( $p=0.007$ ), increased likelihood of neonatal NICU admission ( $p=0.002$ ) and lower 1- and 5- minute Apgar scores ( $p=0.004$ ).<sup>17</sup> Several mechanisms have been proposed suggested about this vicious effect of uric acid on pregnancy outcomes. One study showed inhibition of placental system amino acid transport with uric acid treatment, as a result of uric acid-induced stimulation of intracellular redox signaling cascades, which ultimately causes intrauterine growth restriction.<sup>18</sup> Another study proposed to elicit a concentration-dependent attenuation of trophoblast invasion and integration into a uterine microvascular endothelial cell monolayer; therefore, uric acid is able to induce the formation of a dysfunctional placenta.<sup>19</sup> These studies demonstrate that newborns of mothers with elevated serum uric acid levels are at increased risk for perinatal distress.<sup>19</sup>

The development of insulin resistance related to hyperuricemia in pregnancy most likely has the same mechanism as in non-pregnant adult women. There are two proposed hypotheses for hyperuricemia which aggravate insulin resistance and alter glucose metabolism: via the inhibition of nitric oxide (NO) release from endothelial cells (which normally mediate glucose uptake to skeletal muscle), or from adipocytic secretion of uric acid, which mediates inflammatory cytokines and induces oxidative changes in the adipocytes.<sup>11</sup>

In physiological conditions, insulin resistance increases during mid-pregnancy and normalize upon delivery.<sup>20</sup> In 24-28 weeks of gestation, several metabolic changes take place to trigger insulin resistance, which was determined using homeostatic model for insulin resistance (HOMA-IR), instead direct effect of placental hormones (human placental lactogen, prolactin, progesterone, and placental leptins).<sup>20</sup> Other contributory factors associated with insulin resistance among pregnancy are pre-conceptional obesity, the presence of diabetogenic hormones (cortisol, tumor necrosis factors- $\alpha$ , and interleukin's) and hyperuricemia.<sup>15,21</sup> Boaz et al reported that pregnancy with hyperuricemia and gestational hypertension but not preeclampsia strongly correlated with increased insulin resistance ( $45 \pm 31.2\%$  vs.  $79.7 \pm 33\%$ ;  $p=0.018$ ).<sup>15</sup> However maladaptive process of  $\beta$ -cells or to higher insulin demands may result in GDM.<sup>20</sup>

### Hyperuricemia, Gestational Diabetes and Pregnancy

From our literature review hyperuricemia already established as an independent risk factor for gestational diabetes in early pregnancy. Earlier in the first trimester of pregnancy, a study by Laughton et al found that the risk for GDM increases 3.25-fold in patients with uric acid level  $\geq 3.6$  mg/dL (95% CI: 1.35-7.83). They also found that hyperuricemia risk for GDM is concentration-dependent ( $p=0.003$ ), and independent of BMI.<sup>14</sup> A study by Plescakova et al found that pregestational BMI, early pregnancy level of uric acid, and xanthine levels are associated with GDM.<sup>11</sup> Similar results have also been discovered in Asian populations but with different cut off value (see Table 1).

**Table 1. Summary of Studies on The Association between Hyperuricemia with GDM in Asian Populations**

No	Author	Population	Methods	Result
1.	Fawzy et al <sup>22</sup>	273 pregnant first trimester patients with low risk for type 2 DM	Prospective observational study	Higher risk for developing GDM in patients with uric acid level $> 3.1$ mg/dL (sensitivity: 77.8% and specificity: 66.5%)
2.	Chauhan et al <sup>23</sup>	300 pregnant first trimester patients with low risk for type 2 DM	Prospective observational study	83% patients with uric acid level $> 5$ mg/dL developed GDM (sensitivity 62.5% and specificity 99%)
3	Ganta et al <sup>24</sup>	312 pregnant first trimester patients with low risk for type 2 DM	Prospective observational study	Higher risk for developing GDM in patients with uric acid level $> 3.5$ mg/dL (mean uric acid level in GDM and non-GDM group $3.59 \pm 1.10$ , $p=0.001$ )
4	El-Gharib et al <sup>25</sup>	250 pregnant first trimester patients with	Prospective observational study	Higher risk for developing GDM in patients with uric acid level $> 4$ mg/dL (sensitivity 44.7% and specificity 89.6%)

		high risk for type 2 DM			
5	Nader et al <sup>26</sup>	80 pregnant first trimester patients with low risk for type 2 DM	Prospective observational study		Higher risk for developing GDM in patients with uric acid level > 3.11 mg/dL (sensitivity: 100% and specificity: 74.2%)
6	Rasika et al <sup>27</sup>	70 pregnant first trimester patients with low risk for type 2 DM	Prospective observational study		Uric acid in <15 weeks gestation more significantly associated with risk of development GDM compared to 24 and 24 week gestation (Pearson's correlation = 0.735)

From the different phenomena described in mid-pregnancy (second trimester), and the postpartum period it can be concluded that there is a non-significant association between hyperuricemia with GDM risk. However, contrary to that of uric acid, the negative outcomes of xanthine level in postpartum is associated with gestational age at delivery.<sup>11</sup> However, the effect of uric acid levels on diabetes mellitus (DM) required further study because only 5.9% of women developed type 2 DM or other types of DM after 1 year observation.<sup>11</sup>

## Conclusion

The development of insulin resistance by hyperuricemia in pregnancy has the same mechanism as non-pregnant adults. Hyperuricemia increases insulin resistance via inhibition of NO release from endothelial cells, and the other is from adipocytes secretion of uric acid that precisely mediates inflammatory cytokines and induces oxidative changes in adipocytes. However, the effect of uric acid levels on diabetes mellitus requires further study because only 5.9 % of women developed type 2 DM or other types of DM.

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