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FIRST TRIMESTER URIC ACID LEVEL DURING PREGNANCY - A RISK FACTOR FOR GESTATIONAL DIABETES MELLITUS AND HYPOTHYOIDISM

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ABSTRACT

The study examined the relationship between serum uric acid levels and pregnancy complications, specifically gestational diabetes mellitus (GDM) and subclinical hypothyroidism. Fifty non-diabetic, euthyroid pregnant women were included in the study, with their uric acid levels measured in the first trimester. The participants were then monitored throughout pregnancy, and oral glucose challenge test (OGCT), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) levels were assessed between 24-28 weeks of gestation. The findings demonstrated a direct correlation between elevated serum uric acid levels (> 4.6 mg dL^{-1}) and GDM ($p < 0.017$). The study also revealed a significant association between uric acid levels, glucose metabolism, and thyroid hormone concentrations ($p < 0.0001$) as pregnancy progressed. Elevated maternal serum uric acid was identified as a reliable early indicator of GDM.

Keywords: Gestational diabetes mellitus, glucose challenge test, pregnancy, subclinical hypothyroidism, uric acid

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is a significant concern during pregnancy, with potential adverse health effects on both the mother and baby if left unaddressed (Modzelewski *et al.,* 2022; Wang *et al.*, 2022). According to the latest estimates of International Diabetes Federation (IDF), GDM worldwide affects approximately 14.0% of pregnancy cases, contributing to around 20 million births each year (Lee *et al.*, 2018). Women with GDM face a higher risk of complications such as pre-eclampsia, gestational hypertension, and even pregnancy termination (Kondracki *et al.,* 2022). Additionally, GDM increases the likelihood of long-term complications like cardiovascular issues, obesity, and impaired carbohydrate metabolism, which may lead to the development of type 2 diabetes (T2DM) in both the mother and the child in the future. The growing incidence of GDM also places a significant economic burden, emphasizing the need for greater awareness and attention (Miller and Lim, 2021).

In early pregnancy, serum uric acid levels generally decrease, often falling to 3 mg dL^{-1} or lower, due to the uricosuric effect of estrogen and increased renal blood flow. However, by the third trimester, uric acid levels rise, reaching approximately 4–5 mg dL^{-1} by term (Kumar and Singh, 2019). It has been observed that women predisposed to pre-eclampsia tend to have slightly elevated serum uric acid levels in the first trimester, along with a relative reduction in urinary urate excretion (Asgharnia *et al*., 2017; Colmenares-Mejia *et al.,* 2023). During initial assessments, pregnant women with pre-eclampsia often show significantly increased serum uric acid levels. Some studies have indicated a potential link between the extent of this increase and the severity of maternal symptoms, as well as fetal complications, including the risk of delivering infants with small gestational age and an increased likelihood of fetal mortality (Roberts et al., 2005; Khan et al 2022).

Thyroid hormones are crucial for maintaining overall health and well-being, playing a significant role in regulating normal metabolic processes in the body. The complex and inverse relationship between thyroid-stimulating hormone (TSH) and other thyroid hormone levels indicates that TSH is a more sensitive marker of overall thyroid function (Taylor *et al.,* 2023). The rate of overt hypothyroidism and subclinical hypothyroidism (SCH) during pregnancy is approximately 2-3% and 0.3-0.5%, respectively (Bajaj *et al*., 2022). Overt hypothyroidism in pregnancy can be challenging to distinguish from normal pregnancy symptoms, leading to potential adverse effects on both maternal and child health, ranging from anemia to miscarriage. If the pregnancy continues, there may be increased risk of preterm delivery and other complications (Yadav *et al*., 2021). Therefore, this study aimed to evaluate the relationship between uric acid levels, gestational diabetes, and hypothyroidism during pregnancy.

MATERIALS AND METHODS

The cohort study was conducted at the Antenatal Outpatient Department of Sree Balaji Medical College and Hospital in Tamil Nadu, India, from November 2018 to December 2019. It involved 50 expectant women in their first trimester, aged between 20 and 35 years. The study received institutional ethical clearance from the institutional ethical committee vide reference No. 002/SBMCH/IHEC/2017/985.

Inclusion criteria: The study included non-diabetic, euthyroid pregnant women with less than 12 weeks of gestation, who were regularly monitored over a 28-week period.

Exclusion criteria: Pregnant women in their first trimester with complications such as hypertension, known thyroid disease, renal disease, liver disease, or those taking medications that elevate serum uric acid levels (including diuretics and aspirin) were excluded from the study.

Confidentiality was strictly maintained throughout the study. Participants were informed about the voluntary nature of their participation and their right to withdraw at any time, for any reason. Verbal consent was initially obtained from the participants, followed by written consent. All participants underwent a general physical examination, abdominal assessment, and detailed history and demographic information was collected.

Venous blood samples were drawn, and serum separated from each participant. Serum uric acid levels were measured using the uricase method with a Roche Cobas 6000 Chemistry Analyzer during the first trimester (Zhao *et al.,* 2009). All 50 participants were closely monitored and followed. Between 24-28 weeks of gestation, TSH concentration and the oral glucose challenge test (OGCT) were conducted according to the American Diabetes Association (ADA) criteria (Rani *et al.,* 2016; Pramanik *et al.,* 2020).

For GDM screening, fasting blood samples (after 8 h fasting) and urine samples were collected. The participants were then given 75 g oral glucose in 250 mL water, and the blood samples were collected 2 h later. GDM was diagnosed if plasma glucose levels exceeded the following thresholds: fasting blood sugar (FBS) > 95 mg dL^{-1} and OGCT >180 mg dL^{-1} after 2 h. Additional demographic data were also collected.

Serum uric acid levels were measured using the uricase method with the ERBA uric acid kit. Glucose was estimated using the GOD/POD (glucose oxidase/peroxidase) method with the ERBA glucose kit, and TSH was measured using the IRMA (immunoradiometric assay) kit. Serum FT4 concentration was determined using an enzymatic immunoassay (EIA) kit. The collected data were analysed using SPSS software, version 23, and the p-value was calculated. Categorical data were presented as actual numbers and percentages.

RESULTS AND DISCUSSION

The study assessed serum uric acid levels in pregnant women during their first trimester and revealed that 62% had uric acid levels within the normal range, while 38% exhibited elevated levels exceeding 4.6 mg dL^{-1}. Among the participants, 36% were primiparous, and 64% were multiparous (Table 1). Out of the 50 women studied, 16 were diagnosed with gestational diabetes, while 34 had normal glycemic levels. Half of the study population aged between 26-30 years fell into the GDM group, while the remaining 50% (20-25 years: 34%, and 31-35 years: 16%) were in the non-GDM group.

Table 1: Age and parity distribution, first trimester serum uric acid level (mg dL^{-1}) and GCT between 24-28 weeks in the study cohort

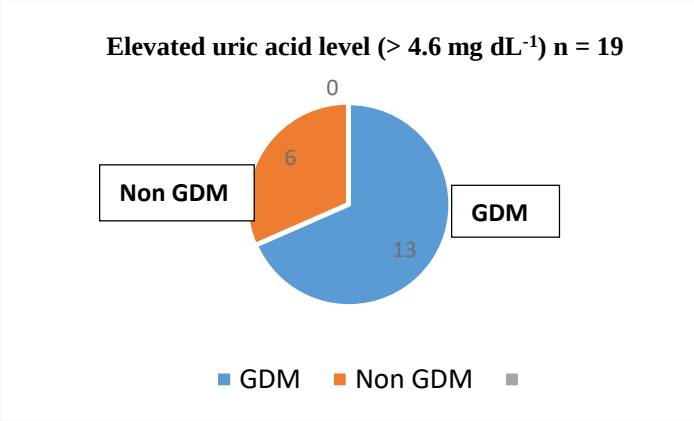
GDM/ non-GDM	Percentage (%)	Age in years (% samples)	Parity		Uric acid concentration (1st trimester)
			Primi (34%)	Multi (64%)	
GDM (n = 14)	28	26-30 (50%)	16%	20%	19%
Non GDM (n = 36)	72	20-25 (34%)	20%	44%	31%
		31-35 (16%)			

Based on the ADA criteria for confirming the gestational diabetes, a positive diagnosis requires any two elevated values in the oral GTT/GCT: FBS > 95 mg%, 1-h blood glucose > 180 mg%, and 2-h blood glucose > 155 mg%. Among the 19 pregnant women with elevated serum uric acid levels, 13 tested positive for GDM (Fig. 1). A positive correlation was observed between serum uric acid levels exceeding 4.6 mg dL^{-1} and the oral glucose challenge test results. Hyperuricemia was found in 19 (38%) of the pregnant women, with 13 of them being diagnosed with GDM. Additionally, subclinical hypothyroidism (SCH) was identified in 14 women (Table 2). The normal TSH and FT4 values in pregnant women differ from those in non-pregnant women. In this study, SCH was defined based on ATA criteria: TSH above the trimester-specific reference range, and FT4 concentration between 0.7-1.8 ng dL^{-1}. Subclinical hypothyroidism is characterized by elevated TSH concentrations (≤ 10 mL U L^{-1}) and low serum FT4 levels (Cignini *et al.,* 2012; Moleti *et al.,* 2014).

Table 2: TSH and FT4 level in subclinical hypothyroid cases

Parameters	No. of cases	Mean	Standard deviation	P value
TSH (mU L^{-1})	14	4.706	0.803	p<0.0001
FT4 (ng dL^{-1})	50	1.003	0.140	P <0.0001

Fig. 1: GDM and Non-GDM population among pregnant women with increased 1st trimester uric acid concentration (mg dL^{-1})



The study population was divided into two groups (Table 3): A risk group (elevated serum concentrations of various analytes) and a non-risk group (serum concentrations within normal limits). OGCT and TSH levels were analysed in the 3rd trimester (24-28 weeks) and compared with serum uric acid levels (Table 4), with highly significant p-values observed.

Hyperuricemia or elevated serum uric acid concentration is recognized as a significant risk factor that increases insulin resistance and gestational diabetes mellitus, thereby negatively impacting both maternal and child health. Estrogen plays a protective role against hyperuricemia and gout by enhancing the renal clearance of uric acid. This protective mechanism is further supported by the uricosuric effect of estrogen and an increased glomerular filtration rate (GFR). In India, the incidence of gestational diabetes mellitus is reported to be 17% (Srinivasan, 2022).

Table 3: Comparison of uric acid level, OGCT& TSH among groups

Parameters	Risk group (↑concentration)	Non risk group
Uric acid (1st trimester)	N = 19 (> 4.6 mg dL^{-1})	N = 31(< 4.5 mg dL^{-1})
OGCT (2nd trimester)	N = 14 (> 155 mg dL^{-1})	N = 36 (< 155mg dL^{-1})
TSH (2nd trimester)	N = 6 (≥10 mL U L^{-1})	N = 44 (0.2-3 mL U L^{-1})

Table 4: Comparison of GDM (mg dL^{-1}) and subclinical hypothyroid (SCH) (mL U L^{-1}) cases among the increased uric acid concentration group (N = 19)

Parameters	No. of cases	Mean	Standard deviation	P value ($p < 0.05$)
OGCT (mg dL^{-1})	13	188.769	19.846	<0.0001
Uric acid (mg dL^{-1})	19	5.156	0.5	<0.017
TSH (mL U L^{-1})	14	4.706	0.803	<0.0001
FT4 (ng L^{-1})	50	1.003	0.140	<0.0001

The study found that pregnant women tested positive for subclinical hypothyroidism and GDM with elevated TSH levels, despite having normal thyroid hormone levels during first-trimester screening. This finding is consistent with research conducted by Rao *et al*. (2017), which also reported elevated uric acid levels during the first trimester associated with a higher risk of GDM among the South Indian population (Rao and Uthraraj, 2017). During pregnancy, the iodide pool is reduced due to the transfer of iodine to the feto-placental unit and increased renal clearance of iodine. This results in a higher demand for iodine during pregnancy compared to non-pregnant women. Many studies have shown that reference intervals for both free thyroid hormones and TSH change throughout pregnancy, leading scientific societies to recommend using gestation-specific reference ranges for interpreting results at different gestational ages (Moleti *et al*., 2014). Untreated hypothyroidism during pregnancy can lead to serious maternal complications, including preterm delivery, intrauterine fetal demise, and an increased rate of perinatal mortality (PNM). In new borns, hypothyroidism can result in cognitive, neurological, and developmental defects, underscoring the crucial role of thyroid hormones in fetal brain development (Bajaj and Sarita., 2022; Klubo-Gwiezdzinska *et al.*, 2011; Zhao, *et al.*, 2022)

Conclusion: This investigation highlights the association between elevated serum uric acid levels in early pregnancy and the development of gestational diabetes mellitus (GDM), as well as its connection to subclinical hypothyroidism with advancing gestational age. As a result, incorporating serum uric acid concentration into the antenatal screening process during the first trimester may aid in the prevention and management of GDM. Additionally, continuous monitoring of thyroid hormone levels in the second and third trimesters shows significant potential for improving the early detection and management of thyroid dysfunction during pregnancy, thereby preventing adverse maternal and fetal outcomes related to hypothyroidism.0

Ethical statement: The study was carried out after obtaining the ethical approval from the Institutional ethical committee vide reference No. 002/SBMCH/IHEC/2017/985.

Conflict of interest: The authors have no competing interests relevant to this manuscript.

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