

Serum Uric Acid and Plasma Glucose Levels in Normal Pregnancy

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Abstract: There are existing reports of an association of uric acid with glucose metabolism and their impact on adverse pregnancy outcomes. Hyperuricemia is linked to glucose homeostasis and basically to all components of the metabolic syndrome in the general population. Based on this premise, our study aimed at determining the level of serum uric acid and plasma glucose in second and third-trimester normal pregnancies with a view of establishing cut off values in Makurdi, Nigeria. The hospital-based case-control study involved a total of 103 participants aged 18-35 years attending the antenatal and the general health check up clinics. The participants comprised of 81 normal pregnant females in their second and third trimesters compared with 22 non pregnant controls. Their fasting plasma glucose and serum uric acid levels were compared among age-matched non-pregnant women (n=22), second (n=38), and third (n=43) trimester pregnancies. Serum uric acid level in second (5.89 ± 0.85 mg/dl) and third (6.23 ± 1.30 mg/dl) trimester pregnancies were significantly ($p=0.000$) higher than the non-pregnant controls (3.80 ± 1.11 mg/dl). A significant ($p<0.01$) increase in plasma glucose was observed in third-trimester pregnancies (5.19 ± 0.64 mmol/l) compared to second-trimester pregnancies (4.87 ± 0.79 mmol/l) and controls (4.65 ± 0.51 mmol/l). The study provided cut-off values for uric acid, glucose, and further points the need for prenatal care in terms of screening and diagnosis of pregnancy complications in all pregnant women including those considered at low risk.

Keywords: Pregnancy, Serum Uric Acid, Plasma Glucose, Second Trimester, Third Trimester

1. Introduction

Uric acid is the final product of purine degradation formed mainly in the liver, intestines, and vascular endothelium. The precursors of uric acid are endogenous (damaged, dying, dead cells) and exogenous (dietary) proteins, and mainly excreted by the kidneys (65%) and intestines (35%) [1]. At physiologic concentrations, uric acid exhibits excellent antioxidant activity and as such accounts for two-thirds of the total plasma antioxidant capacity [2]. Hyperuricemia constitutes elevated uric acid above its physiologic levels in the plasma and is enhanced either by increased uric acid production and impaired renal uric acid excretion or both [3]. Hyperuricemia, on the other hand, propagates oxidative

damage and serve as a risk factor for much pathology by promoting inflammation and endothelial dysfunction [2]. Elevated serum uric acid is closely associated with insulin resistance and type 2 diabetes mellitus [4]. A meta-analysis of a prospective cohort and a critical review concluded that serum uric acid is a strong and independent predictor of diabetes in middle-aged and the elderly [5].

In healthy pregnancies (table 1), uric acid decreases from an average of 4.2 mg/dl pre-pregnancy to 3.1 ± 1.1 mg/dl in the first trimester due to the uricosuric effects of estrogen and increase in renal blood flow, then slowly increases during gestation to an average of 5.1 ± 1.2 mg/dl from 35 weeks gestation to term [6, 7].

Table 1. References of serum uric acid and fasting plasma glucose values in pregnant and non-pregnant females.

STATUS	URIC ACID (mg/dl) Lind <i>et al.</i> [6] Abbassi <i>et al.</i> [7]	FPG (mmol/l) IADPSG [8]
Non-pregnant	3.03-5.88	4.2 - 5.5
First trimester	2.35-3.87	-
Second trimester	2.35-4.71	4.2 - 4.4
Third trimester	3.53-6.39	4.0 - 4.3

IADPSG-The International Association of Diabetes Pregnancy Study Group,
FPG-Fasting Plasma Glucose.

Previous studies have demonstrated a correlation between elevated maternal serum uric acid levels with adverse maternal and neonatal outcome [9, 10]. Hyperuricemia has been reported to unfavorably affect both the placenta and maternal vasculature [9]. Uric acid has been shown to be directly involved in the pathogenesis of preeclampsia by promoting inflammation, oxidative stress and endothelial dysfunction [9, 11]. Elevated plasma uric acid is an independent risk factor for preterm birth, low birth weight delivery, and other adverse neonatal outcomes [10, 12]. These bioactivities of uric acid may explain why it is a risk marker of preeclampsia and the development of adverse maternal/infant conditions.

During early pregnancy, glucose tolerance is normal or slightly improved with normal peripheral sensitivity to insulin and hepatic basal glucose production [13]. As gestation age progresses maternal insulin sensitivity declines creating an insulin resistant state to meet the energy demands of both the mother and the rapidly growing foetus [13]. Glucose production increases with maternal body weight, such that glucose production per kilogram body weight does not change throughout pregnancy [13]. Increased fasting blood glucose in pregnant women indicates danger signs that pose a threat to both the mother and the foetus since glucose is an important substrate for metabolism [14]. Data from the hyperglycemia and adverse pregnancy outcomes (HAPO) study, proposed that moderately elevated levels of maternal glucose concentrations are predictive of gestational diabetes mellitus (GDM), fetal macrosomia, the need for delivery by cesarean section and fetal hyperinsulinemia [14]. A study involving 14,036 women demonstrated an association between maternal glucose below the classic cut-off values for the diagnosis of GDM and adverse pregnancy outcomes; increased rates of cesarean deliveries, fetal macrosomia, preeclampsia, and admissions to neonatal intensive care units [15]. Maternal blood glucose levels are associated with perinatal asphyxia [16].

Hyperuricemia is linked to glucose homeostasis and basically to all components of the metabolic syndrome; insulin resistance, type 2 diabetes mellitus, visceral obesity, hypertension, dyslipidemia, atherosclerosis in the general population [17, 18]. Researchers have previously reported an association between hyperuricemia and an increased risk of development of GDM [19, 20].

Other previous findings of an association of uric acid with glucose metabolism and their impact on adverse pregnancy outcomes, informed the conduct of this present study. The

study thus aimed at determining serum uric acid and fasting plasma glucose levels in normal pregnant women, with the view of establishing cut-off values that will enable the effective monitoring of pregnant women during antenatal care in Makurdi, Nigeria.

2. Materials and Methods

2.1. Study Design

The case-control and hospital-based study involved a total of 103 participants. Their fasting plasma glucose and serum uric acid levels were compared among age-matched non-pregnant women (n=22), second (n=38), and third (n=43) trimester pregnancies.

2.2. Area of Study

The study was conducted at the Federal Medical Centre Makurdi (FMCM), Nigeria. The hospital is located in Makurdi, the capital of Benue state. The hospital renders tertiary health care services to the populace of the entire state. The populace is comprised mainly of the Tiv, Idoma, Igbo and other indigenous ethnic minorities. People from other parts of the country have come to settle in the state; these include the Igbo, Yoruba, Hausa, and Fulani. These ethnic groups are predominantly farmers and have similar cultural and traditional ways of life.

2.3. Selection of Participants

Individuals were eligible to participate in the study if they: (a) were within the reproductive age of 18 to 35 years; (b) had no history of hypertension and were not using antihypertensive medications; (c) were free of any other major systemic illnesses (e.g. renal disease, gout, liver disease, cancer, diabetes mellitus); (d) were free from pregnancy complications. Individuals who refused to take part in the study were excluded. All subjects were availed with informed consent, and the study was approved by the institutional ethical committee.

A sample of 81 female participants who fulfilled the inclusion criteria, were randomly drawn from women in their mid-gestation upwards and attending the ante-natal clinic at the FMCM, Nigeria from June to August 2018. Anthropometrically matched non-pregnant women (n=22) adjudged to be apparently healthy were randomly selected among female patients attending the same hospital for a general check-up within the same period.

2.4. Data Collection

Participants provided information on their demographic characteristics, detailed medical history, dietary, and lifestyle habits. All participants were required to fast for 12 hours before intravenous blood sample collection for biochemical determinations. Physical examination was carried out by trained staff and physicians using standard protocols.

Body weight and height were measured with the participant barefoot and wearing light clothing. Body weight to the nearest 0.1 kg and height to the nearest centimeter were measured and BMI was calculated as weight (kilograms)/height (meters squared).

Systolic and diastolic blood pressure (SBP and DBP) of the participants was measured twice in a seated position after a 5-min rest using a mercury sphygmomanometer. Normotensives were defined as systolic BP ≤ 120 and/or diastolic BP ≤ 80 mmHg according to the guidelines of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of high blood pressure [21].

2.5. Laboratory Measurements

Participant's blood samples were collected into plain and fluoride oxalate vacutainer tubes then centrifuged at 3000 rpm for 10 minutes within 1 hour of blood collection. Serum and plasma were respectively used for the determination of uric acid, glucose levels using Randox reagent kits (Randox Laboratories Ltd., County Antrim, UK) on a spectrophotometer (Optima SP-300 Spectrophotometer; Optima INC. Tokyo, Japan) immediately after separation. Serum uric acid and plasma glucose were measured respectively by adopting the uricase and glucose oxidase

endpoint colorimetric methods. The widely accepted cut-off values used in defining elevated uric acid and glucose levels are presented in table 1.

2.6. Statistical Methods

Data were presented as means and standard deviations for continuous variables. Analysis of variance was used for between-group assessments followed by least significant difference *post hoc* honestly significant difference test. All statistical analyses were performed using the IBM Armonk, NY, USA, SPSS version 21. A two-sided $P < 0.05$ was considered statistically significant.

3. Results

Table 2 presents the anthropometric, serum uric acid and plasma glucose levels in non-pregnant and pregnant women. A significant ($p < 0.01$) change in uric acid, glucose level was observed when the control, second and third-trimester groups were compared. No significant ($p > 0.05$) change in blood pressure and maternal age was observed among the three groups compared. A breakdown of the results as revealed by a *post hoc* analysis is presented in table 3. Serum uric acid level in second and third-trimester pregnancies was significantly ($p = 0.000$) higher than the non-pregnant controls, whereas no significant ($p > 0.05$) difference was found between the two trimesters. A significant ($p = 0.003$) increase in plasma glucose was observed in third-trimester pregnancies compared to controls, no significant ($p > 0.05$) increase was observed in second-trimester pregnancies. However, third-trimester pregnancies showed a significant ($p = 0.036$) elevated plasma glucose compared to second-trimester pregnancies.

Table 2. Uric acid and fasting plasma glucose levels in matched pregnant and non-pregnant females.

Parameter	Control n=22	2 nd Trimester n=38	3 rd Trimester n=43	F-value	P-value
Age years	29.50 \pm 5.45	27.08 \pm 4.44	28.95 \pm 5.31	2.09	0.129
SBP mmHg	105.91 \pm 12.60	108.42 \pm 11.51	104.88 \pm 10.77	0.99	0.376
DBP mmHg	67.50 \pm 9.73	69.21 \pm 9.97	67.21 \pm 7.97	0.53	0.591
Uric Acid mg/dl	3.80 \pm 1.11	5.89 \pm 0.85	6.23 \pm 1.30	37.31	0.000*
FPG mmol/l	4.65 \pm 0.51	4.87 \pm 0.79	5.19 \pm 0.64	5.18	0.007*

*significant, SBP- systolic blood pressure, DBP- diastolic blood pressure, FPG- fasting plasma glucose

Table 3. Post hoc test comparing uric acid and fasting plasma glucose levels among the trimesters of pregnancy with controls.

Parameter	Control n=22	2 nd Trimester n=38	P-value	Control n=22	3 rd Trimester n=43	P-value	2 nd Trimester n=38	3 rd Trimester n=43	P-value
Age years	29.50 \pm 5.45	27.08 \pm 4.44	0.076	29.50 \pm 5.45	28.95 \pm 5.31	0.680	27.08 \pm 4.44	28.95 \pm 5.31	0.098
SBP	105.91 \pm 12.60	108.42 \pm 11.51	0.415	105.91 \pm 12.60	104.88 \pm 10.77	0.733	108.42 \pm 11.51	104.88 \pm 10.77	0.168
DBP	67.50 \pm 9.73	69.21 \pm 9.97	0.486	67.50 \pm 9.73	67.21 \pm 7.97	0.904	69.21 \pm 9.97	67.21 \pm 7.97	0.327
Uric Acid	3.80 \pm 1.11	5.89 \pm 0.85	0.000*	3.80 \pm 1.11	6.23 \pm 1.30	0.000*	5.89 \pm 0.85	6.23 \pm 1.30	0.178
FBG	4.65 \pm 0.51	4.87 \pm 0.79	0.221	4.65 \pm 0.51	5.19 \pm 0.64	0.003*	4.87 \pm 0.79	5.19 \pm 0.64	0.036*

*significant, SBP- systolic blood pressure, DBP- diastolic blood pressure, FPG- fasting plasma glucose

4. Discussion

Reports by other previous studies revealed the independent association of elevated serum uric acid levels with a higher risk of development of GDM, preeclampsia and adverse

pregnancy outcomes [14, 20]. It is based on this premise that the present study determined the level of serum uric acid and plasma glucose in second and third-trimester normal pregnancies with a view of establishing cut off values to be used during monitoring of ante-natal care patients in our

environment.

The present study observed a significant change in serum uric acid levels of pregnant women compared to non-pregnant controls. The uric acid levels of both the second and third-trimester pregnancies were higher than that of non-pregnant controls. Our finding of raised serum uric acid level in normal pregnant women compared to non-pregnant controls is consistent with the observations of Lind *et al.*, Ahaneku *et al.*, Nduka and Ekeke, Okonkwo *et al.*, in various study areas and populations [6, 22-24]. Lind *et al.*, studied the changes in serum uric acid concentrations during normal pregnancy [6]. In their study, pre-pregnancy values of uric acid concentrations decreased significantly by 8 weeks gestation, and this reduced level was maintained until about 24 weeks. Thereafter, the concentrations increased such that at term, they were greater than the pre-pregnancy values in the majority of patients and remained elevated until at least 12 weeks after delivery. The serum uric acid obtained in this study is comparable to non-pregnant females and third-trimester pregnancy reported by Lind *et al.*, and Abbassi-Ghanavati *et al.* [6, 7]

This present study observed mean uric acid levels of 3.80 ± 1.11 in non-pregnant controls which is within the reference range of non-pregnant females presented in table 1. The observed mean value of uric acid in non-pregnant women is also comparable with those in other populations. Omotayo *et al.* (Nigeria), Diwan (India), Bawah *et al.* (Ghana) respectively observed 3.53mg/dl, 3.97mg/dl, 3.82mg/dl mean values in non-pregnant women [25-27]. The mean value of uric acid level observed during mid-gestation (5.89 ± 0.85 mg/dl) in this present study was comparable with non-pregnant females but higher than the second-trimester reference values proposed in table 1. Whereas the third-trimester uric acid mean value of 6.23 ± 1.30 mg/dl was higher than the upper limit of the non-pregnant reference and comparable with the values observed in third-trimester reference. In a Nigerian population, Okonkwo and colleagues previously found a mean uric acid level of 6.05mg/dl in third-trimester normal pregnancies, which is comparable with the present study [25]. In pre-eclamptic pregnancies, Ekun *et al.*, Pramanik *et al.*, Deshpande *et al.*, Kasraian *et al.* respectively reported mean uric acid levels of 6.69, 6.27, 6.21, 6.20mg/dl comparable to the present study [28-31].

Increasing evidence suggests that an elevated serum uric acid in pregnancy may not only be a valuable biomarker for preeclampsia but may also have a contributory role in the pathogenesis of maternal and fetal manifestations [9, 12]. Amini *et al.*, assessed the association of maternal hyperuricemia with adverse pregnancy and neonatal outcomes in normotensive singleton pregnant women; maternal hyperuricemia significantly associated with preterm and small-for-gestational-age (SGA) delivery and the development of neonatal intraventricular hemorrhage [12]. Wolak *et al.*, showed that high uric acid level during normal pregnancy, associated with increased atherosclerotic damage later in non-pregnant life [32]. The higher the uric acid level during pregnancy, the higher the risk for subsequent

hospitalizations from an atherosclerotic complication, includes significant atherosclerotic-related morbidity [32].

During normal pregnancies, serum uric acid concentration decreases by 25–35 % in early pregnancies, but then increases throughout the pregnancy, primarily as the result of altered renal handling [10]. Renal handling of uric acid is complex and involves four sequential steps, namely 1. Glomerular filtration, 2. reabsorption of about 98–100 % in proximal convoluted tubules, 3. Secretion into the lumen of the distal portion of proximal tubules and 4. Further reabsorption in distal tubules. The net urinary excretion of uric acid is 6–12 % of the amount filtered. The increase in plasma concentration of uric acid at mid and last trimesters of pregnancy may be secondary to elevated tubular reabsorption with decreasing renal clearance of the uric acid [6]. In complicated pregnancies like pregnancy-induced hypertension or pre-eclampsia; 1. hyperuricemia is caused by a decrease in uric acid clearance secondary to inappropriate fall in glomerular filtration rate due to the action of vasoconstrictors such as angiotensin II, norepinephrine and endothelin. 2. Hyperuricemia is also caused by elevated blood lactic acid levels produced by the hypoxic placenta that interfere with uric acid excretion. Besides impaired renal excretion, it is proposed that increased oxidative stress and formation of reactive oxygen species (ROS) during pregnancy forms another source of hyperuricemia [9].

Experimental studies have demonstrated that hyperuricemia provokes endothelial dysfunction through increases in inflammation and oxidative stress [1]. Recent clinical studies have also shown that hyperuricemia is associated with endothelial dysfunction in humans. Experimental and clinical studies have suggested that uric acid is not only a biomarker of cardiovascular risk but also a causal risk factor of endothelial dysfunction [1]. Uric acid passes freely into the fetal circulation and has been found to block vascular endothelial growth factor VEGF-induced endothelial proliferation and may have a direct role in blocking fetal angiogenesis resulting in small for gestation age SGA infants [33]. Uric acid directly inhibits amino acid transfer in the placenta and suppresses fetal growth [9]. Elevated levels of uric acid may have a proliferative and proinflammatory effect on the small blood vessels of the placenta, resulting in SGA fetuses [10].

The present study found high fasting plasma glucose levels in the third-trimester pregnancies compared to non-pregnant controls and second-trimester pregnancies. However, no change was observed in the level of fasting plasma glucose of non-pregnant controls compared with second-trimester pregnancies. Ekhatior and Ebomoyi, Gaya *et al.*, Church *et al.*, Zannat *et al.*, Sufrin *et al.*, found a high level of serum glucose in most of the pregnant women in their third trimester [34-38]. The results of Ekhatior and Ebomoyi in a population of normal pregnant Nigerian women showed that glucose concentration was significantly higher in pregnant women than the control group, and it was highest in the third trimester of pregnancy [34]. Similarly, Gaya *et al.*, in a population of normal pregnant Nigerian women observed a

significantly increased blood glucose levels in the third trimester [35]. Church *et al.* observed that blood glucose levels of pregnant women assessed by first, second and third trimester demonstrated an increase in the blood glucose level as pregnancy progresses [36]. The results of a cross-sectional study by Zannat *et al.*, in normal pregnant women showed that serum glucose levels increased significantly in the third trimester, while a non-significant value was found in first trimester [37]. In a study of normal pregnant women conducted by Sufrin *et al.*, mean serum glucose level was found to be significantly higher in third-trimester pregnant women than non-pregnant women [38].

The mean fasting plasma glucose value of non-pregnant women observed in the present study stood at 4.65 ± 0.51 mmol/l which is within the reference range of 4.2 - 5.5 mmol/l as presented in table 1. A mean fasting plasma glucose level of 4.64 ± 0.79 mmol/l was previously observed in a population of non-pregnant Nigerian women [39]. The present finding of a third trimester fasting plasma glucose mean value of 5.19 mmol/l is in line with the proposed cut-off value (5.10 mmol/l) for the diagnosis of GDM [40]. The International Association of Diabetes Pregnancy Study Group (IADPSG) for the diagnosis of GDM also called the 2013 WHO criteria for GDM proposed that Pregnant women with fasting plasma glucose greater than or equal to 5.1 mmol/l (92 mg/dl) but less than 7.0 mmol/l (126 mg/dl) may be diagnostic of GDM [40]. Seabra *et al.*, observed that second and third-trimester fasting glucose levels of 4.47 to 5.20 mmol/l were associated with an increased risk of pregnancy complications; GDM, macrosomia and cesarean section deliveries [41]. Seabra *et al.*, concluded that the gestational periods in which maternal blood glucose had a greater influence on the appearance of complications were the second and third quarters, indicating vulnerable periods since they are related to intensive developmental phase and fetal growth [41]. Hyperglycemia from any cause can seriously affect both mother and baby and could increase the risk of complications in pregnancy, labour and after delivery in conditions not monitored properly [42]. The increasing frequency of blood glucose level as pregnancy progresses may predispose the women to gestational diabetes and other maternal/fetal complications. The present study observed incremental changes in serum uric acid levels along with fasting plasma glucose when the second and third-trimester pregnancies were compared.

There is evidence that hyperuricemia is related to insulin resistance and decreased birth weight in newborns of normotensive pregnant women [10, 19]. Yoo *et al.*, in a large cross-sectional study of 53,477 non-pregnant females, found that serum uric acid level was positively correlated with fasting serum glucose and insulin resistance, as well as features of the metabolic syndrome [17]. Hyperuricemia is linked to insulin resistance and type 2 diabetes mellitus and basically to all components of the metabolic syndrome; visceral obesity, hypertension, dyslipidemia, atherosclerosis in the general population [17, 18]. Accumulating evidence from different studies suggests that uric acid could play a role in glucose

homeostasis by increasing insulin resistance, inhibiting insulin-mediated endothelial nitric oxide release and by directly acting on adipocyte [43, 44]. As gestation age progresses maternal insulin sensitivity declines, creating an insulin resistant state to meet the energy demands of both the mother and the rapidly growing foetus [13]. Maternal insulin resistance is reported to be mediated by an increase in the levels of estrogen, progesterone, human placental lactogen, human placental growth hormone, cortisol, inflammatory cytokines [13]. Insulin resistance is previously reported to be associated with elevated uric acid in pregnancy and the general population [18, 19]. Increase in secretion of metabolic hormones during pregnancy particularly thyroxine and adrenocortical hormones increase the metabolic rate by about 15% during the third trimester. As protein anabolism occurs, blood glucose levels increase and about 3-4 kg of fat is deposited in the maternal body, increasing blood cholesterol levels [45].

5. Conclusion

This study with other literature on the subject have provided cut-off values for uric acid, glucose, and further points the need of prenatal care in terms of screening and diagnosis of pregnancy complications in all pregnant women including those considered as a low-risk group, for the prevention of consequences.

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