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IMPACT OF SERUM URIC ACID CONCENTRATION ON ULTRASOUND SCANNED PREGNANT WOMEN IN CALABAR, NIGERIA

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ABSTRACT

Objectives: To evaluate the effect of serum uric acid elevation on the fetus and to determine the existence of a connection between hyperuricemia and gestational hyperten sion (pre-eclampsia).
Materials and method: A prospective cross-sectional case-controlled ultrasound scan study was done on 200 singleton pregnant women between 20 to 40 weeks gestational age in a 12-month period. The age range for the cases and control were from 15 to 39 years. Uric acid concentration in the serum obtained from all the women was analyzed utilizing manual colorimetric method. Pearson's correlation and the student t-tests were used to analyze the data obtained.
Results: Maternal serum uric acid had negative correlation with fetal heart rate (FHR) ($p = 0.025$) and a positive correlation with estimated gestational age (EGA) ($p = 0.040$) including estimated fetal weight EFW ($p = 0.046$). A significant positive correlation between uric acid and proteinuria ($p = 0.009$) was observed. Uric acid was higher in pre-eclamptics than gestational hypertensives (8.528±2.679 mg/dl versus 6.542±1.746 mg/dl, $p = 0.016$). Also, uric acid in pregnancy induced hypertension (PIH) was higher than the normotensives (7.535±2.165 mg/dl versus 5.437±1.636 mg/dl).
Conclusion: Maternal hyperuricemia predisposes to fetal bradycardia which may have possibly led to the two fetal demise recorded in the present study. Increased EFW with hyperuricemia may be due to higher body mass index (BMI) of the subjects. Therefore, high serum uric acid has a significant role in foretelling the appearance of pre-eclampsia but not gestational hypertension.

KEYWORDS: Blood pressure in pregnancy, Fetal outcome, Pre-eclampsia, Serum uric acid, Ultrasonography.

INTRODUCTION

At the onset of pregnancy, the circulating maternal serum uric acid drops at a steady rate until it is below 3 mg/dl around the 16th week of gestation, due to the combined effects of the uricosuric propensity of estrogen, increased glomerular filtration rate (GFR) and increased blood volume (Roberts *et al*., 2005; Bainbridge and Roberts, 2008; Johnson *et al*., 2011). The serum uric acid level remains unchanged from the 16th week to the end of the 2nd trimester and rises abruptly from the 3rd trimester to term where a level of 4 to 6 mg/dl is expected to be attained. (Roberts *et al*., 2005; Bainbridge and Roberts, 2008; Johnson *et al*., 2011).

A rapid elevation of uric acid during pregnancy can occur from the 1st trimester and such event is a precursor and predictor of the commencement of gestational hypertension and pre-eclampsia. In fact, the severity of pre-eclampsia is a direct function of the serum level of uric acid (Roberts *et al*., 2005; Johnson *et al*., 2011; Manjareeka and Nanda, 2013; Yalamati *et al*., 2015; Zangana and Hamadamen, 2018; Rizal *et al*., 2019). Reverting serum uric acid to normal levels lowers elevated blood pressure to a normal state (Park *et al*., 2009) but a similar study bizarrely proposed that increasing salt intake reduces serum uric acid concentration (Wang *et al*., 2018).
The surge in uric acid levels in pregnancy is believed to be due to sudden high breakdown of maternal, fetal and

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placental tissues, which may become worse by the additional action of high levels of xanthine oxidase (an enzyme that is involved in the production of uric acid) and the free radical superoxide (O_2^-) (Roberts *et al*., 2005; Johnson *et al*., 2011; Manjareeka and Nanda, 2013; Yalamati *et al*., 2015). However, the basic factor that triggers abrupt upsurge in xanthine oxidase and superoxide is currently not clear. The resulting high values of uric acid destroys the placenta the same way it destroys endothelial tissues of blood vessels. Hyperuricemia subsequently impairs the excretory function of kidneys by increasing their re-absorptive capacity which further elevates the already high concentration of serum uric acid in a vicious cycle (Roberts *et al*., 2005).

A sudden elevation of serum uric acid is an accurate indicator of fetal distress, which is widely implicated in the occurrence of fetal growth restriction and pre-term birth (Odendaal and Pienaar, 1997; Johnson *et al*., 2011). Afterbirth, the ensuing neonatal hyperuricemia incites the development of intraventricular haemorrhage, periventricular leukomalacia and respiratory distress syndrome. Thus, monitoring serum level of uric acid is a higher parameter for predicting fetal distress than hypertension in pregnancy (Odendaal and Pienaar, 1997; Johnson *et al*., 2011; Amini *et al*., 2014). Ultrasonography is known to be non-invasive to the developing fetus, affordable and reproducible as it finds wide application especially in monitoring pregnancy. The present study therefore, seek to evaluate the adverse effects of serum uric acid elevation on fetus and to determine the existence of a connection between hyperuricemia and gestational hypertension or pre-eclampsia. In addition, to estimate serum uric acid concentration in normotensive, gestational hypertensive and pre-eclamptic pregnant women including mean concentration of the different phases of normal pregnancy.

MATERIALS AND METHOD

A 12-month prospective cross-sectional case-control study was carried out to recruit subjects from the antenatal clinic (ANC) of the Department of Obstetrics and Gynecology. The ultrasound scans were done in the Department of Radiology while the blood samples were analyzed for uric acid concentration in the Department of Chemical Pathology, all in the University of Calabar Teaching Hospital (UCTH) from January 2016 to December 2016. Approval for the research was obtained from the Health Research Ethics Committee of the UCTH and informed consent given by the pregnant women. Consenting women were administered questionnaires. The voluntary participants were grouped into two with their gestational age matched. Group one consist of 100 cases (pregnancy induced/gestational hypertensives were 61 and pre-eclamptics 39) while group two, 100 normotensive pregnant women served as the control. The study involved pregnant women below 40 years of age with singleton gestation between 20 and 40 weeks. The maternal age for the hypertensive group ranged from 15 to 39 years with a mean of 30.87 ± 5.02 years while the maternal age for the control group ranged from 19 to 39 years with a mean of 29.86 ± 4.32 years. A 3.5 to 5MHz curvilinear transducer of an AlokaprosoundSSD-3500SX2-Dimensional machine which has Doppler facility (manufactured in 2008 by Aloka Company limited located in Meebusch, Germany) was utilized for the study. Pregnant women on steroids, anti-convulsant and anti-neoplastic drugs, congenital fetal anomaly, Use of illicit drugs (cocaine, heroin, amphetamine), cigarette smoking, alcohol consumption, sickle cell disease and other haematological conditions, pregnancy induced diabetes mellitus, placental anomalies (abruptioplacenta, chorioangioma, velamentous umbilical cord insertion), partial molar pregnancy, leiomyomauteri, pregnant women with tuberculosis, HIV, hepatitis, thyroid disease, hydrops fetalis, pregnancy attained through assisted reproductive technology, gout, renal disease, bleeding disorder, liver disease, cardiovascular diseases were excluded from the study.

Data collection and analysis

In the ANC, all the participants were assessed clinically by obtaining their medical history including vital signs (blood pressure, pulse rate and temperature). Clinically diagnosed cases of pregnancy induced hypertension (PIH) had a second blood pressure measurement obtained two hours apart in the Department of Radiology to eliminate errors. The controls also had two blood pressure assessment done. The height and weight were obtained from each subject to calculate the Body Mass Index (BMI) using the formula weight/height^2 (kg/m^2). Mid-stream urine samples were collected in a sterile universal bottle at the ANC from all the subjects and the presence or absence of protein was determined using the dip-stick method. The maternal serum uric acid concentration was measured using standard laboratory (Uricase) method. The blood samples (5 mls) were obtained, under aseptic precautions, from the ante-cubital vein into a plain sample bottle. These were sent to the chemical pathology laboratory of the hospital (UCTH) where the samples were left to clot for five minutes and then centrifuged at 5000 rpm to obtain the serum. The serum uric acid concentration was determined using manual colorimetric method with randox reagent. The blood samples were frozen (-50 ^{0}C) and after every two months, analysis was done on the batches of samples obtained.

In the ultrasound suite, subjects were made to lie supine on a comfortable couch. Following the application of a generous amount of ultrasound gel on the subject's abdomen, a suitable curvilinear transducer was used to spread the gel. Necessary maneuverings were done in the transverse plane, longitudinal plane and the coronal plane to maximally visualize and assess the developing fetus and its environment. At the end of every ultrasonography examination, the fetal anthropometric parameters [Bi-parietal Diameter (BPD), Head Circumference (HC), Abdominal Circumference (AC), Femur Length (FL), Estimated Gestational Age (EGA), Estimated Fetal Weight (EFW) and Head Circumference to Abdominal Circumference ratio (HC/AC ratio)] were recorded. The ultrasound procedures were all done in the presence of a chaperon. The statistical package for social sciences (SPSS Inc, USA) version 20.0 was used for the data analysis. Pearson correlation was employed with the level of significance taken at $p < 0.05$.

RESULTS

The participants who were hypertensives and control in the diverse age groups were as follows; 3 hypertensives and 1 control in the 15 to 19 years age group, 7 hypertensives and 10 control in the 20 to 24 years age group, 30 hypertensives and 37 control in the 25 to 29 years age group, 37 hypertensives and 36 control in the 30 to 34 years age group and 23 hypertensives and 16 controls in the 35 to 39 years age group. The mean serum uric acid was higher in the last two quarters of the 2nd half of pregnancy (table 1). Since there were no subjects with a 28 weeks gestational age pregnancy in the study, the 2nd quarter consist of data obtained from women with 25 to 30 weeks gestation. In the 20th to 24th week bracket, there were 14 normotensives, 9 gestational hypertensives and 7 pre-eclamptics. The 25thto30th week had 14 normotensives, 10 gestational hypertensives and 6 pre-eclamptics, 31stto35th week recorded 29 normotensives, 15 gestational hypertensives and 14 pre-eclamptics while 36th to 40th week had 43 normotensives, 27 gestational hypertensives and 12 pre-eclamptics (table 1).

Table 1: Mean value of serum uric acid at different gestational stages in normotensives, gestational hypertensives and the pre-eclamptics

	Normotensives		Gestational Hypertensives		Pre-Eclamptics	
EGA (weeks)	Mean (mg/dl)	min-max (mg/dl)	mean (mg/dl)	min-max (mg/dl)	mean (mg/dl)	min-max (mg/dl)
20-24	5.915±1.432	3.9-8.8	5.933±2.133	2.7-9.7	7.050±3.050	3.9-11.3
25-30	4.450±1.613	2.4-7.7	6.230±1.333	4.4-7.8	9.360±2.090	7.3-11.7
31-35	5.362±1.758	2.3-10.2	6.033±1.754	3.5-9.1	9.700±2.975	5.9-17.9
36-40	6.012±1.739	3.0-9.5	7.970±1.964	4.2-15.2	8.000±2.202	4.9-11.0

EGA: Estimated gestational age.

The difference in uric acid concentration noted in the three groups highlights the possible effects that are likely to be present in each group (table 2).

Table 2: Mean values of uric acid and BMI obtained in the groups

	Normotensive	Hypertensive			Gestational Hypertensive	Pre-eclamptic		
	Mean value	Mean value	t-test	p value	Mean value	Mean value	t-test	p value
Serum Uric acid (mg/dl)	5.437±1.636	7.535±2.165	+5.961	0.000*	6.542±1.746	8.528±2.679	-2.455	0.016*
BMI (kg/m^2)	29.15±4.21	34.03±6.55	+6.262	0.000*				

BMI: Body mass index.

The correlation of maternal serum uric acid and the maternal and fetal variables was demonstrated (table 3). An inverse relationship between maternal serum uric acid levels and fetal heart rate was conspicuous but a positive relationship was demonstrated between maternal serum uric acid and EGA and EFW. There were two cases of intrauterine fetal death (absent fetal heart beat) noted in the present study. The first case was the fetus of a 35-year-old with a pregnancy of 25 weeks + gestation having a blood pressure of 170/110mmHg, 2+ proteinuria and her serum uric acid concentration was 11.5 mg/dl. The second was that of a fetus of a 26 years old primigravida at 21 weeks gestation having a blood pressure of 150/100mmHg, 3+ proteinuria and a serum uric acid concentration of 6.9mg/dl.

Table 3: Correlation of serum uric acid with materno-fetal variables in pregnancy induced hypertensive group

	Uric acid (mg/dl)	
	Correlation coefficient (r)	p value
EGA (weeks)	+0.205	0.040*
FHR (Beats per minute)	-0.226	0.025*
EFW (kg)	+0.200	0.046*
Systolic Blood pressure (mmHg)	+0.043	0.673
Diastolic Blood pressure (mmHg)	+0.195	0.052
Proteinuria	+0.258	0.009*
Age (years)	+0.074	0.465

Correlation is significant at p <0.05. EFW: Estimated fetal weight, EGA: Estimated gestational age, FHR: Fetal heart rate.

The correlation between maternal serum uric acid level and the degree of proteinuria revealed a marked increase in uric acid in subjects with proteinuria 3+ (table 4).

Table 4: Variation of serum uric acid concentration with the degree of proteinuria

pre-eclampsia	N	serum uric acid concentration (mg/dl)	min-max (mg/dl)
+1 proteinuria	20	8.120±1.483	5.7-10.8
+2 proteinuria	9	8.211±2.740	4.9-11.5
+3 proteinuria	10	10.570±3.055	6.9-17.9

DISCUSSION

Serum uric acid levels in pregnancy as discovered in the PIH group of the present study, was found to have a positive correlation with EGA (p = 0.040). The concentration of serum uric acid increased especially during the 4th quarter of pregnancy. In the presence of maternal hyperuricemia, the weight of the fetus reduces but our study did not reveal this pattern. This could possibly be due to the effect of a high maternal BMI (Efanga and Akintomide, 2020). Rather a significant positive relationship between maternal serum uric acid and EFW (p = 0.046) showed that the fetal weight appreciates as serum uric acid increases. Results of the present study corroborates Odendaal *et al*. (1997) who noticed that fetal birth weight was slightly higher in mothers with high serum uric acid level. However, Ryu *et al*. (2018) observed a rise in serum uric acid of 6.35 mg/dl will results to a reduction in fetal weight including Saldanha *et al*. (2019) who equally observed a significant correlation between the occurrence of low fetal weight and serum uric acid level above 5mg/dl.

In pregnancies that experience elevated serum uric acid, there is perpetual concern for the well-being of the fetus. In this study, a negative correlation between serum uric acid and FHR (p = 0.025). Maternal serum uric acid passes freely across the placenta into the fetal circulation to exert its anti-angiogenetic propensity and endothelial dysfunction on the cardiovascular system. The pathway through which this cardiovascular injury occurs in hyperuricemia include the down-regulation of micro-Ribonucliec acid-92a (miR-92a), increase in Kruppel-like factor 2 (KLF2) expression and finally the inhibition of vascular endothelial growth factor – A (VEGFA) (Feig *et al*., 2008; Yu *et al*., 2015). We speculated that the resultant fetal hyperuricemia may be responsible for or contributed to fetal bradycardia. With persisting progressive bradycardia, fetal demise is expected at a heart rate of ≤ 55 bpm (Tozzi *et al*., 2003). Hyperuricemia is also assumed to be a cause of fetal hypoxia and a reliable marker for the condition (Vyakaranam *et al*., 2015). In our study, there were two cases of intra-uterine fetal demise (IUFD) and these deaths occurred within the 1st quarter of the 2nd half of pregnancy (20 to 25 weeks of gestational age). The deaths recorded in the index research may be a result of the devastating effects of persisting progressive bradycardia and fetal hypoxia in a 2nd trimester fetus.

It is essential to mention that blood pressure at the onset of gestation had little value in predicting progression to pre-eclampsia (Wu *et al*., 2012). The present study demonstrated a positive correlation between serum uric acid and proteinuria (p = 0.009) which agrees with the findings of Ryu *et al*. (2019) and Enaruna *et al*. (2012), inferring that serum uric acid, apart from being a major element in the sequence of events stimulating pre-eclampsia, also increases in concentration as the degree of proteinuria rises (Roberts *et al*., 2005; Johnson *et al*., 2011; Manjareeka and Nanda, 2013; Zangana and Hamadamen, 2018).

This study demonstrated a reduction in serum uric acid level in normotensive pregnant subjects after the 24th week of gestation which gradually rose from the 31st week till term. However, Prakash *et al*. (2012) observed a different trend in which the fall in uric acid concentration occurred earlier between the 14th to the 26th week of gestation before it increases from the 3rd trimester onwards. In the present index study, the uricosuric effect of estrogen along with an increase in maternal blood volume and GFR were pronounced in normotensives between the 25th to 30th weeks of gestation (early stage of the 3rd trimester) probably

accounting for the drop in serum uric acid during this period.

The serum uric acid level in the pregnancies between the 20th to 24thweek was almost equal in value between the normotensives and gestational hypertensives but from the 25th to 30th week, there was an increase of about 1.5 times in uric acid concentration of gestational hypertensives compared to the normotensives. This finding supports Asgarnia *et al.* (2017). The serum uric acid incremental potency of elevated blood pressure in pregnancy may be meagre in the first and second trimesters of pregnancy but is remarkable in the 3rd trimester as demonstrated in this research.

There was a significant difference between the mean serum uric acid concentration in normotensives (5.437±1.636 mg/dl) and PIH (7.535±2.165 mg/dl). Study by Enaruna *et al*. (2014) established mean value of serum uric acid to be 4.30±0.85 mg/dl for normotensives and 5.96±2.94 mg/dl for the PIH which represents about 28% increase (p = 0.005). Saldanha *et al*. (2018) mean value of serum uric acid was 2.66±0.39mg/dl for normotensives, 5.00±0.174mg/dl for PIH and 3.69±0.95mg/dl for gestational hypertensives at p = 0.001 in the three groups.The present study recorded mean serum uric acid concentration in PIHto be 38.6% higher in normotensive pregnant women while Enaruna *et al*. (2014) recorded serum uric acid level in PIH to be 28% higher in normotensives.

The difference in the mean serum uric acid concentration between gestational hypertensives, 6.542±1.746 mg/dl and pre-eclamptics, 8.528±2.679 mg/dl was significant (p =0.016) in the index study. This result is in line with Wu *et al*. (2012) who observed 4.50±1.01 mg/dl for gestational hypertensives and 5.06±0.78 mg/dl for pre-eclamptics at p = 0.001). High serum uric acid is a reflector of ensuing deleterious effects in the maternal and fetal organs, and it gets to higher concentrations in pre-eclamptics where more damages occur than in gestational hypertensives. A sudden rise in serum uric acid can be regarded as a possible risk marker for the progression to pre-eclampsia from gestational hypertension and the increased occurrence of adverse fetal conditions Wu *et al*. (2012).

The mean serum uric acid concentration in normotensive pregnant subjects in the present study was higher. This may be due to the relatively high BMI of our study participants. However, a lower mean serum uric acid concentration (4.50±1.10 mg/dl) exclusively on normotensive pregnant women was obtained by Amini *et al*. (2014).

A high BMI was recorded in both normotensives (29.15±4.21 kg/m^2) and the PIH (34.03±6.55 kg/m^2) groups which were categorized as overweight and obese respectively. This support Pleskascova *et al*. (2018) that established a positive relationship between serum uric acid level and maternal weight in a Czech Republic based research including Park *et al*. (2009) who observed a positive relationship between serum uric acid and maternal weight.

In the present research, the mean serum uric acid concentration for subjects with mild, moderate and severe pre-eclampsia were 8.120±1.483 mg/dl, 8.211±2.740 mg/dl and 10.570±3.055 mg/dl respectively. This demonstrates a gradual rise in the concentration of serum uric acid with increased proteinuria in the subjects. Prakash *et al*. (2012) found the same trend of serum uric acid concentration to be 6.70±0.603 mg/dl, 7.05±0.402 mg/dl and 7.30±0.810 mg/dl for mild, moderate and severe pre-eclamptics respectively, re-echoing the proportional ascent of serum uric in tandem with the degree of proteinuria, or vice versa as noted in our present study.

Since fetal heart rate fluctuates widely, the reliability of the mean FHR obtained as a direct effect of rising uric acid should be questioned. Studies which assess FHR in pregnant women with hyperuricemia is therefore, recommended. The place of maternal weight in the determination of serum uric acid in normotensive pregnant women appeared not to have been explored. It is recommended that a research be undertaken in assessing serum uric acid in PIH and normotensive pregnant women who are both gestational age and BMI matched.

CONCLUSION

Maternal hyperuricemia predisposes to fetal bradycardia which may have possibly led to the two fetal demise noted in the present study. Increase in EFW noticed with hyperuricemia may be due to higher BMI of the subjects. Therefore, elevated serum uric acid concentration has a significant role in foretelling the appearance of pre-eclampsia but not gestational hypertension.

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CONFLICTS OF INTEREST: Nil

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