International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Ngeri B et al. Int J Reprod Contracept Obstet Gynecol. 2022 Jul;11(7):1861-1871
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20221660

Original Research Article

Serum uric acid as a prognostic marker for preeclampsia at a tertiary hospital in Port Harcourt, Nigeria

Bapakaye Ngeri[1], Peter A. Awoyesuku[1]*, Chinweowa Ohaka[1], Awopola I. Jumbo[1], Omieibi B. Altraide[1], Simeon C. Amadi[1], Ebenezer Ikhobo[2]

[1]Department of Obstetrics and Gynaecology, Rivers State University Teaching Hospital, 6-8 Harley Street, Old G.R.A, Port-Harcourt, Rivers State, Nigeria
[2]Niger Delta University Teaching Hospital, Okolobiri, Bayelsa State, Nigeria

Received: 21 May 2022
Accepted: 09 June 2022

***Correspondence:**
Dr. Peter A Awoyesuku,
E-mail: pawoyesuku@yahoo.co.uk

ABSTRACT

Background: Preeclampsia is a recognized cause of maternal and perinatal morbidity and mortality. Some biomarkers such as uric acid are increased in the presence of the disease. This could serve as a marker of severity and provide a basis for making management decisions. This study sought to determine the association between elevated serum uric acid and adverse pregnancy outcomes in preeclampsia.
Methods: A prospective case-control study was carried out on consenting preeclamptic (95) and normotensive (95) pregnant women in their third trimester of pregnancy. Blood samples were taken for serum uric acid estimation at recruitment and delivery. Their Socio-demographic information was collected through a structured proforma. Data were analyzed using Statistical package for social sciences (SPSS) version 23. A $p<0.05$ was considered statistically significant.
Results: The mean serum uric acid level was higher in the preeclamptic than in the normotensive controls (400.0±105.27 versus 256.31±67.18; p=0.001). High serum uric acid levels were associated with a higher incidence of AKI (p=0.005), birth asphyxia (p=0.002), and low birth weight (p=0.006) compared to preeclamptics with normal uric acid levels. The sensitivity of high uric acid in predicting the outcomes was 78-81% while the specificity was 48%. Serum uric acid ≥334 µmol/l was the threshold for predicting adverse outcomes.
Conclusions: Women with preeclampsia had significantly higher serum uric acid levels. Hyperuricaemia in preeclampsia was associated with a high incidence of acute kidney injury, Birth asphyxia, and low birth weight. Serum uric acid ≥334 µmol/l was the threshold for the prediction of adverse outcomes.

Keywords: Preeclampsia, Serum uric acid, Prognostic marker, Adverse pregnancy outcome

INTRODUCTION

Hypertensive disorders are common in pregnancy, complicating 6-12% of all pregnancies.[1] Preeclampsia, is a form of hypertensive disorder in pregnancy with a reported incidence of 3-7%.[1,2] The prevalence in Nigeria is 1.2-6%.[3,4] Preeclampsia is of particular interest as it is associated with high fetomaternal morbidity and mortality. It is estimated that over 63,000 women and 500,000 babies worldwide die annually from preeclampsia.[1,5] Ninety-eight percent (98%) of these maternal deaths occur in developing countries like Nigeria.[1] This high mortality is attributed to poor access to antenatal care and less optimal intrapartum care.[6] In the developed countries, preeclampsia accounts for 0-1.8% of maternal mortality while in developing nations it is as high as 15%.[7] It is the leading cause of maternal mortality in Nigeria, responsible for 28.2% of maternal deaths.[8]

Preeclampsia is a pregnancy-related "multisystemic disorder characterized by new-onset hypertension of at least 140/90 mmHg with either significant proteinuria or signs of end-organ dysfunction occurring after 20th week of gestation in a previously normotensive and non-proteinuric woman".[9] It can lead to cerebral haemorrhage, pulmonary oedema, retinal blindness, hepatic dysfunction, acute kidney injury (AKI), operative deliveries, and maternal death. Also, there is an increased risk of intrauterine growth restriction, prematurity, birth asphyxia, and perinatal death. In the long term, there is an increased risk of postpartum depression, chronic hypertension, cardiovascular disease, myocardial infarction, venous thromboembolism, and type 2 diabetes mellitus in the woman and the child may have low cognitive ability, type 2 diabetes mellitus, coronary heart disease, and mental health disease.[10-12]

Preeclampsia can be classified based on the clinical parameters as mild or severe; mild preeclampsia is systolic blood pressure 140-159 mmHg and/or diastolic blood pressure of 90-109 mmHg on two occasions at least 4 (four) hours apart. And proteinuria of at least 300 mg/24hours urine or ≥1+ on dipstick urine testing. Severe preeclampsia is blood pressure ≥160/110 mmHg or proteinuria of ≥5 g/24 hours urine or at least 3+ on dipstick testing.9 It is also severe irrespective of the degree of hypertension in the presence of systemic features such as new-onset cerebral or visual disturbances, pulmonary oedema, thrombocytopaenia, progressive renal or liver dysfunction, and intrauterine growth restriction.[13] It can also be classified based on the gestational age of onset into early-onset preeclampsia (PE) which occurs before 34 weeks and late-onset preeclampsia occurring at or after 34weeks gestational age.[14] The early-onset Preeclampsia which is usually associated with high maternal and perinatal morbidity/mortality is considered the severe form while the late-onset preeclampsia is the mild form as it is accompanied by fewer complications.[14,15]

The pathogenesis of preeclampsia remains uncertain as no common etiological factor is found in all preeclamptic women; hence several theories have been proposed.[16] Central to these theories are maternal vascular endothelial dysfunction and defective placentation. In the abnormal placentation theory, there is a default in uterine spiral artery remodelling.[16] The process that converts the spiral arteries into a large capacitance and low resistance vessel to improve supply to the placenta and the foetus.[17] The resulting vasoconstriction, hypoxic ischemia, and release of metabolites into the system cause endothelial dysfunction, hypertension, and end-organ damage.[16] Vasoconstriction in the glomeruli and capillary damage leads to reduced glomerular filtration rate, and increase reabsorption of uric acid in the proximal tubules with consequent hyperuricaemia. Furthermore, the ischemic trophoblastic tissues that are shed increases substrate for conversion to purine thus enhancing the production of uric acid in preeclampsia.[17] So in preeclampsia, increased ischemia, trophoblastic tissue shedding, endothelial dysfunction, and altered glomerular filtration contribute to hyperuricaemia. Recently studies have implicated uric acid in the pathogenesis of Preeclampsia resulting in a vicious cycle of the disease.[18,19] Other implicated theories are prostaglandin imbalance, immunologic, genetic, and environmental theories. These pathways are interwoven and believed to be triggered by placenta tissues.[20]

Given the high maternal and perinatal morbidity and mortality, there is a need for early detection of Preeclampsia, which has prompted the development of clinical risk markers. These risk markers comprise maternal demographics, past medical history, obstetric history, and screening for blood pressure and proteinuria in the index pregnancy.[21] Among women considered to be high risk based on maternal demographics, approximately 25% will develop preeclampsia compared to 5% in the general population.[22] Risk factors when used independently may not be effective for a screening test, but they can help in the identification of a high-risk population in which another predictive test may perform better.[23] Based on blood pressure, proteinuria, and symptoms, >20% of women will not meet up the criteria for preeclampsia before the onset of complications.[1] Thus use of these features as independent factors to predict adverse pregnancy outcomes and the basis for the management decision should be done with caution.[24]

With the seemingly low specificity and sensitivity of clinical parameters for the prediction of preeclampsia, laboratory parameters have also been investigated, as aids to the clinical parameters.[21] These include biophysical markers and biochemical markers. An ideal biochemical marker is an element that plays a central role in the pathogenesis, it is present early on or before the clinical manifestation, is easy and inexpensive to test for, with high sensitivity and specificity for the disease, correlates with the severity of the disease and is undetectable or present at a low level in the normal pregnancy.[25]

No single marker has perfectly met the criteria for the prediction of pregnancy outcome.[26] Research has been done on several biomarkers such as tyrosine kinase, vascular endothelial growth factors, placental protein-13, pregnancy-associated plasma protein-A, lactate dehydrogenase, albumin, liver enzymes, platelet, C-reactive proteins, and uric acid.[27,28] In early pregnancy, uric acid concentration falls by 25-35% due to the uricosuric effect of oestrogen, haemodilution, and increased glomerular filtration rate. At term, it slowly rises to levels observed in non-pregnant women.[29-31]

Uric acid can be measured in serum, plasma, urine, and exhaled breath condensate via, the phosphotungstic acid (colourimetry) method, liquid chromatography, uricase-based dry chemistry systems, and biosensor method.[32] Hyperuricaemia is defined as a plasma uric acid level greater than the 90th percentile of values in a normal

pregnant population, generally cited as uric acid level >6.0 mg/dl in women.[21] Hyperuricaemia is the earliest indication of a change in renal function and predates the onset of heavy proteinuria and severe hypertension.[19,21,30] Uric acid assay compared with other biomarkers of preeclampsia such as the angiogenic factors is much cheaper, widely available, with good sensitivity and specificity. It is particularly sensitive to disease progression and the risk of adverse outcome.[33]

Serum uric acid (SUA) has been found to increase in preeclampsia but the correlation with adverse maternal and perinatal outcomes is debated. This study sought to investigate if the change in SUA levels between diagnosis and delivery predicts adverse foetomaternal outcomes. This will possibly enable the development of a protocol for the management of preeclampsia based on serum uric acid value.

Objective

The objective was to determine the association between elevated serum uric acid and adverse pregnancy outcomes in preeclampsia.

Specific objectives

The specific objectives were to compare mean SUA concentration in preeclamptic and normotensive pregnant women at recruitment. To determine the association between SUA level and fetomaternal adverse outcomes in preeclampsia. To assess if the change in SUA value is associated with fetomaternal adverse outcomes. To determine the SUA threshold value for fetomaternal adverse outcomes in preeclampsia women.

METHODS

Study area

This study was conducted in the Rivers State University Teaching Hospital (RSUTH), Port Harcourt, Rivers State, Nigeria. The RSUTH serves as a referral hospital for the primary and secondary health facilities in the state and other neighbouring states in the South-South and South-East Regions of Nigeria. The hospital has several departments including the Department of Obstetrics and Gynaecology where the study was conducted. The department has antenatal, post-natal, gynaecological, and labour wards with a total of 80 beds. It also operates antenatal, postnatal, and gynaecological out-patient clinics. Emergency obstetrics and gynaecological services are offered round the clock. The department has 5 teams with at least two consultants in each team. There is an average annual delivery of over 2000. Ethical approval was obtained from the Research and Ethics Committee of the State before commencement of the study.

Study design and period

This was a prospective case-control study. The study period was from August 2020 to July 2021.

Study population

The study participants were 190 women; 95 preeclamptic and 95 normotensive women in the third trimester (28-36 weeks GA).

Inclusion criteria

All consenting booked preeclamptic and normotensive pregnant women in the third trimester (28-36 weeks).

Exclusion criteria

Women who did not consent. Pregnant women with medical conditions that can affect serum uric acid levels such as chronic hypertension (diagnosis from a history of pre-existing hypertension or hypertension diagnosed before 20 weeks), renal disease (diagnosed from history and serum creatinine estimate at recruitment >90 µmol/l). Pregnant women with obstetric or medical conditions that are likely to be associated with adverse perinatal outcomes such as multiple gestations (diagnosed sonographically in the index pregnancy), diabetes mellitus/gestational diabetes in index pregnancy (as diagnosed from the routine antenatal screening). Preeclamptic patients delivered less than 24 hours from diagnosis.

Sample size determination

The sample size formulae for comparing two groups was used[34]

$$n = (Za + Z\beta)2(S1^2 + S2^2) \div (\mu 1 - \mu 2)^2$$

n = minimum sample size; Zα= significant level of 95% corresponds to a value of 1.96; Zβ= power of the study, set at 90%: corresponds to a value of 0.84; S1= standard deviation of uric acids levels in pregnancy-induced hypertension35 =1.51; S2= standard deviation of uric acid levels in normal pregnancy[35] =0.69; µ1-µ2 = minimum mean difference to be detected between the two groups (the effect size) =0.5

$$n = (1.96 + 0.84)^2(1.51^2 + 0.69^2)0.5^2$$

=(7.84)(2.280+0.476)÷0.25

=(7.84)(2.756)÷0.25=21.607÷0.25=86.4

Adjust for non-response: assuming 10% non-response

n= 86.4 + 8.64 = 95.04=95

Hence 95 subjects per group were recruited into each group.

Data collection instrument

Women were recruited into the study having fulfilled selection criteria and given consent. Data was retrieved by the research team from the participants using the structured proforma. Information collected included maternal age, parity, gestational age, maternal and perinatal adverse outcomes, such as acute kidney injury, Primary post-partum haemorrhage, first minute APGAR score, birth weight, etc.

Study procedure

The nurses identified booked women at 28-36 weeks gestational age with new onset elevated blood pressure and proteinuria in the antenatal clinic or Labour ward and present them to the research team members. The doctor in turn re-assessed patient for eligibility and provided information to obtain informed written consent. Those who consented were interviewed to fill the proforma. For every preeclamptic enrolled, an eligible, and consenting normotensive woman was recruited to form the control group.

The enrolled women at recruitment, had blood sample collected into a labelled bottle, and sent to the laboratory for serum uric acid and creatinine analysis. The preeclamptics were followed up to delivery for repeat sample collection and assessment for foetomaternal outcome. The blood sample taken from the preeclamptics women at recruitment and delivery were analysed for serum uric acid and creatinine difference. The creatinine difference was used to assess for the occurrence of AKI defined by >1.5 fold in baseline creatinine. The SUA difference at recruitment and delivery was used to estimate the change in the changing value of SUA, this was then divided by the diagnosis-delivery interval to extrapolate the daily change in SUA.

Additionally, maternal peripartum events and perinatal outcomes such as primary post-partum haemorrhage, birth weight percentile, and first-minute Apgar score of the preeclamptic women were recorded. Each filled data collection form was stored in a secured electronic locker and the principal researcher collated and analyzed the data at the end of the research.

The blood pressure was measured manually using the mercury sphygmomanometer by Accoson. Two cuff sizes were made available: the normal adult cuff (22-32 cm) and the large adult cuff (32-42 cm). The participant sat down and relaxed for five minutes, and the appropriate cuff was applied to the arm with the lower border of the cuff 2-4 cm above the elbow. The cuffed arm was supported at the heart level. Auscultatory readings were done with a Littmann stethoscope and Korotkoff sounds one and four, were used to assess systolic and diastolic blood pressure respectively, as the inflated cuff was deflated at the rate of 2 mmHg/beat. Hypertension was diagnosed based on systolic blood pressure of at least 140 mmHg and or diastolic blood pressure of at least 90 mmHg taken on two occasions at least 4 hours apart.

Urine analysis for protein was done using Medi-test Combi 2 in random midstream clean-catch urine specimen of the participants. The proteinuria estimation was by visual reading of the dipstick given its sensitivity, availability, and low cost. It was graded on a scale of 0-3+ (0 means no protein, 1+ implies 30 mg/dl, 2+ implies 100 mg/dl and 3+ implies 500 mg/dl). Diagnosis of significant proteinuria was made based on ≥2+ of protein on dipstick. Proteinuria was assessed at the point of recruitment (for preeclampsia and normotensive women) and at delivery.

Specimen collection

Aseptic precautions were observed; 4 mls of venous blood was collected from each participant with a syringe into a properly labelled heparinized lithium specimen bottle. The blood sample was collected from the participant at enrolment from preeclamptic women (before the commencement of treatment) and normotensive women, and then at delivery.

Laboratory procedure

The samples were transferred to the chemical pathology laboratory and analyzed for uric acid by the colourimetry method. The normal serum uric acid in the third trimester is 4-6 mg/dl (237.9 – 356.9 µmol/l).[31,37] The blood samples were centrifuged at 3000 rpm for 30 minutes to separate the serum. The serum was decanted into a clean plain bottle and stored at room temperature. The uric acid reagent was reconstituted by adding 15 mls of buffer into one vial making it the working solution. Four plain test tubes were arranged in the rack and labelled as, sample, standard, quality control, and blank. Next 20 µl of the sample was added to the sample test tube, 20 µl of standard solution to the standard test tube, 20 µl of quality control to the quality control test tube, and 20 µl of distilled water into the blank test tube. Thereafter 1 ml of the working reagent was added to each of the tubes and mixed. The mixed solution was incubated at room temperature for 5 minutes after which each was read with the absorbance at 520 nm wavelength with the spectrophotometer. The reaction was calculated using the formula,

Uric acid concentration = sample÷standardx [standard]

Data analysis

The data collected were entered into an Excel spreadsheet and analyzed using IBM Statistical package for social sciences (SPSS)® software version 23. Categorical data such as the educational level, marital status, and parity were presented in tables as frequencies and percentages, while continuous data such as maternal age, gestational

age, and SUA were summarized with means and standard deviations. The Chi-square test was used to assess the difference in categorical variables when the expected count is greater or equal to five, while Fisher's exact test for the same purpose was used when the expected count was less than five. Statistically significant results were further analyzed with an Odds ratio to assess the degree of association. A student t-test was used to compare the means of continuous variables between two groups. The receiver operating characteristic (ROC) curve was used to determine the threshold for adverse fetomaternal outcomes. The confidence interval (CI) was set at 95% and the level of significance (ά), was set at 0.05. The probability value of the calculated test statistics (p value) <0.05 was assumed to be statistically significant. Also, a confidence interval not containing 0 within its range in a statistical test, or not containing 1 within its range in an odds ratio is considered statistically significant.

Definition of terms

Birth asphyxia is the inability of a newborn to initiate and sustain spontaneous respiration, diagnosed in this study as first minute APGAR score <7. Low birth weight is the birth weight below the 5th percentile for the gestational age (using the WHO foetal growth chart for estimated foetal weight regardless of the sex). Acute kidney injury (AKI) is the abrupt loss of kidney function over hours to days resulting in the inability to maintain electrolyte, acid-base, and water balance; defined based on an elevation in serum creatinine level (a difference in serum creatinine level at diagnosis and delivery of at least 1.5-fold increase).[36] Primary postpartum haemorrhage (PPH) is defined as blood loss over 500 ml in vaginal delivery or 1000 ml in caesarean delivery within the first 24 hours postpartum. This was done using the gravimetric method of blood loss estimation. Hyperuricaemia is defined as plasma uric acid level greater than the 90th percentile of values in a normal pregnant population, cited as >6 mg/dl or >357 µmol/l. Normouricaemia is defined as serum uric acid ≤6 mg/dl or ≤357 µmol/l. Preeclamptic women are women in the second half of pregnancy with hypertension and significant proteinuria (≥2+ on dipstick urine). Normotensive women are pregnant women without hypertension and proteinuria at recruitment.

RESULTS

A total of 190 eligible participants gave consent and were recruited for the study. However, one signed against medical advice before delivery. The delivery blood samples of two preeclamptic women were misplaced at the laboratory.

Table 1 presents the socio-demographic characteristics of the participants. The majority of the respondents are within the age range 30-39 years in the preeclamptic group (49.47%) and the normotensive group (47.37%). The mean age was 29.51±6.22 years in the preeclamptic group and 30.61±5.46 in the normotensive group. There was no significant difference in both groups (p=0.195).

Table 1: Maternal socio-demographic characteristics of participants.

Variables	Maternal Status		χ2/t-test	P value
	Preeclamptic (n=95)	**Normotensive (n=95)**		
Age group (years)	**N (%)**	**N (%)**		
18-29	44 (46.32)	41 (43.16)		
30-39	47 (49.47)	45 (47.37)		0.355γ
40-49	4 (4.21)	9 (9.47)		
Mean (SD)	29.51 ± 6.22	30.61 ± 5.46	1.30t	0.195
Educational Level				
Primary	13 (13.68)	17 (17.89)		
Secondary	54 (56.84)	47 (49.47)	1.17	0.557
Tertiary	28 (29.47)	31 (32.63)		
Marital Status				
Married	89 (93.68)	87 (91.58)	0.077	0.781
Single	6 (6.32)	8 (8.42)		
Parity category				
0	30 (31.58)	30 (31.58)		0.515γ
1	25 (26.32)	17 (17.89)		
2-4	38 (40.0)	46 (48.42)		
5+	2 (2.11)	2 (2.11)		

*Statistically significant (p<0.05); χ2=Chi-Square; t=Student t-test, γ=Fisher's Exact.

The majority, 56.84% (54) of the preeclamptic group had a secondary level of education, while in the normotensive women it was 49.47%. Both groups were similar in their educational status (p=0.557). Most of the participants were married, 93.68% (89) in the preeclamptic group and 91.58% (87) in the normotensive group. There was no difference in the marital status of both groups (p=0.781). In the preeclamptic group, a majority (40.0%) were multiparous followed by nulliparous (31.58%) and in the normotensive group, 48.42% were multiparous and

31.58% were nulliparous, with no significant difference observed (p=0.515).

Table 2 observed a statistically significant association between preeclampsia and serum uric acid concentration at recruitment, as hyperuricaemic patients had a significant proportion in preeclampsia compared to normal patients (86.3% versus13.7%; p≤0.01). The hyperuricaemic patients were 16.73 times more likely to have preeclampsia compared to normal patients (OR=16.73; 95% CI: 7.66-36.55).

Table 2: Comparison of serum uric acid concentration at recruitment in preeclamptic and normotensive women at recruitment.

Variables	Maternal status		Total	χ2	OR (95% CI)	P value
SUA level	Preeclamptic, N (%)	Normotensive, N (%)				
High	63 (86.3)	10 (13.7)	73	62.49	16.73 (7.66-36.55)	<0.01*
Normal	32 (27.4)	85 (72.6)	117			
Mean	400.0±105.27	256.31±67.18		11.22t		0.001*

*Statistically significant (p<0.05); χ2=Chi-Square; t= student t test; OR=Odds Ratio.

Table 3: Association between serum uric acid level and severity of preeclampsia.

Serum uric acid	Grade of preeclampsia		Total	OR	95% CI	P value
	Severe, N (%)	Mild, N (%)				
High	53 (76.8)	10 (16.7)	63			
Normal	16 (23.2)	16(45.7)	32	5.300	2.01-13.95	<0.01*
Total	69 (100)	26(100)	95			

*Statistically significant (p<0.05); OR=Odds Ratio.

Table 4: Association between serum uric acid at recruitment and maternal adverse outcome in preeclamptic women.

Variables	Acute kidney injury (n=92)		χ2	OR (95% CI)	P value
SUA level	Yes, N (%)	No, N (%)			
High	42 (79.2)	20 (51.3)	7.99	3.63 (1.46-9.05)	0.005*
Normal	11(20.8)	19 (48.7)			
Total	53 (100)	39 (100)			
Mean	427.23±113.04	365.64±83.86	2.95t		0.004*
	Primary postpartum haemorrhage (n=94)		**χ2**	**OR (95% CI)**	
SUA level	**Yes, N (%)**	**No, N (%)**			
High	10 (66.7)	53 (67.1)	0.001	0.981 (0.30-3.17)	0.975
Normal	5 (33.3)	26 (32.9)			
Total	15 (100)	79 (100)			
Mean	385.71±125.61	405.97±102.35	0.66t		0.51

*Statistically significant (p<0.05); χ2=Chi-Square, t =student t-test OR=Odds Ratio.

Table 5: Association between serum uric acid and fetal adverse outcomes in preeclamptic women.

Variables	Apgar score (1st minute) (n=94)		χ2	OR (95% CI)	P value
SUA	**Asphyxia, N (%)**	**Normal, N (%)**			
High	40 (81.6)	23 (51.1)	9.89	4.25 (1.68-10.97)	0.002*
Normal	9 (18.4)	22 (48.9)			
Total	49 (100)	45 (100)			
Mean	420.04±117.54	380±87.60	1.85t		0.07
	Birth weight percentile (n=94)		**χ2**	**OR** (95% CI)	**P value**
SUA	**<5 (LBW), N (%)**	**≥5 (Normal), N (%)**			
High	43 (78.2)	20 (51.3)	7.47	3.40 (1.39-8.34)	0.006*
Normal	12 (21.8)	19 (48.7)			
Total	55 (100)	39 (100)			
Mean	411.64±101.19	385.87±110.69	1.17t		0.252

*Statistically significant (p<0.05); χ2=Chi-Square; t=student t test; OR=Odds Ratio.

Table 6: Accuracy of SUA in the prognosis of foetomaternal outcome in preeclampsia participants.

Pregnancy outcome	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
AKI	79.2	48.7	67.7	63.3	66.3
AS<7	81.6	48.9	63.4	71.0	66.0
<5 per Bwt	78.2	48.7	68.3	61.3	66.0

Table 7: Association between changing values of serum uric acid between diagnosis and delivery relates to adverse outcomes in preeclamptic women.

Pregnancy outcome	Uric acid change (n=92)	P value	OR	95%CI	
AKI yes	15.71±52.93	0.92	1.00	0.99	1.01
No	14.65±49.77				
PPH yes	14.02±77.71	0.92	1.00	0.99	1.01
No	15.48±45.77				
AS≥7	8.79±49.51	0.22	0.99	0.98	1.00
<7	22.32±52.93				
Bwt<5per	16.14±52.97	0.85	1.00	0.99	1.01
≥5per	14.02±49.61				

Table 8: Threshold of serum uric acid level predictive of foetomaternal adverse outcome.

Adverse outcome	Threshold SUA(µmol/l)	Sensitivity (%)	Specificity (%)	AUC	P value
Low AS	≥343	83	31	0.61	0.073
<5 perc Bwt (LBW)	≥350	82	49	0.61	0.066
AKI	≥343	79	27	0.52	0.071
All Adverse	≥334.	80	33	0.49	0.98

A statistically significant association was observed between preeclampsia and mean serum uric acid concentration at recruitment, as patients with a highly significant mean value of Serum Uric Acid had preeclampsia (400.0±105.27 versus 256.31±67.18; p=0.001).

Table 3 demonstrates the association between serum uric acid and severity of preeclampsia, 76.8% of hyperuricaemic preeclamptic women had severe preeclampsia compared to 23.2% of normouricaemic preeclamptic women. There was a significant association between hyperuricaemia and the severity of preeclampsia (p=0.01). The women with SUA >6 mg/dl were five times more likely to have severe preeclampsia than preeclamptic women with normal SUA (OR 5.30, CI 2.01-13.95).

Table 4 observed a statistically significant association between acute kidney injury and serum uric acid concentration at recruitment. Preeclamptic women that were hyperuricaemic had a higher proportion of AKI compared to those with normal values of serum uric acid (67.8% versus 39.4% p=0.008). Also, preeclamptic women that are hyperuricaemic were 3.24 times more likely to have AKI compared to preeclamptic women that had normal serum uric acid (OR=3.24; 95%CI: 1.34-7.86). No statistically significant association was observed between primary post-partum haemorrhage and serum uric acid concentration at recruitment (p=0.975). There was a statistically significant association between AKI and mean serum uric acid concentration at recruitment. Preeclamptic women with AKI had higher serum uric acid compared to preeclamptic women without AKI. (427.23±113.04 versus 365.64±83.86; p=0.004).

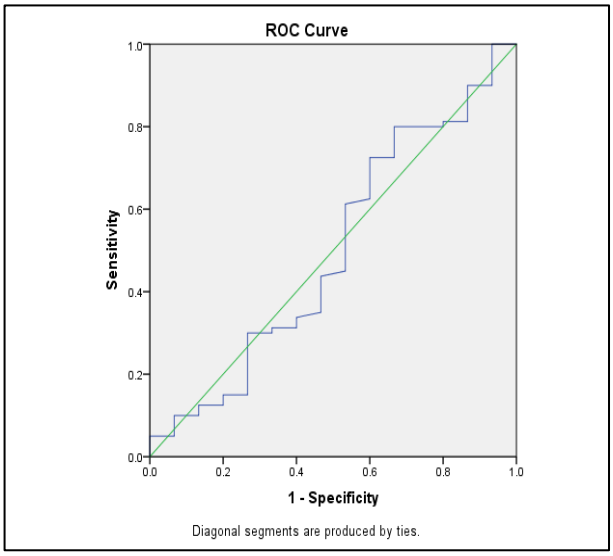

Figure 1: Threshold value of serum uric acid for all significant foetomaternal adverse outcomes.

In Table 5 there was a statistically significant association between APGAR score at 1 minute and serum uric acid concentration. Preeclamptic mothers with hyperuricaemia showed a higher significant proportion of having babies

with asphyxia compared to normouricaemic preeclamptic women (81.6% versus 18.4% p=0.002). The preeclamptic mothers with hyperuricaemia were 4.25 times more likely to have babies with asphyxia compared to preeclamptic mothers with normouricaemia (OR=4.25; 95% CI: 1.68-10.77). There was no significant association between mean serum uric acid and birth asphyxia (p=0.07). Similarly, preeclamptic mothers with hyperuricaemia had a higher proportion of having babies with low birth weight (78.2% versus 21.8%, p=0.006). The preeclamptic mothers with hyperuricaemia were 3.4 times more likely to have babies with low birth weight compared to preeclamptic mothers with normouricaemia (OR=3.40; 95% CI: 1.39-8.34).

Table 6 shows the sensitivity of serum uric acid was highest for predicting birth asphyxia (APGAR score <7 in the first minute) but specificity was poor. The accuracy of the serum uric acid for predicting adverse foetomaternal outcomes was about 66%.

In Table 7, no statistically significant association was observed between changing values of serum uric acid at diagnosis and delivery, as it relates to adverse outcomes in the preeclamptic women. For preeclamptic women with AKI, the change in mean uric acid was 15.71 µmol/l which was similar to those without AKI (P-value 0.92). Also, the risk of AKI for each unit change in uric acid was not increased (OR 1.00). Period change in SUA did not increase PPH (OR 0.92), 1st minute APGAR score <7 (OR 0.22), and <5 birth weight percentile (OR 0.85).

Threshold of serum uric acid level predictive of foetomaternal adverse outcome

The optimal serum uric acid value at diagnosis of preeclampsia which was predictive of birth asphyxia was 343 µmol/l. At this value, 83% of preeclamptic women can be correctly predicted to deliver babies with birth asphyxia (sensitivity 83%), and 31% of these women can be correctly predicted to have babies with normal Apgar score (specificity 31%). However, 69% of these women will be wrongly predicted to have asphyxiated babies (false positive rate of 69%) as shown in Table 8.

The optimal serum uric acid value at diagnosis of preeclampsia which was predictive of low birth weight was 350 µmol/l. At this value, 82% of preeclamptic women can be correctly predicted to deliver babies with low birth weight (sensitivity 82%), and 49% of these women can be correctly predicted to have babies with normal birth weight (specificity 49%). However, 51% of these women will be wrongly predicted to have low birth weight babies (false positive rate of 51%) as shown in Table 8.

The optimal serum uric acid value at diagnosis of preeclampsia which was predictive of acute kidney injury was 343 µmol/l. At this value, 79% of preeclamptic women can be correctly predicted to have acute kidney injury (sensitivity 79%), and 29% of these women can be correctly predicted to have normal kidney function (specificity 29%). However, 71% of these women will be wrongly predicted to have acute kidney injury (false positive rate of 71%) as shown in Table 8.

The optimal serum uric acid value at diagnosis of preeclampsia which was predictive of all significant foetomaternal adverse outcomes (birth asphyxia, LBW, and AKI) was 334 µmol/l. At this value, 80% of preeclamptic women can be correctly predicted to have either of these adverse outcomes (sensitivity 80%), and 33% of these women can be correctly predicted to have a normal outcome (specificity 33%). However, 67% of these women will be wrongly predicted to have adverse outcomes (false positive rate of 67%) as shown in Figure 1 and Table 8.

DISCUSSION

Preeclampsia is a pregnancy-specific condition, a major cause of maternal and perinatal morbidity and mortality. Serum uric acid is a useful and inexpensive biomarker associated with oxidative stress, thus might be useful in guiding the course of management of the condition. This study compared the serum uric acid level in preeclamptic and normotensive pregnant women in the third trimester (28-36 weeks). Both groups were similar in their socio-demographic characteristics. Preeclampsia is often known as a disease of primigravida, however, in this study multiparous women account for a higher proportion (40.0%) of preeclampsia. This variation could be due to increased maternal age in multiparous women as age is a risk factor for preeclampsia.

The mean SUA of the preeclampsia group was much higher than the normotensive group. This finding was consistent with the study by Sultana et al, Obagah et al and Ugwuanyi et al.[38-40] This elevated SUA in preeclamptic women supports the theory of hypoxia and ischemia of the placenta tissue that increases substrate for increased uric acid production by xanthine oxidase, coupled with a poor renal clearance of uric acid in preeclampsia.

The severity of preeclampsia is usually determined by elevated blood pressure and degree of proteinuria. This study showed a significant association between elevated SUA and the severity of preeclampsia. It was shown that preeclamptic women with hyperuricaemia were four times more likely to have severe preeclampsia than normouricaemic preeclamptic women. This agrees with the study by Ryu et al.[41] This study revealed that a significantly greater percentage of severe preeclamptic women had hyperuricaemia compared to mild preeclamptic women. It is comparable with findings by Ugwuanyi et al, Ryu et al and Zulfu et al, which showed that severe preeclamptic women are more likely to have abnormal serum uric acid.[40-42] This could be due to hyperuricaemia being a marker of decreased renal clearance following renal damage in severe preeclampsia. This leads to activation of the renin-angiotensin system

which causes further elevation of the blood pressure in hyperuricaemic women.

Considering the role of serum uric acid in the pathophysiology of preeclampsia, it may be an important predictor of the fetomaternal outcome. In this study, acute kidney injury (AKI) was three times higher in the hyperuricaemic preeclamptic women compared to the normouricaemic group (P value 0.005, OR-3.63) and, since booked preeclamptic women with renal disease were excluded, it is unlikely due to pre-existing renal pathology in the study participants. Hence uric acid is seen as the cause of the AKI. It could also be that AKI occurred due to an established mechanism in preeclampsia which leads to reduced uric acid excretion thereby causing hyperuricaemia. This possible chain reaction could further explain the devastating impact of preeclampsia on renal function. The finding of this study was similar to values expressed by Kondreddy et al which showed a higher occurrence of ARF in preeclampsia cases with hyperuricaemia.[43]

In this study, the association between hyperuricaemia in preeclamptic women and primary postpartum haemorrhage (PPH) was not statistically significant. This non-significance may probably be due to the absence of haemolytic complications such as severe thrombocytopaenia in this group, as well as the use of prophylactic oxytocics post-delivery to reduce the risk for PPH. This finding was similar to the finding of the study by Ahmed et al.[5]

This study also evaluated the association between SUA and perinatal outcomes in preeclamptic participants. About 81.6% of neonates of hyperuricaemic preeclamptic women had a first-minute APGAR score <7 compared to only 18.4% in the normouricaemic preeclamptic women (P value 0.014). Preeclampsia is associated with decreased placenta perfusion, thus the fetuses are chronically hypoxic. This finding is supported by results from Ugwuanyi et al.[40] But contrary to this, findings from Asgharma et al and Priya et al showed no statistically significant difference for birth asphyxia between the hyperuricaemia and normouricaemic groups.[44,45] This can probably be attributed to the five minutes APGAR score used for assessment of birth asphyxia in their study, after some resuscitation may have improved the APGAR score thus reducing the number of babies with a score <7 under the hyperuricaemic group.

The birth weight percentile for gestational age at delivery with SUA in preeclampsia was also found to be statistically significant. This study showed that more neonates of the hyperuricaemia preeclampsia group had low birth weight (LBW) compared to neonates in the normouricaemic group, P-value of 0.006 (OR 3.40). This may be attributed to reduced placenta function caused by hyperuricaemia toxicity in preeclampsia leading to reduced amino acid transport. This finding is supported by Enaruna et al and Zangana et al.[46,47]

High SUA had high sensitivity in predicting acute kidney injury, low birth weight, and birth asphyxia but had poor specificity. This could be due to hyperuricaemia from other contributors other than preeclampsia such as obesity, diet, etc. The accuracy is fair in predicting these pregnancy adverse outcomes.

The management of preeclampsia remote from term could be challenging as the effort to prevent prematurity may need to be balanced with the risk of complications associated with the progression of the disease. Acknowledging the fact that preeclampsia is a progressive disease despite blood pressure control. This study estimated the change in serum uric acid in the prediction of adverse pregnancy outcomes in preeclampsia. The result showed no significant association between changing values of serum uric acid and adverse outcomes in the preeclamptic pregnancy.

The threshold value of SUA for adverse pregnancy outcomes was at a cut-off ≥334 µmol/l in this study. This differs from the study by Ryu et al which showed a threshold value of 378 µmol/l.[41] This variation may be due to differences in gestational age, as uric acid rises with gestational age. In this study, preeclampsia SUA was analysed between 28-36 weeks while in the study by Ryu et al SUA was estimated at delivery.

Limitations of the study include the fact that the feeding habit, that could influence SUA, was not evaluated in the participants and blood sample collection and analysis for uric acid were not specific to a particular time of the day. Being a single institutional-based study, the findings cannot be generalized and a multi-center or community-based study will be needed to validate these findings.

CONCLUSION

Women with preeclampsia had significantly higher serum uric acid levels. Hyperuricaemia in preeclampsia was associated with a high incidence of acute kidney injury, Birth asphyxia, and low birth weight. Serum uric acid ≥334 µmol/L is a threshold for the prediction of adverse foetomaternal outcomes. While high serum uric acid is fairly accurate in predicting some adverse fetomaternal outcomes, however, the periodic change in serum uric acid was not associated with adverse foetomaternal outcomes. Serum uric acid should be done for women with severe preeclampsia to serve as a guide in counselling the woman on the possible outcome. Periodic serum uric acid level change was not predictive of the severity, and so cannot be used in the conservative management for preterm preeclampsia. There is a need to search for more appropriate biomarkers that will serve in conservative management. There is also a need for long-term follow-up of the preeclamptic women with persistent

hyperuricaemia, as well as their babies, to investigate the long-term effect of preeclampsia in this population.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the contributions of the interns and resident doctors who voluntarily assisted in collecting samples and data from the participants.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Ngeri B, Awoyesuku PA, Ohaka C, Jumbo AI, Altraide OB, Amadi SC et al. Serum uric acid as a prognostic marker for preeclampsia at a tertiary hospital in Port Harcourt, Nigeria. Int J Reprod Contracept Obstet Gynecol 2022;11:1861-71.