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■ Original Article

The Role of Serum Uric Acid in Predicting Adverse Pregnancy Outcome in Preeclampsia at Aminu Kano Teaching Hospital

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ABSTRACT

Background: Pre-eclampsia is a complex multi-systemic complication of pregnancy. Serum uric acid has been studied as one of the prognostic factors for adverse pregnancy outcomes in pre-eclampsia. The study evaluated adverse pregnancy outcomes associated with hyperuricemia in pre-eclampsia in Aminu Kano Teaching hospital (AKTH), Kano. ***Study design:*** This was a hospital based prospective cohort study. **Methodology:** One hundred consecutive pre-eclamptic patients admitted into labour ward during the study period were recruited. They were managed according to standard treatment protocol. Their socio-demographic and clinical variables such as age, parity, admitting blood pressure, proteinuria, estimated gestational age, and presence of symptoms, fetal birth weight, Apgar scores and admission into special care baby unit were recorded. Adverse perinatal outcomes of IUGR, IUFD and Birth Asphyxia as well as Maternal complications of Eclampsia, HELLP syndrome and acute renal failure were recorded. Levels of maternal serum uric acid, liver enzymes, platelets and Bilirubin were determined and recorded. **Results:** Seventy percent had severe preeclampsia. Majority (43%) of the cases were unbooked, with no formal (15%) or only primary education (43%). Mean gestational age was lower (34.32±3.212 vs 35.11±3.315, p<0.001), and the babies weighed less (2.58±0.8 vs 3.26±0.6, p <0.001) in severe pre-eclamptic group. Hyperuricaemia (Serum Uric Acid =450ìMol/l) is found in 39% of patients and is significantly associated with intrauterine fetal death (IUFD), HELLP syndrome, severe hypertension and elevated liver enzymes (LD, AST). The mean platelets count was lower and significantly associated with hyperuricemia.

Keywords: Serum uric Acid, Preeclampsia, adverse pregnancy outcome,

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Introduction

Pre-eclampsia is a disorder of widespread vascular endothelial dysfunction and vasospasm that occurs after 20 weeks of gestation and present as late as 4-6 weeks postpartum.[1] This condition seems linked to oxidative stress within the placenta.[1] Pre-eclampsia is the most serious medical disorder of pregnancy, and complicates 5-10% of pregnancies and results in more admissions in the antenatal period than any other disorder.[2] Preeclampsia and Eclampsia are the leading cause of maternal mortality in Northern Nigeria, accounting for 40 to 43.1% of maternal deaths.[2]

Uric acid is the end product of purine metabolism catalysed by the enzyme xanthine oxidase/dehydrogenase. This bifunctional enzyme in its dehydrogenase form produces uric acid and reduced nicotinamide adenine dinucleotide and in the oxidase form produces uric acid and superoxide. The enzyme is upregulated and the oxidase form increases proportionally with hypoxia.[3]

There is 25-35% decline in serum uric Acid in first and second trimesters, which could be due to increased renal clearance as a result of increased glomerular filtration rate and increased distal tubular secretion and increase in plasma volume, or due to decreased proximal tubular re-absorption.[3] Its level begins to rise in the second half of pregnancy due to raised fetal production, decreased binding to albumin as well as decline in its clearance until it approaches pre-pregnancy level in the third trimester[3,4] In preeclampsia, serum uric acid is not markedly elevated in mild form of the disease but significantly elevated in severe disease.[3,4] Increased uric acid production occurs in the setting of hypoxia, local acidosis, increased tissue breakdown or with reduced renal function as seen in preeclampsia and can increase oxidative stress.[3,4] This rise in serum uric acid has been shown to have correlation with increasing blood pressure and degree of glomerular injury and precedes the proteinuric stage of the disease explaining the poor perinatal outcome in the absence of proteinuria and minimally elevated blood pressure.[4,5] Uric acid clearance also drops disproportionately compared to urea and creatinine.[3-5] The characteristic renal lesion of preeclampsia "glomeruloendotheliosis" has been found to be present only in women with hyperuricaemia.[3,5] Uric acid might be causally related to hypertension.[3,5] Serum Uric Acid can promote endothelial dysfunction, damage and inflammation, which will lead to oxidation, there by propagating preeclampsia. The resultant tissue hypoxia leads to increased trophoblastic friability and shedding, with increased purine metabolism leading to hyperuricaemia.[3,4]

It has been suggested that in humans, uric acid might aggravate hypertension by increasing salt sensitivity, vascular smooth muscle proliferation and reduce endothelial nitric oxide bio-availability.[3-5]

Because maternal uric acid passes freely into the placenta, a rise in uric acid could lead to an inhibition of angiogenesis in the third trimester, leading to adverse fetal manifestations in form of oligohydramnios, intrauterine growth restriction, intrauterine fetal death, intrapartum fetal distress and birth asphyxia, even in the absence of maternal manifestations of severe disease.[3,5-6] One study found serum uric acid to be a better predictor of fetal low birth weight than blood pressure or proteinuria.[5-8] Evidence suggests the role of hyperuricemia as a marker of worsening condition in preeclampsia, suggestive of end organ damage.[4-8] Hyperuricemia is association with increased incidence of both abruption placentae and progression to Eclampsia, as well as higher incidence of caesarean delivery and increased maternal mortality.[2,5,8-10]

In our environment, preeclampsia occurs late in pregnancy but evolves rapidly to severe disease.[2,9] Thus, ability to detect the most severe form of preeclampsia would allow closer surveillance and early intervention to improve outcomes.[2,6-10]

Methods and Material

This was a prospective cohort study conducted at obstetrics and Gynaecology Department of Aminu Kano Teaching Hospital with approval of ethical

committee of the hospital, between 3rd March 2014 and 23rd July 2014.

One Hundred Pre-eclamptic Patients were recruited consecutively as they were admitted into the labour ward, having been counselled and consented for the study.

Socio-demographic variables and clinical characteristics such as age, tribe, marital and booking statuses were obtained and recorded on the proforma. In addition, the gestational age at delivery, birth weight, Apgar scores as well as admission to special care baby unit were noted. Adverse perinatal outcomes of intrauterine growth restriction (IUGR), Birth Asphyxia and Intrauterine fetal death (IUFD) were recorded. Maternal adverse outcomes of Eclampsia, Acute renal failure and HELLP syndrome were also recorded.

Blood samples collected under aseptic conditions in Lithium Heparin specimen bottles were centrifuged for 5-10 minutes at 3000 rpm and separated. The plasma was harvested with clean pasture pipette and placed in an empty 5ml plane bottle and coded for identification. It was kept at -200c until analysis. Assay of maternal serum uric acid, liver enzymes and serum creatinine was done in the chemical pathology laboratory while the Platelet count was determined in haematology laboratory. Serum Uric Acid concentration was determined using Lambert- Beer Law.

The Data obtained was analyzed using the Statistical Package for Social Science (SPSS.16 Inc, Illinois). Percentages, means and standard deviations were calculated. Where appropriate, risk was estimated using odd ratio while chi-square was used to test for significance at 95% confidence interval. Student t-test and ANOVA (Analysis of Variance) were used to compare groups. Logistic regression was used to test for the effect of compounding variables. Level of significance was set at $P<0.05$.

The Sensitivity, specificity and predictive values were also calculated. Tables were used to illustrate patterns in the variables.

Results

A total of 100 patients were recruited into this study. The mean age and parity of the patients was 26.81±6.031 and 2.2156±2.643 respectively. Significant proportion (43%) of the cases were unbooked. Thirty (30%) of the patients were referred, of which Thirteen (43.3%) booked at the referring facility. Fifty Eight (58%) of the patients had no formal or only primary level of education, while 28% have secondary level of education. Majority (70%) of the patients were of Hausa tribe, with 93% of them being married. Thirty Seven (37%) of the patients were nulliparous ($p<0.001$). Only 11 cases had a family history of pregnancy induced hypertension ($p=0.983$). Seventy (70%) of patients had severe pre-eclampsia, with only 6% of patients presenting earlier than 26 weeks of age. The mean gestational age at admission was lower and the babies weighed less in severe pre-eclampsia compared to mild form of it (34.32±3.213 vs 35.11±3.315; $p<0.001$) and (2.58±0.8 vs 3.26±0.6; $P<0.001$) respectively. This was shown in Table 1 and 2.

Hyperuricemia was observed in 39% of the patients and is significantly associated with elevated blood pressure and laboratory parameters as shown in table 3. The mean serum uric acid level differs significantly between mild and severe pre-eclampsia; (438.65±97.146 VS 385.43±88.029) P 0.017.

Hyperuricemia (Serum Uric Acid >450mg/dl) is significantly associated with severe hypertension (sensitivity; 89.7%, specificity; 68.9%, Positive predictive value: 64.8%, Negative predictive value: 91.3%, OR 95% CI: 3.958 (1.231-12.726) P0.015. Liver enzymes were also significantly elevated in the hyperuricaemic group (Lactate dehydrogenase; 349.34±105.67 vs 239.56±65.34 P0.02, AST; 32.08±24.09 vs 23.09±14.03 P 0.004). The mean platelets count is lower and significantly associated with hyperuricaemia (189.05±86.923vs 231.52± 67.251 P 0.007). This is illustrated in table 3.

The risk for adverse maternal outcomes associated with hyperuricemia is shown in table 4.

The sensitivities, specificities, predictive values and relative risks for the adverse maternal outcomes are as follows; HELLP syndrome; Sensitivity 77, specificity 100, PPV 100, NPV 62.9, x2 4.837, p0.028. Acute renal failure; sensitivity 51, specificity 100, PPV 100, NPV 62.2, x2 3.192, p 0.074. Eclampsia; OR (95%CI) 0.425 (0.559-4.189. P 0.406). After logistic regression for compounding variables, HELLP syndrome and severe hypertension are significantly associated with hyperuricemia.

The risk for adverse fetal outcome is shown in table 5. The sensitivity, specificity, positive and negative predictive values of the perinatal outcome studied are as follows; Asphyxia; (sensitivity; 30.8, specificity; 82, PPV 52.2, NPV; 64.9., OR (95%CI); 2.02(0.787-5.189), p 0.14). Intrauterine growth restriction; (sensitivity; 30.8, specificity; 80.3, PPV; 50, NPV; 64.5, OR (95%CI); 1.815(0.718-4.59), p0.205). Intrauterine fetal death; (sensitivity; 68.89, specificity; 83.56, PPV; 20.53, NVP; 97.52, OR (95%CI); 4.23(0.076-0.318), p<0.026). Admission to special care baby unit; (sensitivity; 28.2, specificity; 68.9, PPV; 36.7, NPV; 60, OR (95%CI); 0.868(0.359-2.10), p 0.754). After logistic regression for the effect of compounding variables, intrauterine fetal death (P 0.026) is still significantly associated with hyperuricemia.

Table 1: Characteristics of patients with Preeclampsia at AKTH

Category	Bp<160/110(30)	BP>=160/110(70)	X2	P-Value
Age (mean ±SD)	26.39±8.138	27.48±5.063	-1.173	0.272
Parity (mean ±SD)	2.153±2.32	2.123±2.843	0.132	0.802
GA at delivery (wks)*	35.11±3.315	34.32±3.212	-9.794	<0.001
Birth weight(kg)*	3.26±0.6	2.58±0.8	-11.165	<0.001
Booking status				
Booked	18(60)	9(12.86)	-12.517	<0.001
Unbooked*	8(26.67)	35(50)		
Referred	4(13.32)	26(37.142)		
Educational status				
None	2(6.66)	13(18.571)		
Primary	15(50)	28(40)		
Secondary	10(33.33)	18(25.71)		
Tertiary	3(10.00)	11(15.71)		
Mode of delivery				
SVD	18(60)	38(54.28)	20.165	<0.001
IOL	4(13.33)	12(17.14)		
C/S*	8(26.66)	20(28.57)		

*Key: significant after regression analysis.

Table 2: Relationship of preeclampsia, Birth weight at Gestational Age at Deliveries

Category	Bp<160/110(30)	BP>=160/110(70)	T-test	P-Value
GA at delivery(wks)	34.32±3.212	35.11±3.315	-9.794	<0.001
Birth weight (kg)	2.58±0.8	3.26±0.6	-11.165	<0.001

Table 3. Relationship between Serum uric acid and laboratory parameters

Variable (mean±SD)	Uric acid umol/l <450	Uric acid umol/l >450	T-test	P-Value
Platelets ($x10^9$)	186.2±61.3	189.05±86.923	0.162	0.007
AST	23.09±14.03	32.08±24.09	-2.776	0.015
LD	239.56±65.34	349.34±105.67	-4.086	0.001
Bilirubin	19.98±5.809	27.87±10.593	-4.803	<0.0001

Table 4: Relationship between Serum uric acid and maternal outcomes

Outcome	Sensitivity	Specificity	PPV	NPV	X^2/ OR 95% CI	P-Value
HELLP Syndrome	77	100	100	62.9	4.837	0.028
ARF*	51	100	100	62.2	3.192	0.074
Severe PE	89.7	68.9	64.8	91.3	3.958(1.231-12.726)	0.015
Eclampsia*					.425(0.559-4.189)	0.406

*Not significant after logistic regression
Key; ARF: Acute renal failure; HELLP: Hemolysis, Elevated Liver Enzymes, low Platelets.

Table 4: Relationship between Serum uric acid and maternal outcomes

Outcome	Sensitivity	Specificity	PPV	NPV	OR (95% CI)	P-Value
Asphyxia	30.8	82	52.2	64.9	2.02(0.787-5.189)	0.14
IUGR	30.8	80.3	50	64.5	1.815(0.718-4.59)	0.205
*IUFD	68.89	83.56	20.53	97.52	4.23(0.076-0.318)	0.026
SCBU Adm	68.9	82.68	36.7	60	0.868(0.359-2.10)	0.754

* Significant after logistic regression
Key: IUGR; intrauterine growth restriction, IUFD; intrauterine fetal death, SCBU; special care baby unit, Adm; admission, PPV; positive predictive value, NPV; Negative predictive value, OR; Odd ration.

Discussion

In this study, the mean age of 26.81 years in patients with Preeclampsia is lower than 30 reported Benin, probably due to the younger age at marriage in the northern part of the country.[9]

A significant proportion (43.0%) of cases were unbooked and majority (58.0%) had no formal (15%) or only primary school (43%) level of

education. This is in keeping with similar findings in the region.[10,11] This points to the dual predicament of girl child in our setting, with low level of education and resulting low socioeconomic status, which further decreases the utilization of the available health resources in our environment.

Thirty Seven (37%) of the subjects were nulliparous, which constitute a significant risk factor for preeclampsia in this study, as reported in other studies.[2,10,11] Caesarean section was a mode of delivery in 31% of these patients, more so in patients with severe pre-eclampsia ($p < 0.001$). This agrees with findings in several studies on hypertensive disorders in pregnancy.[1,3,9,12] Feto-maternal conditions and unfavorable cervix may be contributory.

Thirty Nine percent of cases had hyperuricemia, which has a positive correlation with the severity of pre-eclampsia (p 0.015). Several studies have correlated rise in serum uric acid with severity of maternal disease and an even stronger association with adverse perinatal outcome.[3-8,12-14]

A rise in serum Uric acid, which passes freely into the placenta, could lead to adverse fetal effects, ranging from oligohydramnios, intrauterine growth restriction, intrapartum asphyxia as well as intrauterine fetal death.[3,5,6,12,14] This is ascribed to its ability to inhibit endothelial cell proliferation.[3-8,13,14] This effect on fetal kidneys is postulated to result in reduction of kidney growth as well as reduction in the number of nephrons.[5,6,14]

The mean birth weight of 2.58kg in severe preeclampsia is less than that of mild disease (3.4kg). This may be related to lower gestational age at birth and intrauterine growth restriction. The mean gestational age at delivery of 34.32 weeks (severe) and 35.11 weeks (mild) is less than 36.6 weeks (case) reported in Benin.[9] These negative effects on perinatal outcome in this study, have been reported in other studies to be independent of hypertension and proteinuria.[5-8,14,15] Other studies found hypertension, in the absence of hyperuricemia as being favorable on fetal outcome.[5-8]

This study found a positive correlation between hyperuricaemia and adverse perinatal outcome of low birth weight and intrauterine fetal death.[13-16] Intrauterine fetal death still remained high after logistic regression analysis. Similar study in Dhaka reported 5.3 times higher risk of Prematurity, IUFD and stillbirth in the hyperuricaemic group.[15] Although this study found a low positive predictive value of hyperuricaemia for all the perinatal outcomes studied, the sensitivity and negative predictive values were high. The high negative predictive value of hyperuricaemia will enhance its use as a screening tool for adverse perinatal outcomes, allowing for timely delivery.

This study also established an association of Hyperuricaemia with HELLP syndrome. This is in agreement with studies that correlates rising serum uric acid with disease progression.[15]

Some researchers have suggested a causal relation between uric acid and hypertension, through the role of uric acid in vascular smooth muscle proliferation and increased salt sensitivity.[13-6,14-16] This may in part explain the finding of a significantly higher blood pressure among the hyperuricaemic group in this study.

Liver enzymes (LD, ASAT) as well as Bilirubin were found to be significantly elevated in the hyperuricaemic group. This, coupled with low platelets count found in this study, is in agreement with reported similar findings.[16-19]

Conclusion

Results of this study suggests that hyperuricemia would identify group of preeclamptic patients at increased risk of adverse perinatal outcome of intrauterine fetal death and adverse maternal outcome of HELLP syndrome as well as severe Hypertension.

Recommendations

By using single or serial measurements, Hyperuricemia in Preeclampsia should be used as an indication for delivery, in order to avert adverse complications of fetal demise, HELLP syndrome and severe Hypertension.

Limitations

Majority of the cases in this study had little or no formal education. This affected estimation of gestational age. Ultrasound scan was used for gestational age estimation, by adjustment to the acceptable margin of error.

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Conflict of interest

There are no conflicts of interest.

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