Original Research Article

Serum uric acid: a biochemical prognostic indicator of pregnancy outcomes among pre-eclampsia patients at the federal medical centre, Yenagoa

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ABSTRACT

Background: High levels of uric acid concentration over normal pregnant values have been reported previously in established preeclampsia, hence it was suggested to be a useful biochemical prognostic marker of the disease.
Methods: This is a hospital based prospective case control study where 100 patients with preeclampsia were recruited consecutively as they were admitted. 100 non-pre-eclamptics were also recruited as control. The foetomaternal data, adverse perinatal outcomes, maternal serum uric acid levels as well as complications of preeclampsia were recorded into the protocol. Statistical analysis was done using SPSS 22.0. Level of significance was set at $p<0.05$.
Results: The mean age in the study group was 28 ± 6.7 years while in the control group it was 31 ± 6.5 years. The difference in age was not statistically significant ($p=0.53$). The mean serum uric acid level was significantly higher amongst participants with preeclampsia than in those without preeclampsia (405.6 ± 995 µmol/L versus 232.7 ± 26.3 µmol/L, $p=0.00$). Uric acid was statistically associated with the occurrence of eclampsia ($p=0.03$), Severe hypertension (0.03) and birth asphyxia ($p=0.01$).
Conclusions: The mean serum uric acid was higher in preeclampsia than non-preeclampsia patients. High levels of uric acid were found in eclampsia, severe hypertension and birth asphyxia. However, the prognostic accuracy for uric acid was low for most pregnancy outcomes.

Keywords: Pre-eclampsia, Eclampsia, Uric acid, Pregnancy outcomes

INTRODUCTION

Preeclampsia has remained a major challenge to obstetric practice and it is a common complication of pregnancy associated with high maternal and perinatal morbidity and mortality especially in developing countries.[1] Preeclampsia is a pregnancy associated multiorgan disorder caused by altered trophoblastic invasion and endothelial cell dysfunction.[2] It accounts for about 12-18% of pregnancy related deaths.[2] Preeclampsia is a pregnancy specific disease characterized by hypertension and proteinuria arising de novo after the 20th week of gestation in a previously normotensive and non proteinuric woman. The exact cause of preeclampsia remains unclear. The central pathology to the development of preeclampsia lies in the placenta.[4] The incidence is higher in conditions with increased placental mass like twin pregnancy, molar pregnancy, diabetic pregnancies and hydrops foetalis.[4] Genetic and immunological theories have also been implicated.[4]

Biochemical indices of preeclampsia include serum calcium, trace elements assay, serum uric acid assay, serum beta human chorionic gonadotropin as well as serum fibronectin.[5] Serum uric acid is a reliable index of foetal wellbeing when pregnancy is complicated by preeclampsia. With hyperuricaemia, prognosis for the foetus is poor irrespective of level of blood pressure.[6] It identifies women with increased risk of adverse maternal and particularly foetal outcome.[6]

Uric acid is a product of purine metabolism generated during the breakdown of nucleic acids (DNA and RNA) and adenosine triphosphate.[7] Its main metabolism is by the kidneys. In normal pregnancy, serum uric acid concentration initially falls by 25-30% due to elevation in renal clearance secondary to increased glomerular filtration rate or reduced proximal tubular reabsorption due to change in its production rate.[8] Later in pregnancy, the serum uric acid level increases possibly due to rise in foetal production, decreased binding to albumin, and a decline in uric acid clearance until towards the end of pregnancy when they approach the non-pregnant value.[8] However, uric acid concentration is increased over normal pregnant values in established preeclampsia and there are several potential origins for raised uric acid concentration in preeclampsia. It is usually secondary to altered renal function, increased tissue breakdown, increased oxidative stress and increased activity of xanthine oxidase.8 The first report of increased maternal serum uric acid concentration in preeclampsia/eclampsia was published in 1917.[9] Subsequently some studies reported positive association between elevated uric acid levels and the severity of preeclampsia. Maternal serum uric acid was reported to be useful in the prognostication of the disease and may reflect the severity of the condition.[10,11] However, others concluded that uric acid levels, although significantly elevated in women with preeclampsia compared with those of normotensive pregnant women, but was not a good prognostic indicator of severity of maternal and foetal complications.[12]

This study revealed serum uric acid as a prognostic indicator among preeclampsia patients and non-preeclampsia patients and also determined pregnancy outcomes associated with them.

The ability to detect the mild form of preeclampsia would allow closer surveillance and early intervention to improve outcome.[13] The resultant effect of this study will help reduce the perinatal and maternal morbidity and mortality associated with preeclampsia.

METHODS

The study was conducted in the Obstetrics and Gynaecology Department of the Federal Medical Centre, Yenagoa. It was a prospective case control study by systematic sampling selection. The first group of the study population comprised 100 consecutive preeclamptic patients admitted for management into our antenatal ward and labour ward. The second group (control) of the study population comprised 100 consecutive non-preeclamptic patients admitted for management into the antenatal ward and labour ward. The values of their serum uric acid were evaluated on admission. Patients were followed up to delivery and their pregnancy outcome evaluated. The study was carried out from the 1st of April 2018 to the 30th of September 2018.

Ethical approval

Written and informed consent was obtained from every participant in this study. The hospital research and ethics committee examined and approved this research work. Inclusion criteria constituted all preeclampsia patients admitted into the antenatal ward and labour ward of Federal Medical Centre, Yenagoa, who consented to be part of the study within the study period and the controls were normal healthy pregnant women whose serum uric acid levels were assessed within the same period. Exclusion criteria included patients with chronic hypertension, chronic hypertension with superimposed preeclampsia, pregnancy induced hypertension, renal disease, diabetes mellitus, heart failure and ischemic heart disease. Women who refuse to give consent were also excluded from the study.

Sample size

The sample size for the study was calculated using the formula:[14]

$$n = z^2 pq/d^2$$

n= minimum sample size, z= standard normal deviation set at 95% confidence limit=1.96, p= prevalence of preeclampsia in previous study, q=1-p (complementary probability), d= margin of error = 5%=0.05

Prevalence of preeclampsia that was used in this study based on a previous study done in Bayelsa state was 5.6%.1 Therefore, giving an attrition of 10%, the minimum sample size was 89. However, this was adjusted to 100 for ease. Thus, 100 patients who met the inclusion criteria were recruited for this study. In our centre, about 400 patients register for antenatal care per month and about 5%-10% when followed up to the third trimester are estimated to develop preeclampsia. This study was carried out within 5 months.

Patients were recruited consecutively as they were admitted into the antenatal ward and labour ward with preeclampsia. Thorough history and examination were used in selecting patients based on the inclusion and exclusion criteria. The blood pressure was measured with the use of manual sphygmomanometer. A patient was said to be hypertensive when her blood pressure was persistently equal to or greater than 140/90 mmHg measured at least 6 hours apart.

Specimen collection

Urine collection was done in the antenatal ward and labour ward. Patients were trained and instructed adequately on how to collect clean catch midstream urine. The urine specimen was taken to the laboratory for protein estimation and in suspicious cases, urine microscopy, culture and sensitivity was done to exclude urinary tract infection. The diagnosis of proteinuria was made when two midstream samples of urine collected at least four hours apart showed one or more plus of albumin using dipstick.[15] For the diagnosis and classification of preeclampsia, Davey and McGillivray's classification adopted by the international society for the study of hypertension in pregnancy (ISSH) was used. Patients that met the criteria for preeclampsia were recruited into the study. Once the diagnosis was confirmed, blood specimen was collected from the patient for uric acid analysis. Urine specimen and blood specimen were also collected from normal non preeclamptic as controls. About five millilitres of blood was collected. Serum was separated by centrifugation for ten minutes at 3500 rpm. The supernatant was transferred by pasteur pipette into a test tube for immediate analysis or stored at 2-8 ^{0}C until time of analysis usually within 24 hours. Analysis of uric acid was done by phosphotungstic acid method and the results were read by spectrophotometer.[16]

Data collection

Socio-demographic data and clinical characteristics such as age, tribe, marital and booking status was obtained and recorded in the protocol. In addition, the gestational age at delivery, birth weight, 5-minute apgar scores and admission to special care baby unit was noted. Adverse perinatal outcomes like intrauterine growth restriction (IUGR), birth asphyxia and intrauterine foetal death (IUFD) were also noted. Mothers admitted into intensive care unit were followed up and their outcomes recorded. Maternal adverse outcomes such as eclampsia, acute renal failure and HELLP syndrome were also noted. Laboratory results for uric acid and proteinuria were also collected.

Data analysis

Data entry and statistical analysis was done using statistical package for social science (IBM SPSS for windows version 22.0. SPSS Inc; Chicago, USA).

RESULTS

Socio-demographic characteristics of participants

A total of 200 participants were involved in this study which constituted one hundred preeclamptic women (study group) and one hundred non preeclamptic women (control group) with a 100% response rate. The predominant age group in both the study group and the control group was 25-34 years age group with 52 (52.0%) and 56 (56.0%) respectively. The mean age in the study group was 28±6.7 years, while in the control it was 31±6.5 years. The difference in age between the groups was not statistically significant (p=0.53). Majority of the patients were of the Ijaw ethnic group both in the preeclamptic and control groups with 62 (62.0%) and 56 (56.0%) respectively. Most of the patients were married in both the preeclamptic and control groups with 84 (84.0%) and 92 (92.0%) married respectively. Amongst those that were married, most of the marriages were in the monogamous setting; 78 (92.9%) in the preeclamptic and 89 (97.7%) in the control group. Most of the patients were Christians in both the preeclamptic and control groups with 94 (94.0%) and 96 (96.0%) respectively. The highest level of education was secondary school in the preeclampsia group (58%), while it was tertiary education for controls (54%). Majority 56 (56%) and 54 (54%) of the participants in both the preeclamptic and control groups respectively were business women by occupation.

Maternal history and urinalysis dipstick results

The maternal history and urinalysis dipstick results in both groups revealed that the primipaternity risk was 69% and 45% in the preeclamptic and control group respectively. Almost all (98%) of preeclamptic patients and 100% of controls were in their third trimester of pregnancy. All the preeclamptic patients had one to three pluses proteinuria as against 3% in the control group. Thirty-five (35.0%) of patients of the study group had a positive family history of pregnancy induced hyper tension (PIH) compared to 7% in the control group, Amongst those that have positive family history of PIH in the preeclampsia group, 15 (42.9%) said their sisters and they themselves has had PIH in the past, while 5 (14.3%) said their mothers have had PIH previously. In the preeclamptic group and control group, 28 (28.0%) and 48 (48.0%) respectively has had a previous pregnancy. Amongst those that have had a previous pregnancy in the preeclamptic group, 24 (85.7%) carried their pregnancy to term, while, 3 (10.7%) had miscarriages, and 1 (3.6%) had ectopic pregnancy. Amongst those that have had a previous pregnancy in the control group, 35 (72.9%) carried their pregnancy to term, while 11 (22.9%) had miscarriages, and 2 (4.2%) had ectopic pregnancy.

Maternal symptoms, foetal parameters and maternal adverse pregnancy outcomes

All the participants with preeclampsia showed symptoms in keeping with the disease as follows; severe nausea and vomiting (42%), frontal headache (24%), right upper quadrant epigastric pain (6%). None of the control group had such symptoms. Based on maternal pregnancy outcomes in the preeclamptic group, 7% had HELLP syndrome, 27% had eclampsia and 10% developed acute renal failure while none of the controls had such outcomes. Abnormal foetal heart rate was found in 23% of those with preeclampsia compared to 9% of the control

groups. After delivery, the preeclamptic mothers had 40% of their babies admitted into the special care baby unit, 20 (20.0%), 10 (10.0%) and 26 (26.0%) of their babies had intrauterine growth retardation, intrauterine foetal death and birth asphyxia respectively. While, in the control group, none of the participant's babies had IUGR, 2 (2.0%) had IUFD and 6 (6.0%) had birth asphyxia.

Mean serum uric acid levels in preeclampsia and control groups

The mean serum uric acid level (405.6±99.5) in the preeclampsia group was found to be greater than the mean serum uric acid level in the control group (232.7±26.3). The observed difference was statistically significant p=0.001, (Table 1).

Table 1: Mean serum uric acid levels in preeclampsia and control groups.

Group	Mean± SD	Mode	Range	t-test	p-value
Preeclampsia group	405.6±99.5	343	421 (701-280)	16.8	0.001
Control group	232.7±26.3	213	119 (290- 171)		

Table 2: Relationship between high maternal serum uric acid levels and maternal/foetal complications in preeclampsia participants.

Risk	Complications						
High uric acid level n=69	**HELLP N (%)**	**Eclampsia N (%)**	**ARF N (%)**	**IUGR N (%)**	**IUFD N (%)**	**Birth asphyxia N (%)**	**Severe HTN N (%)**
Present	3(4.34)	13 (18.8)	5(7.24)	9 (13)	6 (8.7)	15 (21.8)	61(88.4)
Absent	66 (95.7)	56 (81.2)	64 (92.76)	60 (87)	63 (91.3)	54 (78.2)	8(11.6)
P value	P=0.46	P=0.03*	P=0.27	P=0.13	P=0.07	P=0.001*	P=0.03*

Fisher's exact test * signifies statistically significant(p<0.05)

Table 3: Prognostic accuracy scoring for serum uric acid as a biochemical marker in maternal/foetal outcomes in preeclampsia participants.

Pregnancy outcome/ serum marker	Sensitivity	Specificity	PPV	NPV	Accuracy
Severe Hypertension	85	50	87.1	45.45	0.78
HELLP	100	22.68	3.84	100	0.25
Eclampsia	100	25.29	16.67	100	0.13
Acute renal failure	100	23.15	6.41	100	0.27
IUGR	90.91	23.59	12.82	95.45	0.31
IUFD	85.71	22.58	22.22	95.65	0.27
Birth Asphyxia	80.95	24	22.97	81.81	0.35

Relationship between elevated uric acid levels and maternal/foetal complications in the preeclampsia patients.

No client in the control group had a high serum uric acid level while 69% of preeclampsia group had high uric acid levels. Amongst these, 3 (4.34%) developed HELLP syndrome, 13 (18.84%) developed eclampsia,5 (7.24%) developed acute renal failure,61(88.4%) had severe hypertension, (13%) of them had babies with IUGR, 6 (8.69%) suffered IUFD and 15 (21.75) had babies who suffered birth asphyxia. The association between elevated uric acid and eclampsia, severe hypertension and birth asphyxia were statistically significant with p values of 0.03, 0.03 and 0.01 respectively. While the association between elevated urea levels and HELLP syndrome,

acute renal failure, IUGR and IUFD were not statistically significant (p>0.05) see (Table 2).

Prognostic accuracy scoring for serum uric acid as a biochemical marker in maternal/foetal outcomes in preeclampsia participants.

The ability of the uric acid marker to predict adverse pregnancy outcomes was measured. In terms of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the uric acid marker and calculated as shown in (Table 3) and.

The prognostic accuracy was highest for severe hypertension, low for other outcomes and lowest for eclampsia (Figure 1).
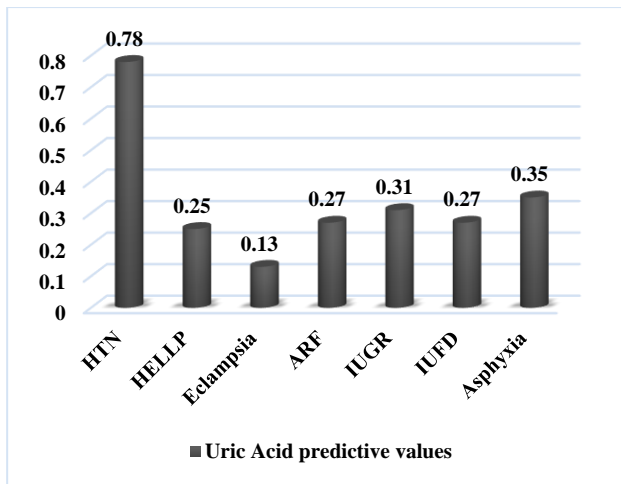
HTN=hypertension, HELLP syndrome, ARF = acute renal failure, IUGR= intrauterine growth retardation, IUFD= intrauterine foetal death, birth asphyxia

Figure 1: Prognostic accuracy of serum uric acid in predicting adverse pregnancy outcomes.

DISCUSSION

In this study, the mean age of cases and controls were 28±6.7 and 31±6.5 respectively. The mean age of cases is higher than 27±4.9 and 27.2±5.6 years reported in calabar and ogun states respectively.[17,18] The results from this study are consistent with the usual risk factors for preeclampsia including primipaternity and family history of preeclampsia.[4] Primipaternity was more common in the study group (70%) than in the control group (45%) with the difference being statistically significant (p=0.00). This is in keeping with theories surrounding the origins of preeclampsia identifying pregnancy by a new spouse or partner as a risk factor for the condition.[4]

More women in the study group (35%) as compared to the control group (7%) had a family history of hypertensive disease in pregnancy. This is in keeping with genetic factors being implicated in the development of preeclampsia where daughters of women with preeclampsia are about four times more likely to develop the disease than daughter in-laws and it has been established that it is familial.[4,19]

This study reported a significantly higher mean serum uric acid level amongst participants with preeclampsia than in those without preeclampsia. This increased amount of serum uric acid amongst clients with preeclampsia has been reported by several studies and this increased amount is thought to correlate with the severity of the disease condition.[5,10,20,21] Antenatal patients with renal disease were excluded from taking part in this study and as such, it is unlikely that renal disease would have contributed to the higher levels of serum uric acid amongst the study population.

In this study, majority (94%) of the patients recruited into the study group were at least 34 weeks gestational age

and there was a statistically significant association between high serum uric acid levels and eclampsia, IUGR as well as birth asphyxia (p<0.05). This is in keeping with another study where irrespective of the preeclamptic status of the patient, the serum uric acid levels are bound to rise as pregnancy approaches term.[5]

The severity of preeclampsia was determined by clinical features and/or abnormal laboratory parameters. The adverse pregnancy outcomes in this study were considered as features of severe preeclampsia. The ability of the uric acid marker to predict an adverse pregnancy outcome was measured. The prognostic accuracy of uric acid in predicting pregnancy outcomes was low in this study except for severe hypertension. This corroborates with previous studies where it was reported that although uric acid was significantly elevated in women with preeclampsia compared to the normotensives, it was not a good prognostic indicator of severity and maternal or foetal outcome.[12]

There have been conflicting reports on the ability of serum uric acid to predict adverse pregnancy outcomes.[22-24] The wide variation in gestational ages may have accounted for the different opinions found in these studies. Similar findings concluded that uric acid was not a consistent predictive factor for the development of preeclampsia, but its levels generally increase once the disease manifests and the plasma levels approximately correlates with disease severity.[21,23] From these findings, we suggest that a combination with other biochemical markers will improve the predictability of pregnancy outcomes in preeclampsia.

Limitation

This was a hospital-based study. The results may not reflect the findings in other tertiary institutions in Nigeria or the west African sub-region.

CONCLUSION

The mean serum uric acid was higher amongst participants with preeclampsia than in those without preeclampsia. Serum uric acid was found to be useful prognostic indicator for foetomaternal outcomes in women with preeclampsia. However, the prognostic accuracy of serum uric acid level in predicting maternal and foetal outcomes was low. Therefore, an additional biochemical marker may be useful to improve its prognostic accuracy in pregnancy outcomes of these patients.

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