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Accuracy of Combined Measure of Serum Uric Acid and Beta Human Chorionic Gonadotropin (β hCG) Versus Serum Beta Human Chorionic Gonadotropin Alone as Prognostic Indicators of Pregnancy Outcome of Preeclampsia

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Authors' contributions

This work was carried out in collaboration among all authors. Author EOSA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors DOA, ELK and LO managed the analyses of the study and the literature searches. Authors BEK and PCO managed the laboratory analysis. All authors read and approved the final manuscript.

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ABSTRACT

Background: Measurement of variety of biological, biochemical and biophysical markers in pregnancy implicated in the pathophysiology of preeclampsia have been proposed to predict its development.
Aim: To evaluate the accuracy of combined measure of maternal serum uric acid level and quantitative serum beta hCG versus serum beta hCG alone as prognostic indicators of pregnancy outcome among preeclamptic patients at the Federal Medical Centre, Yenagoa.

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Methods: This is a hospital based prospective case control study by systematic sampling selection. The two groups comprised of 100 consecutive patients each, one with pre-eclampsia (study group) and the other without pre-eclampsia (control) admitted for management into the antenatal ward and labour ward over the seven-month period of the study. The values of their serum uric acid and beta hCG levels were evaluated on admission and followed up. Data entry and statistical analysis was done using statistical package for social science (windows version 22.0. SPSS Inc; Chicago, USA). Level of significance was set at $P < 0.05$.

Results: The mean quantitative serum β hCG level amongst the subjects (26776.6 ± 19590.5) was statistically significantly higher ($p < 0.001$) than the mean quantitative serum β hCG level amongst the control (7973.6 ± 4193.7). The prognostic accuracy in predicting pregnancy outcomes were: HELLP syndrome (0.33, 0.44), Eclampsia (0.50, 0.39), Acute Renal Failure (0.44, 0.33), IUGR (0.43, 0.39), IUFD (0.38, 0.27) and Birth Asphyxia (0.49, 0.38) respectively for combined measure of serum uric acid and serum β hCG, and serum β hCG alone.

Conclusion: Serum β hCG levels remains a useful prognostic indicator for feto-maternal outcome in preeclamptic women. However, combined measure of serum uric acid and serum β hCG level in prognosticating pregnancy outcome in preeclamptic women was shown to have a better accuracy than serum β hCG.

Keywords: Preeclampsia; pregnancy outcome; prognostic indicators and accuracy; beta hCG.

1. INTRODUCTION

Worldwide, the prevalence of preeclampsia varies significantly due to its wide variation in epidemiological studies [1]. Estimates of prevalence of preeclampsia by World Health Organisation (WHO) shows that the prevalence of preeclampsia is seven times higher in developing countries (2.8% of live birth) than in developed countries (0.4% of live birth) [1]. Preeclampsia affects about 5-10% of all pregnancies [1]. The prevalence of preeclampsia in India and Iran is 4% to 8% and 5% respectively [2,3]. In Brazil, it is 8.9% [4]. In United State of America, preeclampsia occurs at a rate of 81.4 per 1000 deliveries [5]. In Bangladesh the prevalence is about 10% [6]. The prevalence in Ethiopia is 7.3% [7]. In Benin Nigeria, the prevalence is 6.3% [8]. In Usman Danfodiyo University Teaching Hospital (UDUTH) Sokoto, the prevalence is 6% [9]. In Birnin Kudu Jigawa the prevalence is 9% [10]. In southern Nigeria, the prevalence rate of preeclampsia is between 5.6% to 7% [11]. In Calabar the prevalence is 1.2% [12] and in Niger Delta University Teaching Hospital the prevalence is 5.6% [11]. The reported incidence shows great variations which may be attributed to differences in definition, population composition, demographic and obstetric characteristic, access to and availability of antenatal services [12].

An association has been reported between preeclampsia and elevated third trimester human chorionic gonadotropin levels. Physiological concentrations of human chorionic gonadotropin is significantly increased in vitro capillary formation and migration of endothelial cells in a dose-dependent manner and has a novel function in uterine adaptation to early pregnancy. A recent study by Kalkunte et al found higher hCG levels in serum from preeclamptic pregnancies at term compared with serum derived from normal pregnancies [13]. Vandane et al found a strict relationship between severe preeclampsia and elevated serum beta hCG levels. Their findings also suggested that severe preeclamptic women have higher hormonal changes than mild preeclamptic women and reflects the abnormal placentation in these patients [14,15].

The concentration of uric acid is elevated over normal pregnant values in confirmed preeclampsia cases. There are many potential origins for elevated uric acid concentration in preeclampsia. It is usually secondary to increased tissue breakdown, altered renal function, increased activity of xanthine oxidase and increased oxidative stress [16]. Uric acid is filtered, reabsorbed and secreted by the kidney [17]. The most widely recognised explanation for hyperuricaemia in preeclampsia is decreased excretion and increased reabsorption of uric acid [16]. The time at which serum uric acid concentration starts to increase reflects the time of onset of the preeclampsia. The importance of measuring serum uric acid in hypertensive pregnancy is greatest in late pregnancy, between 24 to 32 weeks of gestation. Low levels indicate a good prognosis for the fetus. Increasing or high

levels at this time indicate high- risk cases which are better managed in the hospital [17]. In preeclampsia, Hyperuricaemia is the first biomarker of the clinical chemistry considered as an early evidence of the disease, in pregnancies ≤ 20 weeks of gestation [18].

Measurement of variety of biological, biochemical and biophysical markers in pregnancy implicated in the pathophysiology of preeclampsia have been proposed to predict its development [19]. Although there is no single predictor of preeclampsia among women at either low or increased risk of preeclampsia, it is recommended that at booking for antenatal care, women with markers of increased risk for preeclampsia should be offered obstetrics consultation [20]. Women at increased risk should also be considered for risk stratification involving a multivariable clinical and laboratory approach [20].

Considering the prevalence of preeclampsia worldwide, particularly in the developing countries of which Federal Medical Centre Yenagoa is part of, it will be imperative to study more locally and contribute to the African literature of preeclampsia and its prevention.

The objective of this study is to evaluate the accuracy of combined measure of maternal serum uric acid level and quantitative serum beta hCG versus serum beta hCG alone as prognostic indicators of pregnancy outcome among preeclamptic patients at the Federal Medical Centre, Yenagoa.

2. MATERIALS AND METHODS

The study was conducted in the Obstetrics and Gynaecology Department of the Federal Medical Centre, Yenagoa. The hospital is a tertiary health institution that provides all levels of health care services to patients especially in Bayelsa, Rivers and Delta states. 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 the antenatal ward and labour ward of Federal Medical Centre, Yenagoa over the period of the study. 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 and beta hCG levels 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 30 of September 2018.

Sample size: The sample size for the study was calculated using the formula:

$$n=z^2pq/d^2 \text{ [21]}$$

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% [11]. 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.

Method: 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 while the patient was in supine position on a couch with a left side tilt. An appropriate size cuff that covers at least 2/3rd of the upper arm was used. The systolic blood pressure was taken at the first point the sound was heard while the diastolic blood pressure was taken as Korotkoff V.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. This involved initial cleaning of the vulva with copious amount of clean water. The labia were parted, and the first part of the urine was voided and the next stream of urine (about 5 millilitre) was collected into a clean, dry urine bottle with

patient's name and number written on it. Trained nurses were recruited to supervise the process. 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. Protein estimation was based on the colour changes of the dipstick compared to the corresponding colour chart on the reagent container. 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 [22]. 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 (healthy pregnant women) as controls. About Five millilitres of blood was collected via aseptic procedure into a plane specimen bottle. Serum was separated by centrifugation for ten minutes at 3500rpm. The supernatant was transferred by Pasteur pipette into a test tube for immediate analysis or stored at 2-8°C until time of analysis usually within 24 hours. Analysis of uric acid was done by Phosphotungstic acid method [23] and the results were read by spectrophotometer.

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, beta hCG and proteinuria were also collected.

Data Analysis: Data entry and statistical analysis was done using statistical package for social science (windows version 22.0. SPSS Inc; Chicago, USA). Percentages, means and standard deviations were calculated. Chi-square was used to determine association between qualitative variables. Student t-test was used to determine association between quantitative variables. Level of significance was set at $P < 0.05$. Tables were used to illustrate patterns of variables. Sensitivity, specificity, predictive values and accuracy were calculated for the serum markers in relation to fetal and maternal outcomes of women who had preeclampsia.

3. RESULTS

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 ($p = 0.53$). The mean quantitative serum β hCG level amongst the subjects (26776.6 ± 19590.5) was statistically significantly higher ($p < 0.001$) than the mean quantitative serum β hCG level amongst the control (7973.6 ± 4193.7). 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 businesswomen by occupation.

There was no statistically significant ($p =0.09$) association between the combined markers and the occurrence of eclampsia. Amongst those with elevated markers, 21.56% (11/51) had eclampsia. There was no statistically significant ($p =0.45$) association between the combined markers and the occurrence of acute renal failure. Amongst those with elevated markers,

7.84% (4/51) had acute renal failure. There was no statistically significant (p =0.15) association between the combined markers and the occurrence of HELLP syndrome. Amongst those with elevated markers, 5.88% (3/51) had HELPP syndrome. There was a statistically significant (p = 0.007) association between the combined markers and the occurrence of severe hypertension. Amongst those with elevated markers, 96.07% (49/51) had severe hypertension. There was no statistically significant (p = 0.44) association between the combined markers and the occurrence of IUGR. Amongst those with elevated markers, 15.68% (8/51) had IUGR. There was no statistically significant (p =0.65) association between the combined markers and the occurrence of IUFD. Amongst those with elevated markers, 3.92% (2/51) had IUFD. There was no statistically significant (p= 0.13) association between the combined markers and the occurrence of birth asphyxia. Amongst those with elevated markers, 33.33% (17/51) had birth asphyxia. Table 1 shows the relationship between biochemical risk factors and maternal/fetal complications in preeclampsia participants. Table 2 reveals the prognostic accuracy of the different serum markers. Fig. 1 displays accuracy of serum markers in predicting adverse pregnancy outcome.

4. 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 respectively [24,25]. The results from this study are consistent with the usual risk factors for preeclampsia including primipaternity and family history of preeclampsia [26]. Primipaternity was less common in the control group (45%) when compared with the study group (70%) and this was 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 [26].

More women in the study group (35%) as compared to the control group (7%) had a family history of hypertensive disease in pregnancy. Genetic factors have been involved in the development of preeclampsia. 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 [26,27].

The relationship between serum β hCG levels and eclampsia (p =0.00) including HELLP (p = 0.04) were found to be statistically significant. However, the association with acute renal failure did not achieve statistical significance (p = 0.05). Serum β hCG levels had a statistically significant association with birth asphyxia (p = 0.00) and IUGR (p =0.00). There was no association between serum β HCG and IUFD (p = 0.05). Estimation of serum β hCG has been used as a marker to determine normal and abnormal pregnancy outcomes and has been found to be associated with severe pre-eclampsia [13,14,15]. Clinical features or abnormal laboratory parameters have been shown to determine the severity of preeclampsia. As a result, the poor pregnancy outcomes in this study are considered as features of severe preeclampsia.

The ability of the combined markers to predict an adverse pregnancy outcome was measured against the ability of the individual markers on their own. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of each of the markers was calculated and then also calculated for the combined marker. The prognostic accuracy in predicting pregnancy outcomes were: HELLP syndrome (0.33, 0.44), Eclampsia (0.39, 0.50), Acute Renal Failure (0.33, 0.44), IUGR (0.39, 0.43), IUFD (0.27, 0.38) and Birth Asphyxia (0.38, 0.49) respectively for serum β hCG and combined measure of serum uric acid and serum β hCG. The combined measure showed a better accuracy in predicting the maternal and fetal outcome than either serum β hCG. While there are a number of biochemical tests that have been used to predict the occurrence or severity of preeclampsia, evidence [16] suggests that a combination of the markers leads to improved predictability as was seen in this study.

The study involved a single estimation of serum uric acid and quantitative serum β hCG. It would have been enriched if several samples were taken to monitor any diurnal variation and document possible disease progression, these are recommended in future studies.

Table 1. Relationship between biochemical risk factors and maternal/fetal complications in preeclamptic participants

Risk	**Complications**						
High serum B-HCG LEVEL n=62	**HELLP n (%)**	**ECLAMPSIA n (%)**	**ARF n (%)**	**IUGR n (%)**	**IUFD n (%)**	**BIRTH ASPHYXIA n (%)**	**SEVERE HTN n(%)**
Present	3 (4.8)	11 (17.7)	4 (6.45)	9 (14.5)	2 (3.22)	15 (24.4)	32 (51.6)
Absent	59 (95.2)	51 (82.3)	58 (93.55)	53 (85.5)	60 (96.8)	47(75.6)	30(48.4)
P value	P=0.11	P=0.01*	P=0.19	P=0.01*	P=0.44	P=0.005*	P=0.001*
Combined marker high level n=51	**HELLP n (%)**	**ECLAMPSIA n (%)**	**ARF n(%)**	**IUGR n (%)**	**IUFD n (%)**	**BIRTH ASPHYXIA n (%)**	**SEVERE HTN n (%)**
Present	3 (5.88)	11(21.6)	4(7.84)	8(15.7)	2(3.92)	17(33.3)	49(96.8)
Absent	48(94.12)	40(78.4)	47(92.16)	43(84.3)	49(96.08)	34(66.7)	2(3.2)
P value	P=O.15	P=0.09	P=0.45	P=0.44	P=0.65	P=0.13	P=0.007*

*Key: * statistically significant P-value*

Table 2. Prognostic accuracy scoring of the different serum markers

Pregnancy outcome/ Serum marker	Sensitivity	Specificity	PPV	NPV	Accuracy
Severe HTN					
B-HCG	80	70	91.42	46.47	0.78
Combined	71.25	90	96.61	43.90	0.75
HELLP					
B-HCG	100	30.92	9.09	100	0.33
Combined	100	42.27	6.81	100	0.44
ECLAMPSIA					
B-HCG	84.61	32.18	28.21	93.33	0.39
Combined	84.62	44.82	18.64	95.12	0.50
ACUTE RENAL FAILURE					
B-HCG	80	30.52	5.71	96.67	0.33
Combined	80	42.11	6.78	97.56	0.44
IUGR					
B-HCG	90.91	32.58	14.29	96.67	0.39
Combined	90.91	44.94	20.00	97.56	0.50
IUFD					
B-HCG	28.57	26.88	7.41	83.33	0.27
Combined	28.57	38.71	5.30	87.80	0.38
BIRTH ASPHYXIA					
B-HCG	76.19	29.33	23.19	81.48	0.38
Combined	76.19	44	27.59	86.84	0.49

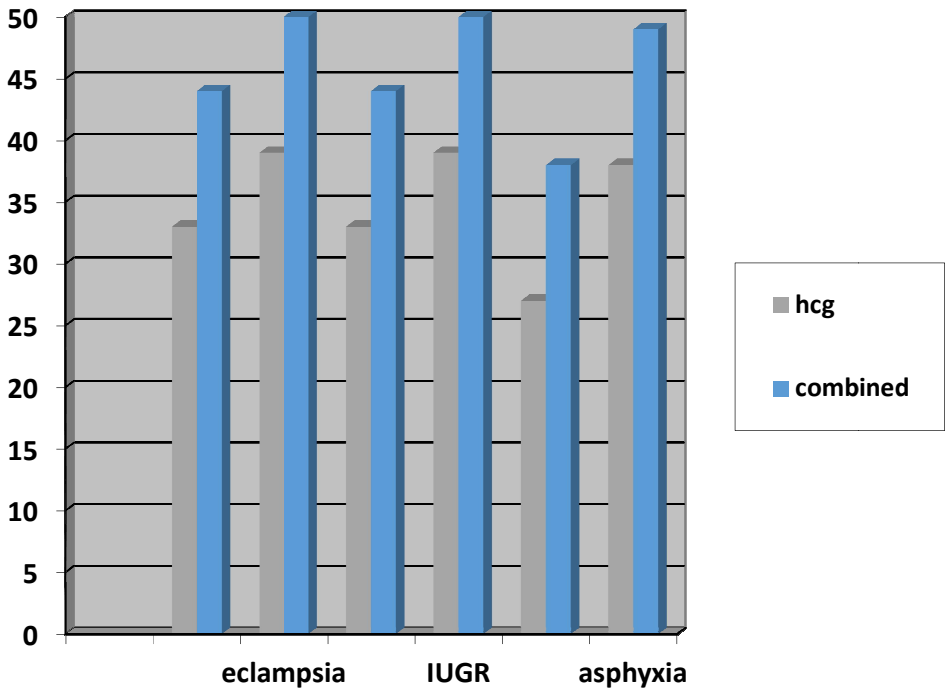

Fig. 1. Bar chart showing the accuracy of serum markers in predicting adverse pregnancy outcome

5. CONCLUSION

Serum β hCG levels remains a useful prognostic indicator for feto-maternal outcome in preeclamptic women. However, combined measure of serum uric acid and serum β hCG level in prognosticating pregnancy outcome in preeclamptic women was shown to have a better accuracy than serum β hCG.

CONSENT AND 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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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