Evaluation Of Uric Acid As A Marker For Maternal And Fetal Outcomes In Nulliparous Women With Pre-Eclampsia At Irrua Specialist Teaching Hospital, Irrua, Edo State

Ohwowhiagbese Ejomafuvwe, Reuben Agbons Eifediyi*, Governor Okome, Mojeed Momoh, Joseph Ikheloa, Joseph Okoeguale and Joseph Eigbefoh

Department of obstetrics and gynaecology, Irrua Specialist Teaching Hospital, Irrua and College of Medicine, Ambrose Alli University, Ekpoma-Nigeria

Abstract: *Background*: Preeclampsia is one of the leading cause of maternal and fetal morbidity and mortality worldwide. The early identification of patients with an increased risk for preeclampsia is therefore one of the most important goals in obstetrics. The availability of highly sensitive and specific physiologic and biochemical markers would allow not only the detection of patients at risk but also permit a close surveillance, an exact diagnosis, timely intervention. Today, several markers may offer the potential to be used, either singly or more preferably in combination analysis, as predictors or diagnostic tools.

Objectives: The aim of the study was to assess the usefulness of uric acid as biochemical marker of maternal, fetal and neonatal outcome in patient with preeclampsia at delivery.

Materials and Methods: This was a prospective case control study involving 82 parturients (forty one (41) with preeclampsia and forty one normotensives) who met the inclusion criteria were recruited into the study. The parturients were categorized based on the presence of gestational hypertension (H), proteinuria (P)and hyperuricemia (U) into four(4) diagnostic criteria/ categories namely presence of both gestational hypertension and proteinuria (HP), presence of gestational hypertention, proteinuria and hyperuricaemia (HPU), presence of hyperuricemia alone (u) and normal values of blood pressure, urinary protein and maternal serum uric acid (NNN).

Results: The study showed that preeclampsia with associated hyperuricaemia was associated with increased small for gestational age (SGA) babies ($p<0.001$), preterm deliveries ($p<0.001$), low birth weight ($p<0.001$) and admission in special care baby unit (SCBU) ($p<0.001$). There were also increased adverse maternal outcomes in this group of patient including increased medically indicated caesarean section ($p<0.001$), maternal seizure ($p<0.001$), thrombocytopenia ($p<0.019$), severe headache ($p<0.001$), proteinuria ($P<0.001$) and visual disturbances ($p<0.046$), in rural Nigerian parturients.

Conclusions: The study revealed that serum uric acid which is simple and inexpensive, should be used in identifying pregnancy with gestational hypertension at risk of infants and maternal complications in Nigeria Sub rural population.

Keywords: Gestational hypertension, proteinuria, hyperuricemia.

1. INTRODUCTION

Hypertensive disorders in pregnancy increases maternal and fetal risk. The greatest impact is associated with the pregnancy-specific syndrome, preeclampsia [1-4].

Pre-eclampsia is a multi-systemic disease characterized by elevated blood pressure of ≥140/90mmHg presenting after 20 weeks of pregnancy with significant proteinuria. Pregnancy induced hypertension (PIH) refers to elevated blood pressure of ≥140/90mmHg after 20 weeks with out significant proteinuria. PIH on its own carries little additional morbidity. Gestational proteinuria is a protein excretion above 300mg per 24hours (equivalent to a protein/creatinine ratio of 30mg/mmol) [4].

The incidence of preeclampsia varies between 3% and 10% of pregnancies and there is no evidence that this has changed appreciably during the last century [1]. It increases perinatal mortality by 5 fold[2] and kills 50, 000 women yearly worldwide [3,4].

Preeclampsia is an important cause of maternal morbidity and mortality as well as a significant contributor to increased perinatal morbidity and mortality rates [5,6,7,8]. It has been shown that babies born by mothers with severe preeclampsia, have a significant reduction in the mean birth weight for gestational age as a result of utero-placental vascular insufficiency which leads to growth restriction as compared with patients with gestational hypertension alone [6]. Early detection and prompt management of patient with proteinuria is therefore beneficial to the patient and fetus.

Elevated uric acid is a common finding in women with of the preeclampsia syndrome which was recognised many years ago [9]. It is one of the most

*Address correspondence to this author at the Department of obstetrics and gynaecology, Irrua Specialist Teaching Hospital, Irrua and College of Medicine, Ambrose Alli University, Ekpoma-Nigeria; E-mail: agbonsgloria@gmail.com

E-ISSN: 2309-4400/17

consistent and earliest detectable changes in preeclampsia and has been cited as a better predictor of fetal risk than blood pressure [9,10]. Despite these findings, uric acid assessment in the evaluation of gestational hypertension has fallen into disfavour. A recent publication stated the utility of measuring serum uric acid levels in hypertensive diseases of pregnancy is limited [10,11]. However, uric acid measurement is performed on regular basis among women with hypertension in pregnancy. The suggestion is to shift from one in which we view uric acid as a simple supportive measure used to confirm the diagnosis of preeclampsia to one in which we appreciate its independent link with adverse outcomes. Preeclampsia remain a condition begging for supportive biological measures linked to the underlying pathophysiology of the disease, and this and other recent studies move us in the right direction toward this goal. Work by Roberts et al is particularly suggestive of the central role of serum uric acid in the pathogenesis and prognosis of preeclampsia.

Robert et al, [12] move beyond the traditional clinical criteria of hypertension and proteinuria by focusing on clinically relevant adverse outcomes, such as small-for-gestational-age infant and preterm delivery. In short, Roberts et al, [12] took uric acid out of the realm of "aiding" in the diagnosis of preeclampsia, which is how serum uric acid has been traditionally viewed, [4] to one in which serum uric acid appears to have an independent link with adverse outcomes. In fact, various studies have increasingly implicated hyperuricaemia with adverse maternal and fetal outcome in preeclampsia as documented above.

Hyperuricemia is a common finding in preeclamptic pregnancies. The elevation of uric acid in preeclamptic women often precedes hypertension and proteinuria [13]. There are several potential origins for uric acid in preeclampsia; abnormal renal function, increased tissue breakdown, acidosis and increased activity of the enzyme xanthine oxidase/dehydrogenase [14]. However, despite hyperuricemia antedating other clinical findings of preeclampsia, it has historically been ascribed to impaired renal function. Outside of pregnancy, hyperuricemia is considered a risk factor for hypertension, cardiovascular and renal disease.

Despite the fact that hyperuricaemia is not a conventionally used diagnostic criterion for preeclampsia and not typically considered a useful aid to management, several observations have suggested that the presence of hyperuricaemia may identify a form of pregnancy hypertension with increased risk.

Redman [15] 25 years ago demonstrated an increased risk of fetal death in preeclampsia with elevated uric acid. Likewise, in another study, there was an increase in small for gestational age among gestationally hypertensive women with proteinuric and nonproteinuric hyperuricaemia. Elevated uric acid has been related to eclamptic seizures [15]. There seems to be a special relationship between the renal lesion of preeclampsia and hyperuricaemia. In a study involving 62 pregnant women with gestational hypertension without proteinuria, the characteristic preeclamptic renal lesion, termed glomeruloendotheliosis, was only present in women with hyperuricaemia [16].

Is it biologically plausible that increased uric acid could be associated with adverse outcome? The hyperuricaemia of preeclampsia has been variably suggested to be associated with lactic acidosis, altered renal function, or oxidative stress [17,18]. The currently favoured concept is that increased circulating uric acid is secondary to reduced renal urate clearance, as can be seen with hypovolaemia. Uric acid is the product of purine catabolism catalyzed 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 expression of the oxidase form increased proportionally with hypoxia. Thus, increased uric acid production occurs in a setting of hypoxia, local acidosis, or increased tissue breakdown or with reduced renal function and can increase oxidative stress-all of which would indicate more severe preeclampsia.

Recent studies provide a potential mechanism to explain why uric acid may be an independent risk factor for small-for-birth-weight infants. Uric acid has recently been shown to reduce endothelial nitric oxide bioavailability and to inhibit endothelial cell proliferation [19-22]. Maternal uric acid passed freely into the placenta [22,23], a rise in uric acid could lead to an inhibition of fetal angiogenesis in the third trimester, which might lead not only to a small infant, but also to the inhibition of kidney growth with a reduction in nephron number [20,21]. A similar association of small-birth-weight infants has been associated with circulating levels of asymmetrical dimethyl arginine, which is another inhibitor of endothelial function [23]. Indeed, there is also accumulating evidence that uric acid may have a potential contributory role in maternal phenotype [24,25], although other factors, including oxidative stress and circulating inhibitors of vascular endothelial growth factor, likely have a more dominant role. In Irrua

Specialist Teching Hospital (ISTH) preeclampsia is an important cause of maternal and perinatal morbidity and mortality. Therefore, the aim of this study was to evaluate uric acid as a marker for adverse fetal and maternal outcome in preeclampsia.

2. STUDY JUSTIFICATION

Despite the fact that hyperuricemia is not a conventionally used diagnostic criterion for preeclampsia and not typically considered a useful aid to management, several observations have suggested that the presence of hyperuricemia may identify a form of pregnancy hypertension with increased risk. Redman 25 years ago demonstrated an increased risk of fetal death in preeclampsia with elevated uric acid. Likewise, in another study, there was an increase in Small for gestational age among gestationally hypertensive women with proteinuric and nonproteinuric hyperuricemia. Elevated uric acid has been related to eclamptic seizures. The duration of hypertension after a hypertensive pregnancy was similar in women with hypertension and either hyperuricemia or proteinuria and longer than in women with gestational hypertension alone. There seems to be a special interrelationship between the renal lesion of preeclampsia and hyperuricemia.

The hyperuricemia of preeclampsia has been variably suggested to be associated with lactic acidosis, altered renal function, or oxidative stress. The currently favored concept is that increased circulating uric acid is secondary to reduced renal urate clearance, as can be seen with hypovolemia.

An important question yet to be resolved is whether, as is suggested by various authors, the adverse outcomes are only present with concomitantly increased uric. This study therefore sought to evaluate maternal serum level of uric acid as a predictor of severity of preeclampsia in nulliparous parturients at delivery as evidenced by poor fetal and maternal outcome in established preeclampsia.

3. MATERIALS AND METHODS

3.1. Study Design

This was a prospective case control study.

3.2. Control

Normal healthy pregnant women without preeclampsia.

3.3. Study Setting

The study was conducted in the obstetric unit of Irrua Specialist Teaching Hospital, Irrua Edo state. It is a tertiary care hospital and a referral centre for parts of Edo, Delta, Kogi and Ondo states. The hospital has 48 obstetrics beds and 42 gynaecological beds and undertakes an average of 1200 deliveries per year.

3.4. Case/Sample Size

The sample size for comparing proportion was calculated using D.W Taylor sample size calculation formula based on the incidence of preeclampsia of 5% of all pregnancies and a confidence level of 95%, which gave a sample size was 41 respondents.

3.5. Study Population/Enrollment Size

Study population was eighty two, with 41 cases of nulliparous women with singleton pregnancies complicated by preeclampsia at delivery and had live birth but with no other obstetric or medical conditions and 41 controls (of normal healthy nulliparous women with singleton pregnancies without preeclampsia at delivery and all had live birth) also at delivery. Sociodemographic and clinical data were ascertained by researcher administered interview at the entry to the study –labour suite and medical chart abstraction after delivery.

3.6. Inclusion Criteria

Eligibility criteria were nulliparous women with singleton gestations that had preeclampsia irrespective of her age, gravidity, and gestational age who presented in labour suite with live fetuses within the study period.

3.7. Exclusion Criteria

All chronic hypertensive, multipara, multiple gestation, chronic renal disease patients, diabetics and maternal ingestion of drugs known to increase or decrease maternal serum uric acid level will be excluded from the study.

3.8. Procedure

Patients were consecutively recruited from labour ward admission, emergency unit of the department, referral from peripheral hospitals. Blood pressure readings were taken using the indirect auscultatory technique with a trained observer with appropriately sizeable cuff (the width of cuff should occupied 2/3 of

the arm measured from the axilla to the antecubital fossa) mercury sphygmomanometer with the patient in the sitting position with the cuff at the level of the heart. The blood pressure readings were usually taken after hospital admission for delivery but before medications or clinical perturbations would alter blood pressure. Phase 1(onset) and phase 5(disappearance) of Korotkoff sound was used for systolic and diastolic respectively.

Three millilitre (3ml) of venous blood sample was taken in a plain bottle under aseptic condition for measurement of maternal serum uric acid level by the uricase colorimetric method after having obtained consent from the patients. Urine was tested for protein with dipstick. Other information concerning the patients were retrieved from the researcher administered proforma questionnaire at the time of admission into the labour ward, antenatal cards, labour ward theatre records and patient casenotes and special baby care unit recordings of the hospital. Maternal and fetal outcome of the cases and controls were correlated with maternal serum uric acid levels.

3.9. Determination of Serum Uric Acid Using the Uricase Enzymatic Colorimetric[211] Method Principle

Uric acid is converted by uricase to allantoin and hydrogen peroxide, which under the catalytic influence of peroxidase, oxidizes 3, 5-Dichloro-2-hydroxybenzenesulfonic acid and 4-aminophenazone to form a red-violet quinoneimine compound.

$$Uric\ acid\ +\ O_2 + 2H_2O \rightarrow^{uricase} Allantoin + CO_{2+} H_2O_{2+} 2H_2O_{2\ +} 3,5-dichloro$$
$$-2-hydroxybenzensulfonic\ acid\ +\ 4-aminophenazone \rightarrow^{peroxidase} N$$
$$-(4-antipyryl)-3-chloro-5-sulfonate-p-benzo-quinoneimine$$

3.10. Procedure

Using fresh dd H_20 perform a new Gain Calibration in cuvette mode. Select UA (uric acid) in the Run Test screen and carry out water blank as instructed.

Pipette into a Cuvette:			
	Reagent Blank SO	**Standard S1**	**Sample**
Dd H_2O	-	-	-
Stand	-	10µl	-
Sample	-	-	10µl
Reage	500µl	500µl	500µl

Mix, incubate for 15min at 20-25^{0}c or 5min at 35^{0}c. Insert into the Monza flowcell holder and press Read within 30mins.

3.11. Calibration for RX Monza

Recommended with change of reagent lot or as indicated by quality control procedure, using CAL standard provided in kit or Randox Calibration Serum level 3.

3.12. For Manual Use

Wavelength:	520nm	Hg 546nm
Cuvette:	1cm light path	
Reaction Temperature:	20-25^{o}c/37^{o}c	
Measurement:	Against reagent blank only one reagent blank per	
	Series is required	

3.13. Pipette into Test Tubes

Reagent Blank (µl)	**Sample (µl)**	**Standard (µl)**	
Sample	-	20	-
Standard (CAL)	-	-	20
Reagent (R1)	1000	1000	1000

Mix, incubate for 15 minutes at 20-25^{0}c, or for 5minutes at 37^{0}c. Measure absorbance of Sample (A_{sample}) and standard ($A_{standard}$) against reagent blank within 30 minutes.

4. MANUAL CALCULATION

4.1. Using a Standard

Serum or plasma

Uric acid concentration= standard conc. X Asample/$A_{Standard\ (µmol/l)}$

Uric acid concentration=standard conc. X Asample/$A_{Standard}$ (mg/dl)

Normal Value: Serum[212]: Women 142-339µmol/l or2.4-5.7mg/dl

5. LIMITATIONS OF THE STUDY

The study was hospital based study. Even though the majority of the women in Nigeria prefer to give birth

in hospitals, there could probably be preeclamptic women who had given birth at home during the study period. Thus not included in the study.

Twenty four hour urinary protein was not collected in most cases. This has been shown to be more accurate in accessing degree of proteinuria.

The study had a small sample size, which may have limited it ability to examine rare events.

Data came from a single centre, which might limit generalizability of the results.

The use of combined biochemical markers had also been shown to be more predictive of severity of preeclampsia. This study however used single marker of severity.

The study was limited to nulliparous women with singleton pregnancies

6. ETHICAL CONSIDERATIONS

Approval for the study was obtained from the ethical committee of the Irrua Specialist Teaching Hospital. Ethical considerations in this study were based on the general ethical principles as applicable to human subjects. These were confidentiality, beneficence, non-malficience and justice.

7. DATA ANALYSIS

Data was analyzed using SPSS (statistical program for social sciences) version16.0 and was presented in statements, frequency tables and figures. Quantitative variables were summarized into the means and standard deviation. Test of significance such as the Chi-squared test and the one way analysis of variance were used as appropriate with the level of significance set at $p < 0.05$.

8. RESULTS

A total of 82 pregnant women were recruited for this study. Forty one (41) women were diagnosed to have preeclampsia and forty one (41) were normotensive. These pregnant women were categorized based on the presence of gestational hypertension (H), proteinuria (P) and hyperuricaemia (U) into four (4) diagnostic criteria/categories namely.

- Presence of both gestational hypertension and proteinuria (HP).
- Presence of combination of gestational hypertension, proteinuria and hyperuricaemia (HPU).
- Presence of hyperuricaemia alone (U).
- Normal values of blood pressure, urinary protein and maternal serum uric acid (NNN).

Table 1: Sociodemographic Factors by Maternal Diagnostic Categories

		HP(N=9)	HPU(N=32)	U(N=5)	NNN(N=36)	P VALUE
Age	**18 – 20**	1(11.1)	1(3.1)	0(0.0)	4(11.1)	χ^2=6.435 p =0.696 df =9
	21 - 24	0(0.0)	5(15.6)	1(20.0)	5(13.9)	
	25 – 28	4(44.4)	10(31.3)	3(60.0)	15(41.7)	
	29 – 33	4(44.4)	16(50.0)	1(20.0)	12(33.3)	
Gravidity	**1**	2 (22.2)	7 (21.9)	0 (0.0)	14 (38.9)	χ^2=6.360 p =0.384 df=6
	2 – 4	6 (66.6)	21 (65.0)	5(100)	20 (55.6)	
	5	1(11.1)	4 (12.5)	0 (0.0)	2 (5.6)	
Occupation	**Skilled**	2(22.2)	7(21.9)	3(60.0)	12(33.3)	χ^2=13.501 p=0.144 df=9
	Unskilled	4(44.4)	13(40.6)	1(20.0)	14(38.9)	
	Unemployed	3(11.1)	10(31.3)	1(20.0)	3(8.3)	
	Others	2(22.2)	2(6.3)	0(0.0)	7(19.4)	
Level of education	**Primary**	1 (11.1)	4 (12.5)	0 (0.0)	7(19.4)	χ^2=13.501 p=0.012 df=6
	Secondary	0 (0.0)	15 (46.9)	4 (80.0)	10(27.8)	
	Tertiary	8 (88.9)	13 (40.6)	1 (20.0)	19(52.8)	
Marital status	**Married**	9(100)	29(90.6)	5(100)	35(97.2)	χ^2=2.455 p=0.484 df=3
	Unmarried	0(0.0)	3(9.4)	0(0.0)	1(2.8)	

There was a statistically significant difference between level of education and maternal categories (p=0.012) in table **1** above.

These categorization followed determination of maternal sociodemographic biodata, blood pressure and dipstick urinary protein recordings and laboratory maternal serum uric acid at admission into labour ward. Haematological investigations were also carried out and other information was extracted from the proforma questionnaire, patient casenotes and neonatologist documentations at delivery.

Table **1** Showed the sociodemographic factors by maternal diagnostic category. The age of the study group ranged from 17 to 33 years with mean age 27.28±0.43 years. Of the 41cases, 32(78%) had gestational hypertension, proteinuria, and HPU, 16 (50%) of which were of the age 29-33 years. Only level of maternal education was shown to have statistical significant different with maternal diagnostic category.

Table **2** Showed the risk factors for preeclampsia. Risk factors such as family history of preeclampsia, season of the year, obesity and presentation at less than or greater than 7 months did not show any significant statistical different in the various maternal diagnostic categories. However, there were statistical significant differences between the mean systolic and diastolic blood pressures in the various maternal diagnostic categories of 0.0001 and 0.001 respectively. Those who had gestational hypertension, proteinuria and HPU. HPU tend to have higher mean systolic and diastolic blood pressures than those with gestational hypertension and proteinuria HP (preeclampsia) and even greater than those with hyperuricaemia alone. In other words, an addition of hyperuricaemia to the conventional definition of preeclampsia could define a subset of high risk gestational hypertensive.

Table **3** Showed severity criteria for preeclampsia in different maternal categories there was statistically significant association between maternal categories and the level of proteinuria ($p<0.001$). A significant association was observed between maternal categories and: presence of headache ($p<0.001$), occurrence of seizure ($p<0.001$). There was no association between maternal diagnostic categories and excessive weight gain ($p=0.058$) and visual disturbance ($p=0.182$).

Table **4** Showed the relationship between fetal and maternal outcomes and maternal diagnostic categories. It also showed the relationship between uric acid and booking status and diagnostic maternal categories. There was a significant statistical association between maternal categories and; uric acid levels ($p<0.001$), booking status ($p<0.001$), fetal outcome ($p<0.001$), maternal outcome ($p<0.001$) respectively.

Studied maternal outcomes considered to be poor included: eclampsia, caesarean section rate, bleeding from punctured sites (DIC), maternal mortality, severe

Table 2: Risk Factors for Pre Eclampsia

		HP(N=9)	HPU(N=32)	U(N=5)	NNN(N=36)	SIG.
Family History of Pre-eclampsia						
	Yes	2(22.2)	3(9.4)	0(0.0)	3(8.3)	χ^2=2.217
	No	7(77.8)	29(90.6)	5(100)	33(91.7)	p =0.529 df =3
Obesity	**Yes**	2(22.2)	8(25.0)	1(20.0)	2 (5.6)	χ^2=5.207
	No	7(77.8)	24(75.0)	4(80.0)	34(94.4)	p =0.157 df =3
G.A >7months	**Yes**	9(100)	31(96.9)	4(80.0)	36(100)	χ^2=7.668
	No	0(0.0)	1(3.1)	1(20.0)	0(0.0)	p=0.053 df =3
Season	**Wet**	5(55.6)	18(56.2)	5(100)	25(69.4)	χ^2=4.409
	Dry	4(44.4)	14(43.8)	0(0.0)	11(30.6)	p=0.221 df=3
Mean BP						ANOVA
(mmHg)	**Systolic**	165.56	185.31	124.00	114.17	P < 0.0001
	Diastolic	105.56	115.31	78.00	72.78	p <0.001

Table **2** The analysis of variance (ANOVA) carried out between the various maternal categories showed that there was a statistically significant difference in mean systolic blood pressure derived from the various maternal diagnostic categories ($P < 0.001$). There was also a significant statistical difference between mean diastolic blood pressure in the various maternal categories ($P=0.001$). The relationship between gestational age and maternal categories was not statistically significant ($P=0.053$).

Table 3: Severity Criteria for Pre Eclampsia in Different Maternal Categories

		HP(N=9)	HPU(N=32)	U(N=5)	NNN(N=36)	SIG.
Level of Proteinuria						
	Nil	0(0.0)	0(0.0)	2(40.0)	33(91.7)	χ^2=128.88 p <0.001 df= 12
	Trace	0(0.0)	0(0.0)	1(20.0)	3(8.3)	
	++	8(88.9)	6(18.8)	2(40.0)	0(0.0)	
	+++	1(11.1)	14(43.8)	0(0.0)	0(0.0)	
	++++	0(0.0)	12(37.5)	0(0.0)	0(0.0)	
Headache	**Yes**	3(33.3)	21(65.6)	0(0.0)	3(8.3)	χ^2=27.806 p <0.001 df=3
	No	6(66.7)	11(34.4)	5(100)	33(91.7)	
Visual Disturbance	**Yes**	0(0.0)	3(9.4)	0(0.0)	0(0.0)	χ^2=4.866 p=0.182 df=3
	No	9(100)	29(90.6)	5(100)	36(100)	
Vaginal Bleeding	**Yes**	1(11.1)	4(12.5)	0(0.0)	2(5.6)	χ^2=1.597 P=0.660 df=3
	No	8(88.9)	28(87.5)	5(100)	34(94.4)	
Excessive Weight Gain	**Yes**	1(11.1)	5(15.6)	2(40.0)	1(2.8)	χ^2=7.495 p=0.058 df=3
	No	8(88.9)	27(84.4)	3(60.0)	35(97.2)	
Previous admission	**Yes**	2(22.2)	5(15.6)	0(0.0)	5(13.9)	χ^2=1.313 p=0.726 df=3
	No	7(77.8)	27(84.4)	5(100)	31(86.1)	
Seizure	**Yes**	0(0.0)	12(37.5)	0(0.0)	0(0.0)	χ^2=21.964 p<0.001 df=3
	No	9(100)	20(62.5)	5(100)	36(100)	

There was a statistically significant association between maternal categories and the level of proteinuria (p <0.001). A significant association was observed between maternal categories and; presence of headache (p <0.001), occurrence of seizure (p <0.001). There was no association between maternal diagnostic categories and excessive weight gain (p = 0.058).

Tables 4: Relationship between Uric Acid Levels and Maternal Categories

		MATERNAL CATEGORIES					
		HP	**HPU**	**U**	**NNN**	**TOTAL**	**SIG.**
Uric acid levels	**Normal**	9(19.6)	0(0.0)	1(2.2)	36(78.3)	46(100)	χ^2=78.75 p <0.001 df=3
	Elevated	0(0.0)	32(88.9)	4(11.1)	0(0.0)	36(100)	
	Total	9(10.9)	32(39.1)	5(6.1)	36(43.9)	82(100)	

There was a statistically significant association between uric acid levels and maternal diagnostic categories (p <0.001).

headache and visual disturbance, placental abruption, admission into ICU and duration of hospital stay.

Studied fetal outcome considered to be poor included: medically indicated prematurity, Apgar score in 5 minutes less than 7, small for gestational age (SGA), respiratory distress syndrome, low birth weight, SCBU admission, hypoglycaemia, presumed neonatal sepsis, duration of hospital stay.

There was statistically significant association between maternal outcome and maternal diagnostic categories (p<0.001). There was also statistically significant association between fetal outcome and maternal categories (p<0.001).

Table **4** also Showed the relationship between uric acid levels and maternal categories. The normal serum uric acid level ranged between 2.4-5.7mg/dl and any level above 5.7mg/dl was regarded elevated. The mean

Table 5: Relationship between Uric Acid Levels and Level of Proteinuria

		LEVEL OF PROTEINURIA						
		0	TRACE	++	+++	++++	TOTAL	SIG.
URIC ACID LEVELS	NORMAL	33(71.7)	3(6.5)	9(19.7)	1(2.2)	0(0.0)	46(100)	χ^2=51.521 p <0.001 df=4
	ELEVATED	2(5.5)	1(2.8)	7(19.4)	14(38.9)	12(33.3)	36(100)	
	TOTAL	35(42.7)	4(4.9)	16(19.5)	15(18.2)	12(14.6)	82(100)	

There was a statistically significant relationship between uric acid level and level of proteinuria (p<0.001).

Table 6: Relationship between Uric Acid Levels and Mode of Delivery

		Mode Of Delivery							
		Svd Term	C.s Term	Svd Preterm	C.s Preterm	Failed Induction Emcs Preterm	Failed Induction Emcs Term	Total	Sig.
Uric Acid Levels	Normal	36(78.3)	1(2.2)	2(4.3)	0(0.0)	1(2.2)	6(13.0)	46(100)	χ^2=37.568 p < 0.001 df=5
	Elevated	6(16.6)	4(11.1)	4(11.1)	14(38.9)	2(5.6)	6(16.7)	36(100)	
	Total	42(51.2)	5(6.1)	6(7.3)	14(17.1)	3(3.7)	12(14.6)	82(100)	

There was a statistically significant association between uric acid level and mode of delivery (p < 0.001).

uric acid levels in the maternal categories were 9.09±0.47, 4.19±0.27, 6.06±0.57, 4.18±0.12 for HPU, HP, U and NNN respectively. There was a statistically significant association between uric acid levels and maternal categories (p<0.001).

Table **5** Showed the relationship between uric acid levels and the levels of proteinuria. There was a statistically significant relationship between uric acid levels and levels of proteinuria (p< 0.001). As the levels of proteinuria increased so did the chance of hyperuricaemia in maternal serum.

Table **6** Showed the relationship between uric acid levels and modes of delivery. There was a statistically significant association between uric acid levels and modes of delivery (p< 0.001). 36 women had elevated uric acid of which 16(44.5%) had medically indicated preterm caesarean section and 10 also had caesarean section though term making a total of (72.2%) of patient with elevated uric acid.

We had 2 patients, not shown, admitted into ICU and one died. Autopsy was however not carried out because relations vehemently refused.

Table **7** Showed the relationship between uric acid levels and presence of severity criteria for preeclampsia/ complications/poor maternal outcomes. There was a statistically significant association between uric acid levels and the presence of visual disturbance (p<0.001), severe headache (p<0.001), proteinuria (p< 0.001), occurrence of seizure (p< 0.001) and thrombocytopenia (p<0.019).

Table **8** showed the gross relationship between maternal uric levels and fetal and maternal outcomes. There were statistically significant relationship between uric acid levels and fetal and maternal outcomes which were (p< 0.001) and (p< 0.001) respectively.

Table **9** Showed the relationship between uric acid levels and the specific poor fetal outcomes:

The relationship between uric acid levels and admission into SCBU was statistically significant (p< 0.001).

The relationship between uric acid levels and small for gestational age was statistically significant (p< 0.001).

Table 7: Relationship between Uric Acid Levels and Presence of Severity Criteria for Preeclampsia/Complications/Maternal Outcomes

	URIC ACID LEVELS			
		NORMAL	ELEVATED	TOTAL
HEADACHE	YES	6(13.0)	21(58.3)	27(32.9)
	NO	40(87.0)	15(41.7)	55(67.1)
	TOTAL	46(100)	36(100)	82(100)
	SIG.	χ^2=18.76	p<0.001	df=1
	URIC ACID LEVELS			
		NORMAL	ELEVATED	TOTAL
PLATELET COUNT	NORMAL	45(97.8)	30(83.3)	75(91.5)
	THROMB	1(0.2)	6(16.7)	7(8.5)
	TOTAL	46(100)	36(100)	82(100)
	SIG.	χ^2=5.43	p<0.019	df=1
	URIC ACID LEVELS			
		NORMAL	ELEVATED	TOTAL
MODE OF DELIVERY	SVD	38(82.6)	10(27.8)	48(58.5)
	C.S	8(17.4)	26(72.2)	34(41.5)
	TOTAL	46(100)	36(100)	82(100)
	SIG.	χ^2=25.02	p<0.001	df=1
	URIC ACID LEVELS			
		NORMAL	ELEVATED	TOTAL
VISUAL DISTURBANCE	YES	0(0.0)	3(8.3)	3(3.7)
	NO	46(100)	33(91.6)	79(96.5)
	TOTAL	46(100)	36(100)	82(100)
	SIG.	χ^2=0.54	p<0.460	df=1
	URIC ACID LEVELS			
		NORMAL	ELEVATED	TOTAL
VAGINAL/BLEEDING FROM PUNCTURE SITES	YES	3(6.5)	4(11.1)	7(8.5)
	NO	43(93.5)	32(88.9)	75(91.5)
	TOTAL	46(100)	36(100)	82(100)
	SIG.	χ^2=0.54	p<0.460	df=1
	URIC ACID LEVELS			
		NORMAL	ELEVATED	TOTAL
SEIZURE	YES	0(0.0)	12(33.3)	46(100)
	NO	46(100)	24(66.6)	36(100)
	TOTAL	46(100)	70(85.4)	82(100)
	SIG.	χ^2=17.96	p<0.001	82(100)

There was a significant statistical association between uric acid levels and presence of visual disturbance (P=0.046). There was also a significant statistical relationship between uric acid levels and occurrence of seizure (P<0.001).

Table 8: Relationship between Uric Acid Levels and Maternal Outcome

	URIC ACID LEVELS			
		NORMAL	ELEVATED	TOTAL
MATERNAL OUTCOME	GOOD	38(82.6)	11(30.6)	49(59.8)
	POOR	8(17.4)	25(69.4)	33(40.2)
	TOTAL	46(100)	36(100)	82(100)
	SIG.	χ^2=22.75	p<0.001	df=1

There was a statistically significant relationship between uric acid levels and maternal outcome (P<0.001).

Table 9: Relationship between Uric Acid Levels and Fetal Outcome

		Uric Acid Levels		
		Normal	**Elevated**	**Total**
Admission to Scbu*	**Yes**	4(8.7)	17(47.2)	21(25.6)
	No	42(91.3)	19(52.8)	61(74.4)
	Total	46(100)	36(100)	82(100)
	Sig.	X^2=15.73	P<0.001	Df=1
		Uric Acid Levels		
		Normal	**Elevated**	**Total**
Small for Gestational Age	**Yes**	2(4.3)	14(38.8)	16(19.5)
	No	44(95.7)	22(61.1)	66(80.5)
	Total	46(100)	36(100)	
	Sig.	X^2=15.34	P<0.001	Df=1

Table 10: Relationship Between Maternal Uric Acid Levels And Fetal Outcomes

		Uric Acid Levels		
		Normal	**Elevated**	**Total**
Preterm	**Yes**	3(6.5)	20(55.6)	23(28.0)
	No	43(93.5.)	16(44.4)	59(72.0)
	Total	46(100)	36(100)	82(100)
	Sig	χ^2=22.75	p<0.001	DF=1
		Uric Acid Levels		
		Normal	**Elevated**	**Total**
Gestational Age at Delivery	**28-32wk**	0(0.0)	11(30.6)	49(59.8)
	32-34wks	1(2.2)	25(69.4)	33(40.2)
	34-37wks	2(4.3)	9(25.0)	11(13.4)
	>37wks	43(93.5)	15(41.7)	58(70.7)
	Total	46(100)	36(100)	82(100)
	Sig	χ^2=22.75	P<0.001	DF=1
		Uric Acid Levels		
		Normal	**Elevated**	**Total**
Preterm	**Yes**	3(6.5)	20(55.6)	23(28.0)
	No	43(93.5.)	16(44.4)	59(72.0)
	Total	46(100)	36(100)	82(100)
	Sig	χ^2=22.75	p<0.001	DF=1
		Uric Acid Levels		
		Normal	**Elevated**	**Total**
Gestational Age at Delivery	**28-32wk**	0(0.0)	11(30.6)	49(59.8)
	32-34wks	1(2.2)	25(69.4)	33(40.2)
	34-37wks	2(4.3)	9(25.0)	11(13.4)
	>37wks	43(93.5)	15(41.7)	58(70.7)
	Total	46(100)	36(100)	82(100)
	Sig	χ^2=22.75	P<0.001	DF=1

	Uric Acid Levels			
		Normal	**Elevated**	**Total**
Birth Weight(kg)	**VLBW**	1(2.2)	7(19.4)	8(9.8)
	LBW	1(2.2)	15(41.7)	16(19.5)
	NBW	43(93.5)	13(36.1)	56(68.3)
	HBW	1(2.2)	1(2.8)	2(2.4)
	Total	46(100)	36(100)	82(100)
	Sig	χ^2=32.08	P<0.001	DF=3
	Uric Acid Levels			
		Normal	**Elevated**	**Total**
5min Apgar Score	**<3**	0(0.0)	2(5.6)	2(2.4)
	3-6	2(4.3)	3(8.3)	5(6.1)
	≥7	44(95.7)	31(86.1)	75(91.5)
	Total	46(100)	36(100)	82(100)
	Sig	χ^2=3.283	P<0.194	DF=2

*Special baby care unit.

The relationship between uric acid levels and admission into SCBU was statistically significant.

The relationship between uric acid levels and getational age at admission into labour ward was statistically significant (p<0.001).

The relationship between uric acid levels and preterm delivery was statistically significant (p<0.001).

The relationship between uric acid levels and birth weight was statistically significant (p<0.001).

The relationship between uric acid levels and Apgar score in 5 minutes was however not statistically significant (p<0.194).

The relationship between mean maternal serum uric and maternal diagnostic categories was statistically significant (p<0.0001). The mean maternal serum uric acid was highest in the presence of preeclampsia and hyperuricaemia (HPU) (9.09±0.47 mg/dl) followed by isolated hyperuricaemia (U) (6.06±0.59mg/dl) and preeclampsia (HP) (4.19±0.27mg/dl).

The relationship between mean maternal systolic blood pressure and maternal categories was statistically significant (p<0.0001). The mean systolic blood pressure was highest in the presence of preeclampsia and hyperuricaemia (HPU) (185.31±4.31mmHg) followed by preeclampsia (HP) (165.56±2.94mmHg) and isolated hyperuricaemia (U) (124.00±2.45mmHg).

The relationship between mean gestational age at presentation in labour ward and maternal categories was statistically significant (p<0.001). The mean gestational age at presentation in labour ward is lowest in the presence of preeclampsia and hyperuricaemia (HPU) (249.97±3.72days=35wks+5days) followed by isolated hyperuricaemia (U) (258.20±8.27days=36wks +6days), preeclampsia (HP) (271.78±3.81days=38wks+ 6days) and normal patient (NNN) (39wks+2days).

The relationship between mean birth weight of the babies and maternal categories was statistically significant (p<0.0001). The mean birth weight was lowest in the presence of preeclampsia and hyperuricaemia (HPU) (2.15±0.16 kg) followed by isolated hyperuricaemia (U) (2.22±0.63kg), preeclampsia (HP) (3.03±0.13kg) and normal patients (NNN) (3.15±0.07). Figure **1**

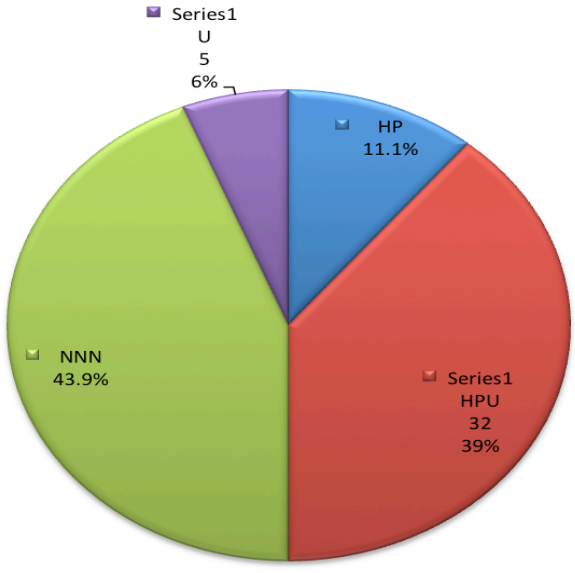

Figure 1: Distribution of subjects by maternal categories.

9. DISCUSSION

Hypertensive disorders in pregnancy increase maternal and fetal risk. The incidence of preeclampsia in this study was 7.6%. This is comparable to incidence in other parts of Nigeria[18] which was quoted to range between 2% to 16.7%. In this study preeclampsia accounted for 4.3% of preterm birth, However, Goldenberg RL and colleagues quoted 15%.

The diagnostic criteria currently used to differenciate high-risk from lower risk women with gestational hypertension are arbitrary. Hence the question: will an addition of maternal serum uric acid to the already established diagnostic classification identify a subset of getational hypertensive with increased maternal and fetal risk outcomes?

In this study 41 preeclamptic patients were compared with 41 normotensive pregnant women. Hyperuricaemia was defined as maternal serum uric acid greater than 5.7mg/dl (340µmol/l). The normal maternal serum uric acid, from reagent used (RANDOX), range from 2.4-5.7mg/dl. Other studies have used various cut off values [24-28].

The age of the studied population ranged from 17 to 33 years with the mean age of 27.28±0.43 years. Of the 41 cases, 32 (78%) had gestational hypertension, proteinuria and hyperuricaemia HPU, 16(50%) of which were of the age 29-33 years. Among the risk factors for preeclampsia which include primigravida, extreme of reproductive age, obesity, unbooked status, unmarried status, family history of preeclampsia, poor socio-economic class, wet season of the year, etc, only level of maternal education was validated to have statistical significant different with maternal diagnostic categories in this study. The reason for this was probably that most patients who had 2-4 previous premarital pregnancy terminations entered into new relationship different from their premarital partners and pregnancy resulted almost immediately following marriage making the pregnancy to behave as primigravida. The results presented indicated that women with preeclampsia with elevated maternal serum uric acid concentration identified a group of hypertensive pregnancies at increased risk for small for gestational age (SGA)($p<0.001$), preterm delivery($p<0.001$), low birth weight($p<0.003$) and admission into special care baby unit (SCBU)($p<0.001$) compared with isolated preeclampsia (HP) or hyperuricaemia (U) or normal maternal blood pressure, urinary protein, and maternal serum uric acid (NNN). It was however not statistically significant with fetal birth asphyxia($p=0.087$). The increased incidence of preterm delivery in the study in most instances reflected the severity of the disease rather than natural history because most early deliveries with preeclampsia were medically indicated preterm inductions and or caesarean section birth. This was similarly reported by Robert JM and colleagues [12].

The relationship of maternal serum uric acid to gestational age at delivery and birth weight in women with preeclampsia is concentration dependent after the cutoff value of uric acid is exceeded. In the presence of preeclampsia, the incidence of preterm delivery and admission into SCBU increased as maternal serum uric acid concentration reach and exceed the cutoff value for uric acid. A similar linear trend was seen for the incidence of SGA among women with isolated hyperuricaemia.

The mean gestational age at presentation in labour ward is lowest in the presence of preeclampsia with maternal hyperuricaemia (35wks+5days) followed by isolated hyperuricaemia (36wks+6days) and preeclampsia (38wks+6day). This is surprising as isolated hyperuricaemia had greater adverse effect on gestational age at delivery than isolated preeclampsia itself. However, most isolated hyperuricaemia were not diagnosed until patient entered into labour and were incidental findings in this study since they were recruited as apparently healthy women. The higher gestational age at presentation of the preeclamptic patients may be due to late onset of presentation in this studied population.

The mean birth weight was lowest in the presence of preeclampsia with hyperuricaemia (2.15±0.16kg) followed by isolated hyperuricaemia (2.22±0.63kg), preeclampsia (3.03±0.13kg) and normal patients (3.15±0.07kg). This is in support of the established adverse effects of hyperuricaemia on the growth of the fetus either when present in isolation or in the presence of hyperuricaemia with preeclampsia as in this study. This is in keeping with results of similar study by Srinivas SK and colleagues [29] who found that there is a linear relationship between maternal serum uric acid beyond the cut off value of serum uric acid concentration and fetal adverse outcomes.

Most studies focused on fetal outcomes which have been well substantiated. The mean maternal uric acid was highest in the presence of preeclampsia with hyperuricaemia (9.09±0.47mg/dl) followed by isolated hyperuricaemia (6.06±0.59mg/dl), preeclampsia

(4.19±0.27mg/dl) and normal pregnancy (4.18±0.12mg/dl). The mean systolic and diastolic blood pressures were highest in the preeclampsia with hyperuricaemia than other maternal diagnostic categories. Generally, as the degree of proteinuria increases so also was an increasing presence of preeclampsia with hyperuricaemia and less chance of isolated hyperuricaemia. This was in keeping with similar study by Robert JM and colleague [12]. Severe headaches were more likely to be complaint of if when there were presence of preeclampsia with hyperuricaemia and the relationship between severe headache and maternal serum uric acid was statistically significant ($p<0.001$). Preeclampsia with hyperuricaemia was more likely to present with seizures. The presence of thrombocytopenia and the degree of severity correlated with presence and degree of severity of hyperuricaemia coexisting with preeclampsia.

Preeclampsia with hyperuricaemia was also associated with increased caesarean section rate in this study mostly due to medically indicated caesarean section for severe preeclampsia with unfavourable cervix. These findings were also collaborated in a similar study by Robert JM and collegues [27]. In a study by Yassaee, the patients were grouped into 2 with maternal serum uric acid cutoff of 6mg/dl was use for normal and elevated maternal uric levels respectively.

There were obvious limitations to this study. Twenty four hour urine collections for the determination of proteinuria were performed on only a small percentage of women. It is well recognized that with the hectic protein excretion of preeclampsia, random urines with negative findings can be associated with increased protein excretion [5]. This could have made us to exclude such women from the study.

The limited time for the study and the size of the studied population may have also reduced the power of the results.

Although women in this study population were socioeconomically diverse, the study was limited to one race and a single centre which may have limitation in generalizability of the results.

RECOMMENDATION AND CONCLUSION

What are the clinical implications of these findings? Based on the limitations of our design, it is important that the relationship we observed are examined prospectively and tests performed to determine whether management based on this additional information positively and cost effectively affects outcomes.

It does appear that serum uric acid- a simple, inexpensive and readily available test- should be additionally evaluated using multi-racial and multicentre prospective case-control study.

Our data suggest that uric acid is at least as important as proteinuria in identifying pregnancies with gestational hypertension with at-risk infants and maternal complications. Although currently available data support the concept that gestational hypertension without proteinuria has an outcome far better than when the hypertension is accompanied by proteinuria, there is still evidence of increased risk. An important question to resolve is whether, as is suggested by our data, the adverse fetal and maternal outcomes are only present with concomitantly increased maternal serum uric acid.

Finally, this finding encourages a reevaluation of the current classification of pregnancy hypertension using different markers of pathophysiology. The research implications are more direct. Including uric acid in the research diagnosis of preeclampsia identifies a more severe group that is likely to have a more homogeneous pathophysiology than when this marker is not included.

REFERENCES

[1] Hubel CA. Oxidative Stress in the Pathogenesis of Preeclampsia. Proc Soc exp biol med 1999; 222: 222-235. https://doi.org/10.1046/j.1525-1373.1999.d01-139.x

[2] Roberts JM. Pregnancy related hypertension. In: Creasy RK, Resnik R, eds. Maternal Fetal Medicine. 4th Ed. Philadelphia, PA: W.B. Saunders 1998: 833-872.

[3] Duley L. Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. Br J Obstet Gynaecol 1992; 99: 547-553. https://doi.org/10.1111/j.1471-0528.1992.tb13818.x

[4] Jason JS and Maria CS. Hypertensive disorders in pregnancy in Dewhurst's Textbook of Obstetrics & Gynaecology, eighth edition. Edited by D. Keith Edmond s. © 2012 John Wiley and Sons, Ltd. pp 101-109

[5] Helewa ME, Burrows RF, Smith J, Williams K, Brain P, Rabkin SW. Report of the Canadian Hypertension Society Consensus Conference: Definitions, evaluation and classification of hypertensive disorders in pregnancy. Can Med Assoc J 1997; 157: 715-725.

[6] Alicia ML. Effects of preeclampsia on mother, fetus and child in Obgyn.net 2010.

[7] Odum CU, Akinkugbe A. The cause of maternal deaths in eclampsia in Lagos, Nigeria.West Afr J Med 1991; 10: 371-6.

[8] Audu L R, Ekele BA. A ten year review of maternal mortality in sokoto, Northern Nigeria. West Afr J Med 2002; 21: 74-6.

[9] Wallenbury HCS. Detecting Hypertensive Disorders of Pregnancy in: Chalmers I, Enkin M, Kileirse MJNC, Eds. Effective care In: Pregnancy And Childbirth. Oxford University Press 1989: 382-402.

[10] Lim KH, Friedman SA, Ecker JL, Kao L, Kilpatrick SJ. The clinical utility of serum uric acid measurements in hypertensive diseases of pregnancy. Am J Obstet Gynecol 1998; 178: 1067-1071. https://doi.org/10.1016/S0002-9378(98)70549-6

[11] Anabel C, Mark AB. Could uric acid have a pathogenic role in preeclampsia; in Nature Review Nephrology 2010; 6: 744-748 https://doi.org/10.1038/nrneph.2010.125

[12] Roberts JM, Bodnar LM, Lain KY, Hubel CA, Markovic N, Ness RB, et al. Uric acid is as important as proteinuria in identifying fetal risk in women with gestational hypertension; Hypertension 2005; 46: 1263-1269. https://doi.org/10.1161/01.HYP.0000188703.27002.14

[13] Powers RW, Bodnar LM, Ness RB, Cooper KM, Gallaher MJ, Frank MP, Daftary AR, Roberts JM. Uric acid concentrations in early pregnancy among preeclamptic women with gestational hyperuricemia at delivery. Am J Obstet Gynecol. 2006; 194: 160. [PubMed: 16389026] https://doi.org/10.1016/j.ajog.2005.06.066

[14] Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Rodriguez-Iturbe B, Herrera-Acosta J, Mazzali M. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003; 41: 1183-90. [PubMed: 12707287] https://doi.org/10.1161/01.HYP.0000069700.62727.C5

[15] Redman CW, Beilin LJ, Bonnar J, Wilkinson RH. Plasma-urate measurements in predicting fetal death in hypertensive pregnancy. Lancet 1976; 1: 1370-1373. https://doi.org/10.1016/S0140-6736(76)93024-5

[16] Nochy D, Birembaut P, Hinglais N, Freund M, Idatte JM, Jacquot C, *et al*. Renal lesions in the hypertensive syndromes of pregnancy: immunomorphological and ultrastructural studies in 114 cases. Clin Nephrol 1980; 13: 155-162.

[17] Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, *et al*. A role for uric acid in the progression of renal disease. J Am Soc Nephrol 2002; 13: 2888. https://doi.org/10.1097/01.ASN.0000034910.58454.FD

[18] Many A, Hubel CA and Roberts JM. Hyperuricemia and xanthine oxidase in Preeclampsia, revisited. Am J Obstet Gynecol 1996; 174: 288-91. https://doi.org/10.1016/S0002-9378(96)70410-6

[19] Kang DH, Finch J, Nakagawa T, Karumanchi SA, Kanellis J, Granger J, *et al*. Uric acid, endothelial dysfunction and pre-eclampsia: searching for a pathogenetic link. J Hypertens 2004; 22: 229-235. https://doi.org/10.1097/00004872-200402000-00001

[20] Feig DI, Nakagawa T, Karumanchi SA, Oliver WJ, Kang DH, Finch J, *et al*. Hypothesis: uric acid, nephron number, and the pathogenesis of essential hypertension. Kid Int Jul 2004; 66: 281-287. https://doi.org/10.1111/j.1523-1755.2004.00729.x

[21] Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, *et al*. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension Nov 2001; 38: 1101-1106. https://doi.org/10.1161/hy1101.092839

[22] Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, *et al*. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity.Hypertension 2002; 40: 355-360. https://doi.org/10.1161/01.HYP.0000028589.66335.AA

[23] Savvidou MD, Hingorani AD, Tsikas D, Frolich JC, Vallance P, Nicolaides KH. Endothelial dysfunction and raised plasma concentrations of asymmetric dimethylarginine in pregnant women who subsequently develop preeclampsia.Lancet. 2003; 361:1511-1517. https://doi.org/10.1016/S0140-6736(03)13177-7

[24] Odendaal HJ, Pienaar ME. Are high uric acid levels in patients with early pre-eclampsia an indication for delivery? S Afr Med J 1997; 87(2 Suppl): 213-218.

[25] Brown MA, Buddle ML. The importance of nonproteinuric hypertension in pregnancy. Hypertens Preg 1995; 14: 57-65. https://doi.org/10.3109/10641959509058051

[26] Bowen RS, Moodley J, Dutton MF: Oxidative stress in pre-eclampsia. Acta Obstet Gynecol Scand 2001; 80: 719-725 https://doi.org/10.1034/j.1600-0412.2001.080008719.x

[27] Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia.Lancet 2001; 357: 53-56. https://doi.org/10.1016/S0140-6736(00)03577-7

[28] Schuster E, Weppelmann B: Plasma urate measurements and fetaloutcome in preeclampsia. Gynecol Obstet Invest 1981; 12: 162-999. https://doi.org/10.1159/000299598

[29] Srinivas SK, Edlow AG, Neff PM, Sammel MD, Andrela CM, Elovitz MA. Rethinking IUGR in preeclampsia: dependent or independent of maternal hypertension. J Perinatol 2009; 29: 680-684. https://doi.org/10.1038/jp.2009.83

Received on 06-12-2017 Accepted on 25-12-2017 Published on 30-12-2017

DOI: http://dx.doi.org/10.20941/2309-4400.2017.05.3