Original Article

Comparative Evaluation of Maternal Serum Uric Acid Levels at Delivery Among Gestational Hypertensive Women and its Effect on Foetal Outcome in Sagamu, Nigeria

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Abstract

Objective: This study was designed to determine the relationship between maternal serum uric acid level at delivery in gestational hypertensive women and subsequent foetal outcome.

Methodology: A cross-sectional study involving 85 women with singleton pregnancy diagnosed with gestational hypertension and preeclampsia, admitted for delivery were recruited and normotensive pregnant women with singleton pregnancy served as control.

Results: Eighty five women had gestational hypertension or preeclampsia while the remaining 85 women were normotensives. Out of the 85 subjects with hypertensive disorder of pregnancy, 32 (37.6%) had gestational hypertension while 53 (62.4%) had preeclampsia. The mean age of the subjects was 31.02±6.02 years. The mean gestational age at delivery of the subjects was significantly lower than the controls. Forty seven (55.3%) of the subjects had hyperuricaemia (serum uric acid >339 µmol/L) whereas only 27.1% of the controls had elevated serum uric acid. The mean uric acid of the subjects was significantly higher than the normotensive controls (381.12±118.54µmol/L Vs 289.84±82.96µmol/L; p=0.002). The foetal outcomes were adversely affected among the hypertensive group compared to the normotensive arm.

Conclusion: There was the adverse foetal outcome in the hypertensives in terms of preterm births, low birth-weight babies and neonatal ward admission. Gestational hypertension with hyperuricaemia was a predictor of the poor foetal outcome but Apgar scores was not affected with the serum uric acid levels.

Keywords: Maternal serum uric acid, gestational hypertension, delivery and foetal outcome

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Introduction

Gestational hypertension and preeclampsia top among diseases that increases foeto-maternal obstetric risk. Preeclampsia, a multi systemic disorder is a significant cause of maternal and foetal mortality and morbidity and is associated with increased numbers of obstetric admissions.[1] Preeclampsia accounts for 70% of

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hypertensive disorders of pregnancy while pregnancy-induced hypertension or gestational hypertension and other forms of chronic hypertension account for 30%. [2] The exact incidence of hypertensive disorders of pregnancy is unknown. Hypertensive disorder complicates about 5 - 10% of pregnancies in Canada, 5.2% in China and 8.5% in Turkey respectively.[3-5] In Nigeria, the prevalence of hypertensive disorders of pregnancy varies in the different regions of the country. In South Eastern Nigeria, a hypertensive disorder of pregnancy complicates between 3.7-11.6% of all deliveries [6,7] and 5.3% prevalence was reported in Sagamu, South Western Nigeria.[8] In Sagamu, hypertensive disorders of pregnancy are responsible for 31.4% of all near miss events and 28% of all maternal deaths.[9,10]

It accounts for as much as 15% of preterm deliveries and 25% of small for gestational age (SGA) infants.[11] Foetal complications of preeclampsia may include placental abruption, preterm birth, intrauterine growth restriction (IUGR) and intrauterine foetal demise. Preeclampsia increases significantly the perinatal morbidity and mortality by increasing the perinatal mortality rate in five-fold.[12] A substantial burden of stillbirth and neonatal mortality in the United States is associated with pregnancy-induced hypertension (preeclampsia and gestational hypertension) especially among nulliparous women and women with any form of hypertension in pregnancy are 1.6 times more likely to have a live birth with small for gestational age and 1.4 times more likely to have a stillbirth as compared with normotensive women.[13]

Many biochemical markers have been recognised in the maternal serum of women with hypertensive disorders in pregnancy. Maternal hyper-uricaemia is one of the earliest detectable and consistent laboratory finding in preeclampsia and has been found to be the better predictor of foetal risk than arterial blood pressure.[14] Hyperuricaemia identifies a population of hypertensive pregnant women at increased risk of adverse maternal and particularly foetal outcome. Although some authors have suggested that the predictive value of serum uric acid is relatively poor both for diagnosis and prognosis, others have suggested that elevated uric acid correlates with poor maternal and foetal outcome, including small for gestational age (SGA) infants, birth asphyxia and foetal death.[15,16] Plasma urate was found to be a better indicator than blood pressure for foetal prognosis. These foetal outcomes were even observed in women with gestational hypertension without proteinuria or any other maternal feature of preeclampsia. Thus, this observation suggests that gestational hypertension in the presence of hyperuricaemia is a disease with increased foetal risk. Nonetheless, the clinical utility of hyperuricaemia in the management of preeclampsia is controversial because it was thought to be a less important marker of maternal hypertensive renal injury than was proteinuria. Thus, this study was therefore designed to determine an association between maternal serum uric acid in women whose pregnancies were complicated by hypertension (gestational hypertension and preeclampsia) at delivery and foetal outcome in Sagamu, Nigeria.

Methodology

The study was a descriptive cross-sectional comparative study involving pregnant women who attended antenatal care or delivered at Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu, Ogun State, Nigeria between July 2015 and January 2016. The minimum sample size required for the study was estimated using the formula for determining sample size when calculating the prevalence of a factor in a descriptive study ($N=Z^2\ pd/d^2$) and using 5.3% prevalence of hypertensive disorder of pregnancy from a local study in Sagamu. Ten percent attrition was allowed. Eighty five women with singleton pregnancy diagnosed with new-onset gestational hypertension and preeclampsia, who were admitted after 28 weeks of gestation for delivery were recruited. A cohort of 85 normotensive pregnant women with singleton pregnancy and comparable to the study group in age, parity and period of gestation were also recruited as the control group. Women with chronic hypertension, chronic renal disease and medical conditions complicating pregnancy such as diabetes mellitus, haemoglobinopathy, thyroid diseases and urinary tract infection were excluded. Also excluded were pregnant women with history of spontaneous preterm rupture of membranes or preterm labour, multifoetal pregnancy, drug history such as allopurinol, probenecid and diuretics, history of gout and or ingestion of alcoholic drinks or beverages within 2 weeks of admission.

The subjects who fulfilled the inclusion criteria were recruited consecutively until the required sample size was reached following informed consent. Maternal serum uric acid was analyzed by the enzymatic colorimetric method. The uric acid assay was done using the commercially manufactured ready to use kit by Randox Laboratories Ltd, 55 Diamond Road, Crumlin, BT29 4QY, United Kingdom. The reference range for serum uric acid level in this study was 142-339µmol/L.

The socio-demographic characteristics of subjects and controls were determined. Following delivery, the foetal outcomes of all participants were determined. The age of gestation at birth, route of delivery, the APGAR scores at first and fifth minute of life, the birth outcome (live birth or stillbirth), birth weight and the need for neonatal admission were all noted. The association and influence of maternal serum uric acid on gestational hypertension and foetal outcome was also determined and compared in the two groups. The Health Research Ethics Committee (HREC) of the Olabisi Onabanjo University Teaching Hospital Sagamu approved the study. Data was analysed using Statistical Package for Social Science (SPSS) windows version 20. A p-value less than 0.05 was considered significant.

Results

Out of the 85 subjects with hypertensive disorder of pregnancy, 32 (37.6%) had gestational hypertension while 53 (62.4%) had preeclampsia. The mean age of the subjects was 31.02±6.02 years and comparable with the controls at 29.40±4.98 years. The mean parity of the subjects was 1.10±1.53 while that of the controls was 0.84±1.01. The mean gestational age at delivery of the hypertensive pregnant women was significantly lower than the normotensive controls (p=0.001) but there was no statistically significant difference in the booking status of the two groups. **(Table I)**

Table I: Socio-demographic Characteristics of the Subjects and Controls.

Characteristics	Subject n=85	Control n=85	P value
Maternal Age (years) Age range	31.02±6.02 18-45	29.40±4.98 20-41	0.105
Mean parity	1.11±1.53	0.84±1.01	0.176
Mean gestational age at delivery (weeks)	37.96±2.46	39.21±2.38	0.001*
Booking status			
Booked	57 (67.1)	67 (78.8)	0.084
Unbooked	28 (32.9)	18 (21.2)	
Educational level			0.416
Primary	03 (3.5)	7 (8.2)	
Secondary	28 (32.9)	28 (32.9)	
Tertiary	54 (63.5)	50 (58.8)	

**p value <0.05; values are presented as number (%), range or mean ± standard deviation. Subject refers to pregnant women with non-protienuric gestational hypertension or preeclampsia. Control refers to pregnant women without hypertension or preeclampsia.*

Forty seven (55.3%) of the subjects had hyperuricaemia (serum uric acid >339 µmol/L) whereas only 27.1% of the controls had elevated serum uric acid. Majority of the women with normal serum uric acid belonged to the normotensive control group. The mean serum uric acid of the subjects was significantly higher than the normotensive controls (381.12±118.54 µmol/L Vs 289.84±82.96 µmol/L; p= 0.002). Out of the 47 subjects that had hyperuricaemia, 38 (80.9%) of them were preeclamptic compared to only 9 (19.1%) with gestational hypertension. Within the hypertensive subjects, the mean serum uric acid of the women with preeclampsia was significantly higher than those with gestational hypertension (411.40±109.47 µmol/L Vs 330.97±117.51 µmol/L, p = 0.003). Expectedly, the degree of proteinuria amongst the subjects was significantly different. The mean proteinuria for preeclamptics was 2.51±0.70 compared to 0.56±0.76 for women with gestational hypertension. **(Table II)**

Table II: Shows the distribution of serum uric acid levels among participants and among the hypertensive group

Serum uric acid levels (µmol/L)	Subject (n = 85)	Control (n = 85)	P value
Serum uric acid ≤339	38 (44.7)	62 (72.9)	0.001*
Serum uric acid >339	47 (55.3)	23 (27.1)	
Mean serum uric acid ±SD	381.12±118.54	289.84±82.96	0.002*
Serum uric acid levels (µmol/L)	**Preeclampsia**	**Gestational hypertension**	**P value**
Serum uric acid ≤339 **(n=38)**	15 (39.5%)	23 (60.5)	0.001*
Serum uric acid >339 **(n= 47)**	38 (80.9)	09 (19.1)	
Mean serum uric acid ±SD	411.40±109.47	330.97±117.51	0.003*

**p value <0.05; Values are presented as number (%), mean ± standard deviation. Subject refers to pregnant women with non-protienuric gestational hypertension or preeclampsia. Control refers to pregnant women without hypertension or preeclampsia.*

Twenty one of the hypertensive women had preterm delivery and out of these, 18 (85.7%) demonstrated elevated serum uric acid levels. Hyperuricaemia was significantly associated with the risk of preterm delivery (p = 0.001). Majority of the women with term delivery had normal levels of serum uric acid. Hypertensive women with elevated serum uric acid had a higher propensity to have Caesarean deliveries than women without hyperuricaemia where vaginal delivery was commoner. There was statistical significant association between modes of delivery and maternal serum uric acid (p=0.041). The incidence of poor Apgar score (score <7) in the 1st minute among subjects with elevated serum uric acid was higher than those with normal serum uric acid levels. The mean Apgar score at 5 minutes was

better in subjects with normal levels of serum uric acid compared to subjects with elevated serum uric acid levels. However, there was no significant difference in the Apgar score at first minute of life. Three (16.4%) of the subjects with hyperuricaemia had stillbirths whereas none occurred in the group with normal serum uric acid levels. There was no statistical significant association between uric acid level and occurrence of still birth (p=0.250). The mean birth weight was significantly lower in mothers with elevated serum uric acid compared to mothers with normal levels of serum uric acid (2.51±0.68 kg vs 3.13±0.56 kg; p =0.000). Twenty six (81.2%) of the low birth weight babies were from hypertensive pregnant mothers with elevated serum uric acid levels compared to 6 (18.8%) from mothers with normal uric acid levels. Very low birthweight babies were not recorded in the subjects with normal serum uric acid levels. The pattern suggests that mothers that had elevated uric acid levels were more likely to deliver very low birth-weight and low birth weight babies. The association between maternal serum uric acid in hypertensive women and birth weight of babies was statistically significant. (p=0.00). Only 4 (13.3%) of the women with normal serum uric acid levels had small for gestational age babies compared to 86.7% with hyperuricaemia. Twenty three babies of all subjects required admission into the neonatal ward and out of these, 18 (78.3%) babies were from mothers with elevated serum uric acid compared to 5 (21.7%) from women with normal serum uric acid levels. There were statistical significant associations between elevated serum uric acid levels and birthweight, small for gestational age babies and need for neonatal ward admission (p values 0.000; 0.000; 0.005 respectively). Low birth-weight, severe birth asphyxia and prematurity were common indications for neonatal admissions for babies whose mothers had elevated serum uric acid levels. There was statistical significant association between elevated serum uric acid levels and indications for neonatal ward admissions among the subjects **(Table III).**

Table III: Shows the relationship between the gestational age at birth, mode of delivery, Apgar scores, birth outcome, birth weight, neonatal admission and the serum uric acid levels among women with gestational hypertension or preeclampsia

Foetal outcome		**Serum uric acid >339µmol/L (n=47)**	**Serum uric acid≤339µmol/Ln=38)**	**P value**
GA (weeks)				0.001 *
	<37 weeks	18 (85.7)	3 (14.3)	
	≥37 weeks	29 (45.3)	35 (54.7)	
Mode of delivery				0.041 *
	Caesarean section	29 (61.7)	15 (39.5)	
	Vaginal Delivery	18 (38.3)	23 (60.5)	
Apgar score	<7	12 (27.3)	9 (23.7)	0.710
at 1 min	≥7	32(72.7)	29 (76.3)	
	Mean Apgar at 1 min	6.55±2.38	6.44±1.88	0.534
Apgar score	<7	3 (6.8)	3 (7.9)	0.852
at 5 mins	≥7	41 (93.2)	35 (92.1)	
	Mean Apgar at 5mins	7.81±2.47	8.76±1.34	0.026
Birth outcome				0.250**
	Livebirth	44 (93.6)	38 (100.0)	
	Stillbirth	3 (16.4)	0 (0.0)	
Birthweight				0.000 *
(kg)	LBW	26 (81.2)	6 (18.8)	
	ABW	21(39.6)	32 (60.4)	
	Mean Birthweight	2.51±0.68	3.13±0.56	0.000*
SGA				0.000 *
	Yes	26 (86.7)	4 (13.3)	
	No	21 (38.2)	34 (61.8)	
NNW admission				0.005 *
	Yes	18 (78.3)	5 (21.7)	
	No	26 (44.1)	33 (55.9)	
Indication for NNW admission				0.037
	SBA	6 (12.8)	3 (7.9)	
	Prematurity	4 (8.5)	0 (0.0)	
	LBW	7 (14.9)	1 (2.6)	
	VLBW	1 (2.1)	0 (0.0)	

*** Fisher's exact test; *p values were significant. Values are presented as number (%), mean ± standard deviation. GA= gestational age; VLBW= very low birth-weight; LBW = low birth-weight; ABW= average birth-weight; NNW= neonatal ward; SGA = small for gestational age, SBA= Severe birth asphyxia*.

After logistic regression for the effect of confounding variables, elevated serum uric acid in women with gestational hypertension or preeclampsia was still significantly associated with poor foetal outcomes and it increases the risk of preterm delivery by 7.2 fold, caesarean delivery by 2.5 fold, low birthweight by 6.6 fold and neonatal ward admission by 4.6 fold in those with serum uric acid greater than 339 micromoles per litre. However, increasing values of uric acid did not increase the likelihood of having poor Apgar scores at five minutes. **(Table IV).**

Table IV: Shows the relationship between elevated uric acid and the foetal outcome after logistic regression

Foetal outcome	Coefficient	Sig	Odd ratio (95% C.I)
Preterm delivery (GA <37 weeks)	1.98	0.003*	7.24 (1.94-27.04)
Caesarean delivery	0.90	0.043*	2.47 (1.03-5.94)
Apgar score at 1 minute	0.19	0.711	1.21 (0.45-3.28)
Apgar score at 5 minutes	-0.16	0.852	0.85 (0.16-4.50)
Low birth weight	1.89	0.000*	6.60 (2.32-18.77)
Small for gestational age	2.35	0.000*	10.52 (3.22-34.42)
Neonatal ward admission	1.52	0.008*	4.57 (1.50-13.95)

**p value = significant; GA = gestational age*

Discussion

Hypertension complicates pregnancy by increasing significantly the maternal and / or foetal morbidity and mortality. Maternal serum uric acid is one of the many biochemical markers elevated in the maternal serum of women with hypertensive disorders of pregnancy and presumed to be associated with an increased risk of adverse maternal and particularly foetal outcomes.[17] These foetal outcomes were also observed in women with gestational hypertension without proteinuria or any other maternal feature of preeclampsia. The mean age and the mean parity of the subjects were comparable to that of the control. The mean age of 31.02±6.02 years in the hypertensive group in this study was similar to 31.30±5.70 years reported in Nnewi, Nigeria [7] and higher than 27.30±6.0 years earlier reported in this centre.[8]

Majority of the participants were booked and had tertiary education. This is in contrast to an earlier study in this centre where a majority were unbooked and illiterate. This difference may be attributed to the emphasis on female education in our environment and brings to light the relationship between education and utilization of health resources. The mean gestational age at delivery for the hypertensive group was significantly lower than that of the control group. The mean gestational age at delivery of 37.96±2.46 for the subjects is comparable to 38.7±2.30 weeks reported in Italy.[18] The mean gestational age at delivery reported in Nnewi was lower than that reported in this study. This may not be unconnected to their unbooked status and low education, as poor utilisation of the antenatal services delayed early diagnosis and prompt intervention of cases. (Table I)

In this study, 62.4% of the subjects had preeclampsia while 37.6% had non-proteinuric gestational hypertension. This study also showed that the mean serum uric acid level at delivery was significantly higher among the subjects than the normotensive controls. This was similar to findings from previous studies.[19,20] Maternal serum uric acid levels were also found to be significantly higher in women with preeclampsia when compared to gestational hypertension. Similar trend was reported by Hawkins et al.[21] Increasing serum uric acid levels appears to coincide with the increase in the blood pressure and precede the development of proteinuria stage of the maternal hypertensive disease. The levels of serum uric acid in severe preeclampsia were significantly higher than mild preeclampsia. This study therefore showed that the degree of hyperuricaemia correlates with the severity of the maternal disease, with increasing uric acid levels as the disease progresses from gestational hypertension to mild preeclampsia to severe form of preeclampsia. Serum uric acid concentration is typically elevated in hypertensive pregnancies and it is likely due to reduced uric acid clearance, diminished glomerular filtration, increased tubular reabsorption and decreased secretion. Studies have shown that uric acid is one of the most sensitive indicators of the disease severity in pregnancy induced hypertensive disorders and can be of great help in monitoring the course of disease process.[17,22] A previous study in Lagos, Nigeria reports that maternal uric acid does not only correlate with severity of maternal disease but could also predict progression from gestational hypertension to preeclampsia.[23]

Researchers have suggested that uric acid itself might be causally related to hypertension and that elevated uric acid might aggravate hypertension by impairment of nitric oxide production in vascular endothelial cells which in part explain the altered endothelial contribution to vascular tone in preeclamptic women. Elevations in circulating uric acid are observed as early as 10th week gestation in women who later develop preeclampsia before measurable alterations in renal function or blood

volume,[24] thus increasing uric acid concentration appears to coincide with the increase in the blood pressure and may precede the development of proteinuria stage of the maternal hypertensive disease. This significant correlation between severity of hypertension and uric acid levels observed in this study is consistent with the reports from Pakistan and United States.[22,24]

Previous studies on clinical utility of maternal serum uric acid levels in hypertensive pregnancy demonstrated that hyperuricaemia was associated with significant increase in perinatal morbidity and mortality.[14] Osakwe et al in a recent prospective cohort study of normotensive women with singleton pregnancy, found that elevated serum uric acid identified women that later developed hypertensive disorders of pregnancy with consequent adverse foetal outcomes such as low birth weight and low Apgar scores. Their study further clearly showed that not only was it an important finding, it was a very useful predictor of the occurrence of gestational hypertension.[25] Similarly, Bellomo et al in their prospective study of 206 primiparas with singleton pregnancy with new onset hypertension, where several biochemical and haematological parameters were assayed to predict the development of preeclampsia, they found out that elevated serum uric acid was a significant and reliable predictor of preeclampsia.[18] Majority of the women with hypertensive pregnancy in our study had increased risk of preterm delivery, low birth-weight, small for gestational age infant and need for neonatal admission. These results were similar to those obtained by other researchers.[13,26] However, in contrast to a study from Ethiopia,[26] there was no statistically significant difference in the Apgar scores at first and fifth minutes. Although the Apgar scores at the 5th minute of life showed an improvement over the scores at the 1st minute, it was not significantly different from that of the normotensive controls. This may be due to their booking status and delivery at a tertiary hospital. It may also reflect the availability of skills in neonatal resuscitation which is obtainable in teaching hospitals like ours. While several studies have correlated elevated uric acid level with adverse foetal outcome [14,18,25] some reported poor correlation.[15] In this study, women with gestational hypertension or preeclampsia coupled with elevated uric acid levels were identified group of pregnancies at increased risk of preterm delivery, operative delivery, low birth-weight, small for gestational age infant, need for neonatal admissions and stillbirths. This is in keeping with reports from other researchers.[19,27,28] To further buttress the negative effect of hyperuricaemia on foetal outcomes, a multicentre prospective cohort study in Iran on normotensive pregnant women with singleton gestation found that maternal hyperuricemia was independently associated with preterm birth, SGA delivery, neonatal intensive care unit admission and the subsequent development of neonatal intraventricular haemorrhage.[29] However, hypertension without hyperuricaemia has been shown to have better foetal prognosis.[12]

Conclusion

The maternal serum uric acid level at delivery of the hypertensive women was higher than those of the normotensive arm despite the comparable socio-demographic characteristics. There was adverse foetal outcome in the hypertensive arm compared to the normotensive controls. In patients with gestational hypertension, elevated serum uric acid may be a predictor of poor foetal outcome and in addition to the increased risk of preterm births, caesarean delivery and low birth-weight babies, there was an increased risk of neonatal ward admissions but the odd of poor Apgar scores was not increased with the elevated serum uric acid levels.

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