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ASSOCIATION OF HYPERURICEMIA WITH PREECLAMPSIA: IS SERUM URIC ACID A GOOD PREDICTOR OF PREECLAMPSIA ? KHARTOUM, SUDAN

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ABSTRACT

Background: Preeclampsia is an important cause of fetal and maternal mortality and morbidity worldwide. Hyperuricemia is a common finding in preeclampsia. Serum uric acid measurement is widely used and investigated for the prediction, diagnosis, follow up and management of pre- eclampsia. The objective of this study is to investigate the association of serum uric acid with preeclampsia and its possible value in predicting preeclampsia. **Materials and Methods:** This is a case control, cross sectional, hospital based study**.** Serum uric acid was measured for 50 pregnant women diagnosed with preeclampsia and 50 normotensive women in the third trimester at Khartoum Teaching Hospital (KTH), Obstetrics & Gynecology Department during June 2011 March 2012. **Results:** The mean serum uric acid for the preeclampsia case group was 7.35mg/dl and for the normotensive group was4.47mg/dl. Statistical probability value and correlation coefficient testing show significance in relationship between blood pressure and serum uric acid level; and for hyperuricemia and preeclampsia (P value =0.000., t test =0.6 is significant). **Conclusion:** Preeclampsia is associated with hyperuricemia. Serum uric acid can be used as a predictor of preeclampsia.

KEYWORDS: Serum uric acid, preeclampsia.

INTRODUCTION

Pre-eclampsia, a pregnancy-specific syndrome that occurs after mid gestation, is defined by the de novo appearance of hypertension (systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg), accompanied by new-onset proteinurea, defined as ≥300 mg per 24 hours1. Previous definitions included oedema, but it is no longer considered as a diagnostic criteria.[1,2] A urine dipstick testing for protein 1 or a protein/creatinine ratio of 0.03 g/mmol appears to be equivalent to 0.3 g/24 hours of proteinurea.[2]

Preeclampsia is one of the syndromes of pregnancy induced hypertension PIH/Gestational hypertension; which also include.
1. Hypertension without proteinuria or pathological oedema.
2. Pre-eclampsia: Hypertension with proteinuria and / or pathological oedema either mild or severe.
3. Eclampsia: Hypertension with proteinuria and / or pathological oedema along with convulsions.[1]

Preeclampsia is associated with serious maternal and fetal complications such as, eclampsia, HELLP syndrome (Haemolysis, Elevated Liver enzymes and Low platelet count), foetal complications5 such as growth restriction, foetal distress and even perinatal death.[1,2,3]

Preeclampsia is an important cause of fetal and maternal morbidity and mortality worldwide.[1,2,3] In countries with poor prenatal care, preeclampsia/eclampsia accounts for 40% to 80% of maternal deaths. Infants of women with preeclampsia have a fivefold increase in mortality compared with infants without the disorder.[3] Much of the fetal mortality is attributable to iatrogenic prematurity. Induced premature delivery resulting from preeclampsia is responsible for approximately 15% of all preterm births.[3] The specialized care of these premature babies place considerable strain on health care resources of developing countries.[3]

Clinical prediction of disease complications may facilitate instigation of timely management to avert mortality and morbidity.[2] Early prediction may also help to decide whether termination of pregnancy might be a better option than expectant monitoring.[1]

Chemical markers of organ and system dysfunction such as elevated level of serum urea, creatinine, liver enzymes, uric acid and others have been extensively studied as possible predictors of preeclampsia.[3,4]

Uric acid is the product of purine metabolism and is synthesized by the enzyme xanthine oxidase. The normal range of serum uric acid varies according to sex and age. In males: 3.0-7.0 mg/dl. In females: 2.4- 6.4 mg/ dl. In children: 2.0- 5.5 mg/dl.[1] Hyperuricemia is a consistent feature of preeclampsia.[1,2,3] Hyperuricemia was hypothesized by many investigators as being associated with clinical severity of preeclampsia and perinatal outcomes.[5]

Elevated level of serum uric acid is a marker of oxidative stress, tissue injury and renal dysfunction, The main causes of elevated serum uric acid in preeclampsia are reduced uric acid clearance secondary to reduced GFR, increased tubular re-absorption and decreased secretion. the pathophysiology of pre-eclampsia is associated with increased trophoblastic tissue shedding, endothelial dysfunction and reduced blood flow in the feto-maternal unit; these factors may also contribute to the hyperuricaemia of preeclampsia. There is evidence for increased generation of uric acid from the ischemic placenta.[2] Some authors suggested a pathogenic role of uric acid in preeclampsia through causing defective spiral arteries vascular remodeling.[2]

From the time its association with pre-eclampsia was first described[6], uric acid has been extensively investigated as a predictor of onset or severity of preeclampsia or its prediction of maternal and fetal complications.[1,2,3,4,5, 6,7,8]

Several studies have reported a positive correlation between elevated maternal serum uric acid level and the adverse maternal and fetal outcomes.[6,7,8,9,10,11,12,13,14]

Hill et al[6] from Mayo clinic studied the metabolism of uric acid in normal pregnancy and toxaemic pregnancy. Roberts[7] et al stated that serum uric acid is one of the most consistent and earliest changes in preeclampsia and could be a better predictor of fetal risk than blood pressure. Ecker[8] et al and Banbrifge[9] et al suggested that serum uric acid is not only a marker of disease severity; but also contributes to the pathogenesis of the disorder. The rise in serum uric acid in preeclampsia is being studied by Roger[10] as being secondary to placental damage rather than an alternation in renal function. Bakheit[11] & Sultana et al[12] compared serum uric acid in preeclampsia to control group, found that rising serum uric acid correlates well with the severity of hypertension. Wakwe & Abudo[13], Redman and Bale[14] found that rise in serum uric acid correlates well with the severity of preeclampsia, the higher the maternal hyperurcemia, the poorer is the fetal outcome. Priya[1] et al proved that serum uric acid is a good predictor of foetal complications of pre-eclampsia but not of maternal complications. Livingston[15] et al conducted a large cohort including 1505 women admitted to hospital with preeclampsia, the serum uric acid concentration, corrected for gestational age via a Z score, they concluded that serum uric acid is clinically useful in predicting adverse perinatal outcomes but not maternal outcomes.

On the other hand, A number of studies argued against the value of serum uric acid in preeclampsia.: Thangaratinam[5] et al conducted a large systematic review, investigating the accuracy of serum uric acid in predicting complications of preeclampsia; covering 18 primary articles recruiting a total of 3913 women using the pooling likelihood ration(PL), they concluded that serum uric acid is a poor predictor of maternal and fetal complications in women with preeclampsia. Talaulikar[2] et al reviewed 60 articles on the utility of serum uric acid in preeclampsia; some were favoring this utility while others disputed it Talaulikar[2] et al concluded that increased uric acid level is not useful for prediction, diagnosis and/or management of pre-eclampsia. Fadel[16] et al data argued against the postulated role of serum uric acid in preeclampsia.

AIMS AND OBJECTIVES
The aim of this study was to investigate the association of serum uric acid with preeclampsia.

Objectives
To measure the serum uric acid level in women with preeclampsia,
To measure the serum uric acid level in healthy pregnant women (control group).
To detect whether there is significant difference between the two groups.
To elicit if there is association between the level of serum uric acid and the severity of hypertension.

MATERIALS AND METHODS
This is a case control, hospital based, cross-sectional study conducted in the Obstetrics and Gynecology Department, Khartoum Teaching Hospital (KTH), Sudan, from June 2011 to March 2012. A total number of hundred pregnant women in the third trimester attending the Obstetrics and Gynecology department of Khartoum Teaching Hospital were selected as the study subjects. Among these 50 pregnant women with preeclampsia were selected as cases and 50 normal healthy pregnant women as controls. The criteria adopted to diagnose preeclampsia were: Systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg. The criteria adopted to diagnose significant proteinurea 24-hour urine collection with a total protein excretion of 300 mg / 24 hours., Since edema is not a specific sign; it is not considered part of the diagnostic criteria for preeclampsia.[11]

Inclusion criteria were: pregnant women with gestational age ≥28 weeks, BP≥140/90,24hours protein 300g/dl and who accepted to participate in this study. Exclusion criteria included: Pregnant ladies with any of the following medical conditions were excluded from the study: known hypertensive patients, known diabetics, patients with known renal disease, known gout patients,

patients who received chemotherapy within 4 weeks, patients on thiazide diuretics and those who refused to take part in this study.

Case and control groups were matched in age, gravidity and gestational age.

Ethical approval was obtained from the Research Ethics Board at the Research and Laboratory Unit, KTH. Written consent was obtained from participants.

A detailed history of each patient was taken and complete general and obstetric examination was done. All findings were recorded in pre-designed questionnaire. Hypertension and proteinurea were diagnosed as per the criteria already described. Serum uric acid testing was performed: 5ml of venous blood collected from all participants, measured through the absorbance photometer module of the autoanalyzer COBASINTEGRA400. Data obtained through questionnaire including history, clinical examination, proteinurea and serum uric acid measurements were analyzed through SPSS28. Both control and cases were divided into five age groups, eight gravidity groups and four BP groups, mean serum uric acid for each group was calculated, the degree of correlation (r-test) and the probability test (p-value) were calculated. Data displayed through tables and figures.

RESULTS
The study covered 100 women, Age range was18-40 years old. Age distribution and comparison between case and control groups are presented in Table I.

Age distribution & comparison between the two groups Table1.

Age (years)	Cases	Control
<21	5(10%)	3(6%)
21-25	17(34%)	14(28%)
26-30	7(14%)	15(30%)
31-35	9(18%)	7(14%)
36-40	12(24%)	11(22%)
Total	50(100%)	50(100%)

Gravidity distribution in the case and control groups are shown in table 1.

Gravidity distribution and comparison between cases and controls shown in Table 2.

Gravidity	Cases	Controls
Prima gravidus	24(48%)	14(28%)
Gravida II	11(22%)	14(28 %)
Gravida III	8(16%)	8(16%)
Gravida IV	2(4%)	5(10%)
Gravida V	1(2%)	4(8%)
Gravida VI	3(6%)	1(2%)
Gravida VIII	1(2%)	4(8%)
Total	50(100%)	50(100%

The Mean serum Uric acid for the control group was 4.47 mg/dl. The mean serum uric acid for case group was 7.35mg/dl table (3).

The relation between gravidity and serum uric acid in preeclampsia is calculated; P value =0.458 is statistically not significant, shown in table(3).

The case group was divided into four groups according to BP and the mean serum uric acid for each BP group was calculated.

Distribution of mean serum uric acid according to gravidity of the case group Table 3.

Gravidity	Frequency	Mean serum uric acid mg/dl
Prima gravidus	24	7.68
Gravida II	11	6.97
Gravida III	8	6.95
Gravida IV	2	7.20
Gravida V	1	6.6
Gravida VI	3	7.8
Gravida VIII	1	6.6
Total	50	7.35

Serum uric acid of case group P value =0.458is not significant.

The distribution of mean serum uric acid of control group according to gravidity Table 4.

Gravidity	Frequency	Mean serum uric acid mg/dl
Prima gravidus	14	4.38
Gravida II	14	4.55
Gravida III	8	4.36
Gravida IV	5	4.40
Gravida V		4.70
Gravida VI	1	5.00
Gravida VIII	4	4.42
Total	50	4.47

The relationship between blood pressure and mean serum uric acid is shown in table (5). Statistical probability value and correlation coefficient test were calculated to test for significance in relationship between Blood pressure and serum uric acid level; it proved to be highly significant, P value =0.000., t test =0.6 is significant.

Distribution of mean serum uric acid according to BP Table (5).

Blood pressure mmHg	Frequency	Mean serum uric cid mg/dl
140/90	19	6.45
140/100	3	6.85
150/100	16	7.75
160/100	12	8.35
total	50	7.35

Mean serum uric acid of cases and control groups Table (6).

Group	No	Mean serum uric acid Mg/dl
case	50	7.35
Control	50	4.47

P value =0.000 is significant, r test =0.6 is significant.

DISCUSSION
Mean serum uric acid of the control group was 4.47mg/dl. The normal range is (2.6-6 mg/dl). This finding is in keeping with the medical literature that normal pregnancy is not associated with rise in serum uric acid.[4,6] Serum uric acid of case group was 7.35mg/dl, this is consistent with M Roberts[7] et al who studied 972 cases of preeclampsia patients, the mean serum uric acid was 7.6mg/dl, these are close to our results. Tusukimori et al[17] found mean serum uric acid in preeclampsia to be 6.6± 1.5mg/dl and for normal pregagncy 4.0±0.7mg/dl. Bakhit[11] et al studied serum uric caid in preeclampsia compared to control, found that the mean serum uric acid for controls 4.5mg/dl and for cases 6.5mg/dl.

Thangaratinam[18], Ismail et al studied the accuracy of serum uric acid in predicting complications of preeclampsia, found serum uric acid greater than or equal to 7.25mg/dl is highly predictive of eclampsia.

This study showed that the higher the blood pressure the higher the serum uric acid, P value = 0.000, these results are in concordance with Ecker, Jeffry et al.[14]

CONCLUSION
Hyperuricemia is strongly associated with preeclampsia. The higher the blood pressure in preeclampsia the higher the serum uric acid level. Serum uric acid can be useful as a predictor of preeclampsia.

Conflict of interest
The auther declares no conflict of interest.

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