DIAGNOSTIC ACCURACY OF SERUM URIC ACID IN EARLY PREDICTION OF PREECLAMPSIA IN HIGH-RISK WOMEN

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ABSTRACT

Objective: To estimate the diagnostic accuracy of raised levels of uric acid in serum for early prediction of preeclampsia among high risk pregnant women.

Methods: The study was conducted in department of gynaecology and obstetrics Pakistan Naval ship Hafeez hospital, Islamabad, from April 2019 to October 2019, the cross sectional(validation) research comprised of 237 expecting women between 18 to 40 years of age with gestational age > 20 weeks and with any of the high risk factors. Serum uric acid was estimated in all women and they were followed up for occurrence of preeclampsia till delivery.

Results: The results of the study reported sensitivity 63.9%, specificity 93.7%, positive predictive value 89.9%, negative predictive value 74.7% and accuracy 79.7%. Similar trends (relatively lower sensitivity and high specificity) for serum uric acid test was noted in predicting pre-eclampsia when data was stratified with respect for effect modifiers.

Conclusion: Diagnostic accuracy of raised serum uric acid in diagnosing pre-eclampsia was found fairly well with better specificity and PPV as compared to Sensitivity and NPV. There is a fair chance that patient will develop pre-eclampsia if serum uric acid is raised.

Keywords: Pre-eclampsia, Uric acid, HELLP (**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets) syndrome, eclampsia

INTRODUCTION

A multisystem condition associated with pregnancy is pre-eclampsia that develops after mid-gestation. It is characterized as new-onset hypertension (≥140/90 mmHg) after 20 weeks of pregnancy with proteinuria which is defined as less than 300 mg per 24 hours[(1)]. Preeclampsia is estimated to occur in 4.6 percent (95% CI 2.7-8.2) of pregnancies worldwide[(2)]. In the developed world, preeclampsia affects around 3.4 percent of pregnancies, however, first pregnancies have a 1.5–2 fold higher risk[(3)].

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It complicates about 5-7% of pregnancies and is the third commonly occurring cause of maternal death. Though these pregnancies are at increased risk for maternal and/or fetal mortality or serious morbidity but despite the fact majority of these pregnancies end up in healthy delivery at or near term with good maternal and fetal outcomes [(4)]. Females at high possibility of developing preeclampsia should be closely monitored to identify potentially modifiable risk factors. Several investigators have used combinations of tests to predict preeclampsia and a research for a simple, rapid and noninvasive test is ongoing[(5)].

Elevated blood uric acid levels are a frequently-reported test result in preeclampsia women[(6)]. In preeclamptic women, an increase in uric acid frequently occurs before hypertension and proteinuria. One of the main characteristics of preeclampsia is a unbalanced decrease in uric acid removal. As preeclampsia worsens, uric acid levels in the blood rise; a >5.5 mg/dL result is a reliable sign of the condition, and a level of > 7.8 mg/dL is linked to substantial maternal morbidity[(1, 7)]. In a recent study Khurshid R et al, found uric acid levels in serum as an early biomarker of preeclampsia. They observed that the level of uric acid in serum was greater in pre-eclampsia group as compared to those of non-

pre-eclamptic women (P<0.001). They further found that serum uric acid as a biomarker showed 65% sensitivity, 95% specificity with 95% positive predictive value and 60% negative predictive value[8]. The concentration of serum uric acid has been postulated as biomarker for preeclampsia by multiple observational studies. Although there is disagreement regarding its ability in predicting adverse pregnancy and neonatal outcomes, as well as whether its changes occur before the onset of disease[9]. In earlier meta-analysis on this topic its potential predictive efficacy have been suggested but safe inferences cannot be formed because of the small number of included studies and the heterogeneity of the results that have been given[10].

Although the international literature exists for serum uric acid for the diagnostic accuracy but local studies are in limited number and there is a dire need to conduct such study in local population as prevalence of preeclampsia is different in our society as well as the high risk women due to genetic and geographical differences. If we get better results with raised uric acid comes out to be a good predictor of pre-eclampsia, we can use this as a predictive marker in our settings. It is cost effective and readily available tool and well suited in our population where more people belong to poor socioeconomic status. This will help us in early and accurate recognition of female at higher risk for developing preeclampsia and appropriate management may be started in these female for better outcomes both maternal and perinatal.

Therefore the current study was conducted to determine the diagnostic accuracy of raised serum uric acid for early likelihood of preeclampsia among high risk pregnant female by taking preeclampsia as gold standard.

MATERIAL/SUBJECTS/PATIENTS AND METHODS

A cross sectional study (validation) was conducted in department of Gynecology and obstetrics PNS Hafeez hospital, Islamabad, from April 2019 to October 2019. The sample size calculated was 237; by using sensitivity and specificity calculator taking sensitivity and specificity of the test 65% and 95% respectively, prevalence 19%[8], confidence level 95% and precision 14%. Sampling technique used for sample selection was non-probability consecutive sampling. All pregnant female with gestational age of >20 weeks, with high risk factors, such as, chronic hypertension, nulliparous with extreme ages (<18 years or >40 years), Diabetics (Fasting blood glucose level ≥126 mg/dl), multiple gestations with history of hypertension, preeclampsia or eclampsia in previous pregnancies, family history of preeclampsia and eclampsia and high BMI (>30 kg/m^2) were included in the sample. The ones who were using medication for reducing serum uric acid and women with known history of gout were excluded from the study. The approval of the study from the hospital ethics committee was acquired. Patients were enrolled from the OPD and antenatal clinic of the department. Written Informed consent was obtained from the patients. Serum uric acid was determined at twenty weeks of gestation from the hospital laboratory. A value of 6mg/dL was taken as a cutoff value. A value ≥6mg/dL was considered a positive test and a value < 6mg/dL was considered a negative test. Urine dipstick analysis was done fortnightly. All patients showing urine dipstick analysis 1+ result underwent twenty four hour urine analysis for proteinuria. Results showing proteins ≥0.3g in the 24 hour urine specimen, hypertension of at least BP of 140/90 mmHg recorded on at least two separate occasions and at least four hours apart were labeled as preeclampsia. All the data collection was conducted by the principal investigator to maintain data quality and compliance to the study protocol.

Data was entered on computer software SPSS version 22. Quantitative variables like age, parity, BMI, serum uric acid value were measured as Mean ± SD. Qualitative variables like pre-eclampsia, serum uric acid test, past H/O pre-eclampsia/eclampsia, family H/O pre-eclampsia/eclampsia, chronic hypertension, diabetes and pregnancy induced hypertension were measured as frequency and percentages. Effect modifiers like age, parity, BMI, past H/O pre-eclampsia/eclampsia, family H/O pre-eclampsia/eclampsia, chronic hypertension, diabetes and pregnancy induced hypertension were controlled by stratification and post stratification diagnostic accuracy was computed. Overall accuracy of serum uric acid analysis in predicting preeclampsia was calculated by the formulas of Sensitivity, Specificity, Positive Predictive value, Negative Predictive value and Accuracy.

RESULTS

Out of 237 subjects, there were 170(71.7%) in age 18-30 years and 67(28.3%) in age 31-40 years. The average age was 28.2 and standard deviation 4.3. The average parity was 2.6±0.97, where, 30(12.7%) were nulliparous, 207(87.3%) were multiparous. The mean BMI was 26.5±4.2, where 156(65.8%) had BMI < 30 Kg/m^2 and 81(34.2%) had BMI ≥ 30 Kg/m^2. The information regarding the risk factors is tabulated in first table.

Table 1: Risk factors in study sample

n=237			
Risk factors		**Frequency**	**Percent**
Past h/o pre-eclampsia/ eclampsia	Present	23	9.7
	Absent	214	90.3
	Total	237	100.0
Family h/o pre-eclampsia/ eclampsia	Present	43	18.1
	Absent	194	81.9
	Total	237	100.0
Chronic hypertension	Present	34	14.3
	Absent	203	85.7
	Total	237	100.0
Diabetes	Present	28	11.8
	Absent	209	88.2
	Total	237	100.0
Pregnancy-induced Hypertension(PIH)	Present	20	8.4
	Absent	217	91.6
	Total	237	100.0
Multiple gestations	Present	13	5.5
	Absent	224	94.5

Mean serum uric acid was found to be 5.1 mg/dL ± 1.18 SD. Serum uric acid test was positive in 33.3% (n=79/237) women for pre-eclampsia. 46.8% (n=111/237) women developed pre-eclampsia during follow up. Both the uric acid test results and occurrence of pre-eclampsia were cross tabulated (true positive (TP), false positive (FP), true negative (TN), false negative (FN)) are displayed in table 2. The present study results reported sensitivity 63.9%, specificity 93.7%, positive predictive value 89.9%, negative predictive value and of 74.7% and accuracy 79.7%.

Table 2: Cross-tabulation between serum uric acid test and preeclampsia

n=237				
Uric acid test	Preeclampsia		Total	Predictive accuracy
	Present	Absent		
Positive	71	8	79	Sensitivity: 63.9% specificity: 93.7% PPV: 89.9% N P V : 74.7% accuracy: 79.7% LR ratio:10.1, CI at 95% confidence level is (11.59-59.09)
Negative	40	118	158	
Total	111	126	237	

Similar trends (relatively lower sensitivity and high specificity) for serum uric acid test was noted in predicting pre-eclampsia when data was stratified with respect for effect modifiers in table 3.

Table 3: Stratification for Effect Modifiers

Age group	Uric acid test	Preeclampsia		Total	Predictive accuracy
		PRESENT	ABSENT		
18-30 years	Positive Negative Total	49 30 79	6 85 91	55 115 170	Sensitivity: 62.1% specificity: 93.4% PPV: 89.1% NPV: 73.9% accuracy: 78.8% LR ratio: 9.4
31-40 years	Positive Negative Total	22 10 32	2 33 35	24 43 67	Sensitivity: 68.7% specificity: 94.3% PPV: 91.7% N P V : 76.7% accuracy: 82.1% LR ratio: 12.1
Parity group					
Nulliparous	Positive Negative Total	10 8 18	1 11 12	11 19 30	Sensitivity: 55.50% Specificity: 91.7% PPV: 90.90% NPV: 57.9% Accuracy: 70% LR Ratio: 6.7
Multiparous	Positive Negative Total	61 32 93	7 107 114	68 139 207	Sensitivity: 65.6% Specificity: 93.8% PPV: 89.7% NPV: 76.9% Accuracy: 81.1% LR Ratio: 10.7
Body mass index group					
< 30 Kg/m^2	Positive Negative Total	49 24 73	5 78 83	54 102 156	Sensitivity: 67.1% Specificity: 93.9% PPV: 90.1% NPV: 76.5% Accuracy: 81.1% LR Ratio: 11.1
≥ 30 Kg/m^2	Positive Negative Total	22 16 38	3 40 43	25 56 81	Sensitivity: 57.9% Specificity: 93.1% PPV: 88% NPV: 71.4% Accuracy: 76.5% LR Ratio: 8.3
Past h/o pre- eclampsia/e clampsia					
Present	Positive Negative	7 4	2 10	9 14	Sensitivity: 63.4% Specificity: 83.3% PPV: 77.8% NPV: 71.4% Accuracy: 73.9%

	Total	11	12	23	LR Ratio: 3.1
Absent	Positive Negative Total	64 36 100	6 108 114	70 144 214	Sensitivity: 64% Specificity: 94.7% PPV: 91.4% NPV: 75% Accuracy: 80.3% LR Ratio: 12.2
Family h/o pre-eclampsia/e clampsia					
Present	Positive Negative Total	17 8 25	0 18 18	17 26 43	Sensitivity: 68.0% Specificity: 100% PPV: 100% NPV: 92.6% Accuracy: 93.6% LR Ratio: 10.2
Absent	Positive Negative Total	54 32 86	8 100 108	62 132 194	Sensitivity: 62.8% Specificity: 92.6% PPV: 87.1% NPV: 75.7% Accuracy: 79.4% LR Ratio: 10.1
CHRONIC HTN					
Present	Positive Negative Total	10 7 17	1 16 17	11 23 34	Sensitivity: 58.8% Specificity: 94.1% PPV: 90.9% NPV: 69.6% Accuracy: 76.5% LR Ratio: 10.0
Absent	Positive Negative Total	61 33 94	7 102 109	68 135 203	Sensitivity: 64.9% Specificity: 93.6% PPV: 89.7% NPV: 75.6% Accuracy: 80.3% LR Ratio: 10.1
Diabetes					
Present	Positive Negative Total	7 6 13	1 14 15	8 20 8	Sensitivity: 53.8% Specificity: 93.3% PPV: 87.95% NPV: 70.0% Accuracy: 75.3% LR Ratio: 8.1
Absent	Positive Negative Total	64 34 98	7 104 111	71 138 209	Sensitivity: 65.3% Specificity: 93.7% PPV: 90.1% NPV: 75.3% Accuracy: 80.4% LR Ratio: 10.4
Pregnancy induced hypertension (PIH)					
Present	Positive Negative Total	5 3 8	2 10 12	7 13 20	Sensitivity: 62.5% Specificity: 83.3% PPV: 71.4% NPV: 76.9% Accuracy: 75.0% LR Ratio: 3.8
Absent	Positive Negative Total	66 37 103	6 108 114	72 145 217	Sensitivity: 64.1% Specificity: 94.7% PPV: 91.7% NPV: 74.5% Accuracy: 80.2% LR Ratio: 12.1
Multiple gestations					
Present	Positive Negative Total	4 4 8	0 5 5	4 9 13	Sensitivity: 50.0% Specificity: 100% PPV: 100% NPV: 55.5% Accuracy: 69.2% LR Ratio: 10.1
Absent	Positive Negative Total	67 36 103	8 113 121	75 149 224	Sensitivity: 65.1% Specificity: 93.3% PPV: 89.3% NPV: 75.8% Accuracy: 80.1% LR Ratio: 9.8

DISCUSSION

The frequency of preeclampsia in the developed world is about 3.4 percent, but 1.5-fold to 2-fold higher in 1st pregnancy. Pre-eclamptic women frequently have an increase in uric acid before developing hypertension and proteinuria. Several investigators have used combinations of tests to predict preeclampsia and a research for a simple, rapid and noninvasive test is ongoing[5]. The rise in uric acid levels seems to follow the rise in blood pressure and occur before the onset of proteinuria. Elevated uric acid level in serum is a frequently mentioned test result in preeclampsia female. Although the international literature exists for serum uric acid for the diagnostic accuracy[6]. but local studies are in limited number. Present study was planned to determine the diagnostic accuracy of raised serum uric acid for early pre-eclampsia prediction among high risk pregnant female by taking preeclampsia as gold standard.

Our findings align with the data that has already been published in the literature. Serum uric acid has been identified as an early indicator of preeclampsia in a recent study by Khurshid R et al. They observed that the level of serum uric acid was higher in pre-eclampsia group as compared to those of normal women who are pregnant (P<0.001). The aim of Kunwar S et al. was to determine the serum levels of homocysteine and uric acid as potential biomarkers for the diagnosis of preeclampsia. According to their findings, pre-eclamptic subjects had significantly greater serum levels of homocysteine, that is 6.5±0.7 mg/dl and uric acid levels 13.5±5.4 µmol/l as compared to healthy subjects, which had serum levels of homocysteine 4.3±0.8 mg/dl and uric acid 10.1±4.6 µmol/l. At a cutoff of 5.5 mg/dl maximum sensitivity and specificity (91% and 88%, respectively) were attained. They came to the conclusion that the uric acid level in serum is a more accurate predictor of pre-eclampsia than the homocysteine level in serum[12]. The results are similar to the present study, we, however, took the cutoff value as 6 mg/dL that is the likely reason behind different sensitivity and specificity values in our study. Predictive value for preeclampsia, its severity, and pregnancy outcomes have been determined by Osakwe CR et al using serum uric acid levels. Women who went through eclampsia or pre-eclampsia were observed. They demonstrated that pre-eclampsia was experienced by 10.5% of the women. Serum uric acid's positive and negative predictive values for preeclampsia were 78.9% and 97.1%, respectively[13]. Pregnant women's serum biomarkers for detecting the severity of preeclampsia were identified by Kasraeian M. et al. They studied different serum indicators (aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alanine aminotransferase (ALT) alkaline phosphatase, platelet count (PLT), hemoglobin (Hb), uric acid, total bilirubin, direct bilirubin, creatinine, and) from 450 pregnant women who had preeclampsia of varying severity. Their results revealed that compared to women with mild preeclampsia, those with severe preeclampsia had considerably higher mean levels of uric acid[14].

In one hundred and ten women, Kumar N. et al. evaluated the association between maternal uric acid level in serum and severity of the hypertensive disorders of pregnancy. The sample consists of the patients who were admitted because of hypertensive disorder of pregnancy (Preeclampsia, Eclampsia at ≥34 weeks gestation, Gestational hypertension). In three groups, the levels of maternal serum uric acid were compared in connection to the severity of the illness, the style of delivery, and the maternal outcome. According to their findings, pre-eclamptic women had mean uric acid levels in serum of 6.72 mg/dl, pre-eclamptic women had mean serum uric acid levels of 2.15 mg/dl, and eclamptic women had average uric acid level in serum of 8.71 mg/dl. They came to the conclusion that a strong association was there between maternal serum uric acid, the severity of the condition, and the outcome for the mother[15].

Ghaffar B et al. measured and compared the uric acid concentration and serum lipid profile in pre-eclamptic and healthy pregnant women in a study conducted among local women. Their findings demonstrated that the blood uric acid levels in the pre-eclamptic women were substantially greater (p-value 0.05) than those in the 79 controls (7.35 mg/dl 1.85SD versus 4.92 mg/dl 1.28SD).They came to the conclusion that changes in uric acid levels may aid in the early diagnosis and monitoring of pre-eclampsia cases[16].

In summary, the cumulative evidence on the subject demonstrates that alterations in uric acid levels in serum during early gestational period are linked with the occurrence of pre-eclampsia. The readings of uric acid in serum >6 mg/dl is predictive of pre-eclampsia. Some authors have used other cutoff values and reported better accuracy with lower cutoff values. Diagnostic

accuracy of raised serum uric acid in predicting pre-eclampsia was found fairly good with better specificity and positive predictive value (as compared to sensitvity and negative predictive value.

CONCLUSION

Diagnostic accuracy of raised level of uric acid in diagnosing pre-eclampsia was found fairly good (79.7%) with better specificity (93.7%) and positive predictive value (89.9%) as compared to Sensitivity (63.9%) and negative predictive value (74.7%). There is a fair chance that patient will develop pre-eclampsia if serum uric acid is raised and those women need more meticulous monitoring during the pregnancy. As opposed to that, normal levels of serum uric acid do not completely rule out the chances of developing pre-eclampsia later in the pregnancy. This technique is safe, easily available and cost-effective. We recommend further trials with larger sample size.

REFERENCES

1. Bulusu R, Singh TJJEBMH. Analysis of serum uric acid levels in early second trimester as an early predictor for preeclampsia. 2017;4(3):115-8.

2. Abalos E, Cuesta C, Grosso AL, Chou D, Say LJEjoo, gynecology, et al. Global and regional estimates of preeclampsia and eclampsia: a systematic review. 2013;170(1):1-7.

3. Ananth CV, Keyes KM, Wapner RJJB. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. 2013;347.

4. Priya AR, Jeyapriya K, Kannan NJIJCRR. Accuracy of serum uric acid in predicting complications of preeclampsia. 2016;8(5):13-21.

5. Poon LC, Nicolaides KHJPd. First-trimester maternal factors and biomarker screening for preeclampsia. 2014;34(7):618-27.

6. Livingston JR, Payne B, Brown M, Roberts JM, Côté A-M, Magee LA, et al. Uric acid as a predictor of adverse maternal and perinatal outcomes in women hospitalized with preeclampsia. 2014;36(10):870-7.

7. Prakash S, Sharma N, Kumari P, Kumar AJIJoPS, Research. Serum uric acid as marker for diagnosing preeclampsia. 2012;3(8):2669.

8. Khurshid R, Shamsi A, Fayyaz IJA. Maternal serum uric acid level during pregnancy: A biomarker for preeclampsia. 2016;28(4.11):29.07-5.54.

9. Bellos I, Pergialiotis V, Loutradis D, Daskalakis GJTJoCH. The prognostic role of serum uric acid levels in preeclampsia: A meta-analysis. 2020;22(5):826-34.

10. Taravati A, Tohidi F. Comprehensive analysis of oxidative stress markers and antioxidants status in preeclampsia. Taiwanese journal of obstetrics & gynecology. 2018;57(6):779-90;

11. Bainbridge SA, Roberts JMJP. Uric acid as a pathogenic factor in preeclampsia. 2008;29:67-72.

12. Kunwar S, Thakur RK, Nepal R, Paudel L, Chaulaigai B, Paudel GAJIJ. Potential role of serum homocysteine and uric acid level as a predictive marker for preeclampsia. 2019;5(5):119.

13. Richmond OC, Ikpeze OC, Uzoma EI, Oluchi OJ, Nwadiogo MNJNJoM. The predictive value of serum uric acid for the occurrence, severity and outcomes of pre-eclampsia among parturients at Nnewi, Nigeria. 2015;24(3):192-200.

14. Kasraeian M, Asadi N, Vafaei H, Zamanpour T, Shahraki HR, Bazrafshan KJPJoMS. Evaluation of serum biomarkers for detection of preeclampsia severity in pregnant women. 2018;34(4):869.

15. Kumar N, Singh AKJCHR. Maternal serum uric acid as a predictor of severity of hypertensive disorders of pregnancy: a prospective cohort study. 2019;15(2):154-60.

16. Ghaffar B, Memon SH, Khidri FFJJoLUoM, Sciences H. Assessment of serum lipid and uric acid levels in women with normal pregnancy and pre-eclampsia. 2019;18(02):169-74.