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ACCURACY OF SERUM URIC ACID IN PREDICTING COMPLICATIONS OF PRE-ECLAMPSIA

A. Ramana Priya[1], K. Jeyapriya[1], N. S. Kannan[2]

[1]Assistant Professor of Obstetrics & Gynaecology, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Pillaiyarkuppam, Pondicherry, India, 607402; [2]Associate Professor, Department of General Surgery, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Pillaiyarkuppam, Pondicherry, India, 607402.

ABSTRACT

Introduction: Pre-eclampsia, is a pregnancy-specific syndrome that occurs after mid gestation comprising of gestational hypertension with significant proteinuria. If not treated properly will lead to maternal and foetal complications.

Aims: To study the accuracy of serum uric acid in predicting complications of pre-eclampsia and its effect on pregnancy outcome.

Methods: Sixty pregnant women at term gestation with diagnosis of pre-eclampsia were included in our study after informed consent. For all patients included in the study all routine investigations including serum uric acid were done and recorded. All the patients were followed up until delivery and all maternal and foetal events were recorded. All complications of pre-eclampsia both maternal and foetal were statistically analysed to prove the predictive value of serum uric acid levels.

Results: 18.3% of mothers were between the age group 18-21 years, 26.7% were between 22-25 years, 28.3% were between 26-29 years, and 26.7% were above 30 years. 83.4% of 60 mothers were primi para, 8.3% were para 2, and 8.3% were para 3. The difference in the first minute APGAR in the high risk and no risk category was not statistically significant at p value of 0.1798. The difference in the 5th minute APGAR in the high risk and no risk category was statistically significant at p value of 0.001. 4 out of 42 women (9.52%) with serum uric acid ≥6mg/dl had maternal complications and 7 out of 18 women with serum uric acid <6mg/dl had maternal complications (p value = 0.01) which is statistically significant. Considering less than 2.5 Kg as low birth weight, serum uric acid levels of more than 5.5 are associated with significant low birth weight (p value of 0.01) which is statistically significant.

Conclusion: Our study with a sample size of 60 has proved that serum uric acid is statistically significant predictor (p value 0.01) of foetal complications of pre-eclampsia even though not of maternal complications (p value 0.42).

Key Words: Gestational hypertension, Eclampsia, HELLP syndrome, Maternal death, Intrauterine growth restriction, Foetal distress, Perinatal death

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 proteinuria, defined as ≥300 mg per 24 hours[1].

Previous definitions included oedema, but this sign is non-specific and is observed in many normotensive pregnant women. Thus, oedema is no longer considered part of the diagnostic criteria for preeclampsia.

The incidence of preeclampsia is 2-10%, depending on the population studied and definitions of Pre-eclampsia[2].

It can result in many maternal complications[3,4] such as severe hypertension, eclampsia and HELLP syndrome (Haemolysis, Elevated Liver enzymes and Low platelet count), or foetal complications[5] such as growth restriction, foetal distress and even perinatal death.

Early prediction of these complications might help to decide whether termination of pregnancy might be a better option than expectant monitoring.

Corresponding Author:
K. Jeyapriya, Assistant Professor of Obstetrics & Gynaecology, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Pillaiyarkuppam, Pondicherry, India, 607402; E-mail: sairam_sharmila@yahoo.co.in

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The term 'Hypertensive disorders of pregnancy' includes heterogenous collection of diseases, preeclampsia, eclampsia, chronic hypertension either essential or secondary, chronic hypertension with superimposed pre-eclampsia and transient hypertension.

Pregnancy induced hypertension (PIH) is also known as gestational hypertension:

Hypertension that develops because of pregnancy and regresses postpartum. It may present as any one of the following[3,6-8].

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.

Serum uric acid is a marker of oxidative stress, tissue injury and renal dysfunction, and therefore might be helpful in the prediction of complications of PE. Uric acid is the product of purine metabolism and is synthesised by the enzyme xanthine oxidase. Hypoxia and ischemia of the placenta and cytokines such as interferon induce the expression of xanthine oxidase and therefore increase the production of uric acid and reactive oxygen species. In uncomplicated pregnancies, serum uric acid concentration fall in first trimester 25-35 % due to an elevation in renal clearance secondary to increased glomerular filtration rate or reduced proximal tubular re-absorption and due to changes in its production rate; continue to remain low during second trimester and slowly increase during third trimester, possibly due to raised foetal production, decreased binding to albumin and a decline in uric acid clearance until towards the end of pregnancy when they approach non-pregnant values. Several studies have reported a positive correlation between elevated maternal serum uric acid and adverse maternal and foetal outcomes[9-15].

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. Serum uric acid is a specific laboratory finding in pre-eclampsia. However, there is a high degree of overlap among values found in normal pregnancy, mild pre-eclampsia, severe pre-eclampsia and eclampsia[16] (Table/Fig 1).

AIMS AND OBJECTIVES:

Aims:

To study the accuracy of serum uric acid in predicting complications of pre-eclampsia and its effect on pregnancy outcome.

Objectives:

1. To estimate the serum uric acid levels in term gestation with pre-eclampsia.
2. To evaluate the relationship between serum uric acid and foetal outcome.
3. To know the association between the level of serum uric acid and severity of hypertension.
4. To correlate serum uric acid levels with maternal morbidity and mortality.

MATERIALS AND METHODS

A prospective study to estimate serum uric acid was carried out in 60 pregnant women at term gestation (> 37 weeks of gestation) admitted in Raja Muthiah Medical College Hospital during the period October 2011 – September 2013 with diagnosis of pre-eclampsia (pregnancy induced hypertension and proteinuria with or without pathological oedema). These patients were included in the study after due informed consent. The criteria adopted to diagnose pregnancy induced hypertension[1]: Systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg. The criteria adopted to diagnose significant proteinuria[3,17,18]: One 24-hour urine collection with a total protein excretion of 300 mg / 24 hours. The criteria adopted with reference to oedema[1,2]: Previous definitions included oedema, but this sign is nonspecific and is observed in many normotensive pregnant women. Thus, oedema is no longer considered part of the diagnostic criteria for preeclampsia. Pre-eclampsia patients may or may not have pathological oedema. The criteria adopted to diagnose high-risk serum uric acid level[19]: Values ≥6 mg/dl (360 µmol/l) was cut off level for high risk in our study

Inclusion criteria:

All patients diagnosed as pre-eclampsia as per the above criteria subject to their willingness to participate in the study after informed consent.

Exclusion criteria:

1. History of chronic hypertension
2. Family history of hypertension or diabetes mellitus
3. Pre existing medical illness like heart disease, diabetes mellitus, renal diseases or thyroid disorders.
4. Hypertension before 20 weeks of gestation
5. Patients who are not willing to participate in the study.

Method of study

Out of all cases admitted with the diagnosis of pre-eclampsia, 60 were selected based upon fulfilling inclusion and exclusion criteria. A detailed history of each patient was taken and complete general and obstetric examination was done. All findings were recorded in pre-designed proforma. Hyperten-

sion and Proteinuria were diagnosed as per the criteria already described. For all patients included in the study all routine investigations including serum uric acid were done and recorded. For determination of serum uric acid two methods have been described: 1. Calorimetric method (Caraway's method) and 2. Enzymatic method. Calorimetric method is influenced by many factors in the procedure as well as many contaminating substances in the glassware etc. In the enzymatic method, enzyme uricase has been widely used for uric acid determinations because of its improved specificity[20-22]. Therefore, we used enzymatic method. All the patients were followed up until delivery and all maternal and foetal events were recorded. All complications of pre-eclampsia both maternal and foetal were statistically analysed to prove the predictive value of serum uric acid levels.

RESULTS AND OBSERVATIONS

Distribution according to the age of mothers: 18.3% of mothers were between the age group 18-21 years, 26.7% were between 22-25 years, 28.3% were between 26-29 years, and 26.7% were above 30 years (Table/Fig 2).

Distribution according to Gravida: 60.0% of mothers were primi, 28.3% were second gravid, 8.3% were third gravid and 3.3% were fourth gravid (Table/Fig 3).

Distribution according to Parity: 83.4% of 60 mothers were primi para, 8.3% were para 2, and 8.3% were para 3 (Table/Fig 4).

Distribution according to period of gestation: 28.3% were 37-38 weeks, 2.0% were 38-39 weeks, 33.3% were 39-40 weeks, 18.3% were 40-41 weeks of gestation (Table/Fig 5).

Mean and Standard Deviation of Blood Pressure, Serum Uric acid and Foetal outcome: The mean systolic was 146.33 and standard deviation 7.12. The mean diastolic was 95.67 and standard deviation 6.21. The mean uric acid was 5.25 and standard deviation 1.64. The mean foetal outcome of APGAR 1 minute was 4.05 and standard deviation 1.84. The mean foetal outcome of APGAR 5 minutes was 6.49 and standard deviation 1.19 (Table/Fig 6).

Distribution of Mothers according to Urine Albumin: Urine albumin was 1+ in 26.7% of mothers, 2+ in 43.3% of mothers, 3+ in 26.7 % of mothers and 4+ in 3.3% of mothers (Table/Fig 7).

Distribution of Mothers according to Mode of Delivery: 83.3% of mothers had caesarean section, 6.7% of mothers had abnormal vaginal delivery, another 6.7% had normal vaginal delivery and 3.3% had forceps delivery (Table/Fig 8).

Distribution of Mothers according to IUGR (intra uterine growth retardation) and IUD (intra uterine death): 79.4% of 60 mothers were admitted with IUGR, 14.7% of mothers were admitted with IUD and 5.9% of mothers were admitted with both IUGR & IUD (Table/Fig 9).

Relationship between 1st min APGAR and Serum Uric Acid: 94.4% of babies under high-risk category had an APGAR of less than 5/10 in the 1st minute of their life, whereas 80.0% of the babies under no risk category had an APGAR of less than 5/10 in the 1st minute of their life. The difference in the first minute APGAR in the high risk and no risk category was not statistically significant at p value of 0.1798 (Table/Fig 10).

Relationship between 5th min APGAR and Serum Uric Acid: 55.6% of babies under high-risk category had an APGAR of less than 5/10 in the 5th minute of their life, whereas 11.9% of the babies under no risk category had an APGAR of less than 5/10 in the 5th minute of their life (Table/Fig 11). The difference in the 5th minute APGAR in the high risk and no risk category was statistically significant at p value of 0.001. From this table infers that the mothers whose serum uric acid was more than 6 mg/dl had 4-5 times increased risk of having APGAR of less than 5/10 at 5th min when compared to mothers with serum uric acid less than 6mg/dl.

Maternal complications: 4 out of 42 women (9.52%) with serum uric acid ≥6mg/dl had maternal complications and 7 out of 18 women with serum uric acid <6mg/dl had maternal complications with a statistically significant p value of 0.01 (Table/Fig 12).

Types of Maternal Complications of Pre-eclampsia: 9.1% of mothers developed HELLP, 18.2% of mothers developed Ascites, 27.3% of mothers developed Eclampsia and 45.5% of mothers developed Abruption (Table/Fig 13).

Serum Uric Acid and Baby Weight: Considering less than 2.5 Kg as low birth weight serum uric acid levels of more than 5.5 are associated with significant low birth weight (p value of 0.01) which is statistically significant (Table/Fig 14).

Stepwise regression analysis of predictive value of Serum Uric Acid: Serum uric acid has significantly contributed for predicting the foetal outcome compared to maternal outcome. The predictive value of the variable separately is 0.01. Altogether, the above computations clearly state that serum uric acid will be highly predictive of foetal complications as compared to maternal complications (Table/Fig 15).

DISCUSSION

Total number of patients fulfilling all inclusion criteria and having given consent for the study were 60 (n=60).

Age and gravida/para status: According to Mac Gillvary[23] the relationship of the maternal age and pre-eclampsia incidence gives a 'J' shaped curve with increased incidence among young primi gravida and markedly increased among older primi gravid. According to Duckitt K et al[24], about 60% of the patients in pre-eclampsia group were primigravdae. This correlates well with our present study. In our present study 17 women were between 26-39 years (28.3%) and 16 women were between 22-25 and less than 30 years (26.7%) and only 11women were between 18-21 years (18.3%). 36 (60%) were primigravidae and 24 (40%) were multi gravidae; 83.4% were primi para, 8.3% were second para and 8.3 were third para.

Maternal outcome and serum uric acid: According to Disha Sahijuani et al[25] 10 out of 50 women (20%) with uric acid <6 mg/dl had maternal complications which is statistically significant (p = 0.01). In our study out of 60 women, 1(9.1%) developed HELLP, 2 (18.2%) developed ascites, 3 (27.3%) developed eclampsia and 5 (45.5%) developed abruption. According to Disha Sahijwani et al[25] out of 80 women 6 (24%) developed HELLP, 2 (8%) developed ascites 13 (52%) developed eclampsia and four (16%) developed abruption (16%). According to Liedholm et al[26] out of 26 women 20 had operative delivery i.e. caesarean section with use of any one antihypertensive use of two antihypertensives hydralazine added onto beta blocker with test uric acid cut off of 350 µmol/l. In our study out of 60 women 50 (83.3%) had operative delivery i.e. caesarean section, 4 (6.7%) had normal, 4 (6.7%) had abnormal vaginal delivery and 2 (3.3%) had forceps delivery. In our study out of 60 women, 42 were with serum uric acid ≥6 mg/dl. 4 of them had maternal complications which is statistically significant (p=0.01).

Foetal outcome and serum uric acid: In our study out of 60 women 34 women were admitted with IUGR and IUD in which 27 (79.4%) were with IUGR and 5 (14.7%) with IUD and 2 (5.9%) with both IUGR and IUD. About 94.4% of babies under high risk category i.e. mother with serum uric acid ≥6mg/dl had an APGAR of less than 5/10 in the first minute of their life, where as only 80.9% of the babies under no risk category, i.e. mother with serum uric acid ≤6mg/dl had an APGAR of less than 5/10 in the first minute of life, p value of 0.1798 which is not statistically not significant. Among the babies who had an APGAR of less than 5/10 at fifth minute, 55.6% were under the high risk category i.e. mother with serum uric acid >6mg/dl and only 11.9% of them with APGAR less than 5/10 at fifth minute were under low risk category. The difference in fifth minute APGAR in the high risk and no risk group was statistically significant at p value of 0.001. It is inferred that mothers whose serum uric acid was high had 4-5 times increased chances of delivering baby with less than 5/10 APGAR at fifth minute when compared to mothers whose serum uric acid was normal. Even though the above inferences in our study are, in favour serum uric acid levels ≥6mg/dl is predictive of both maternal and foetal complications at p value of 0.001 and 0.01 respectively, the step wise regression analysis infers that serum uric acid will be highly predictive of foetal complications (p value of 0.01) as compared to maternal complications (p value of 0.42).

In systematic review conducted by Thangaratinam et al[27], on 17 studies[26,24-43] with sample size ranging from 14-504 pre-eclampsia women, it was concluded that serum uric acid is a poor predictor of maternal and foetal complications in women with pre-eclampsia.

Several other studies (six studies) have reported a positive correlation between elevated maternal serum uric acid and adverse maternal and foetal outcomes[9-15].

CONCLUSION

In the past 17 studies with sample sizes ranging from 14 to 504 have concluded that serum uric acid is poor predictor of foetal and maternal complications of pre-eclampsia. Six other studies have reported a positive correlation between elevated maternal serum uric acid and adverse maternal and foetal outcomes. However, our study with a sample size of 60 has proved that serum uric acid is statistically significant predictor (p value 0.01) of foetal complications of pre-eclampsia even though not of maternal complications (p value 0.42). Further studies with bigger sample size may substantiate our conclusion.

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Authors' contribution:

Sl No	Author's name	Author's contribution
1	A. Rmamana Priya	Principal investigator
2	K. Jeyapriya	Manuscript preparation for publication. editing, replying and rewriting after reviewers' report & corresponding author.
3	N.S. Kannan	Editing, replying and rewriting after reviewers' report.

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Table 1: Pregnancy specific ranges for serum uric acid by gestational age (μmol/l): mean ± 2 standard deviations.

Week	Non pregnant	4w	8w	12w	16w	24w	32w	36w	38w	Post partum
Mean ± 2SD	364	328	330	267	285	276	322	344	381	389

Conversion table: Serum uric acid in μmol/l ÷ 60 = Serum uric acid in mg/dl.
Serum uric acid in mg/dl × 60 = Serum uric acid in μmol/l

Table 2: Age Distribution of Mothers.

Age groups	Number of mothers	Percentage
18-21 years	11	18.3
22-25 years	16	26.7
26-29 years	17	28.3
>30 years	16	26.7
Total	60	100

Table 3: Distribution of Mothers according to Gravity.

Gravida	Number of mothers	Percentage
Primi	36	60.0
2	17	28.3
3	5	8.3
4	2	3.3
Total	60	100

Table 4: Distribution of Mothers according to Parity.

Parity	Number of mothers	Percentage
1	20	83.4
2	2	8.3
3	2	8.3
Total	24	100

Table 5: Distribution of Mothers according to Period of Gestation.

Period of Gestation	Number of mothers	Percentage
37-38 weeks	17	28.3
38-39 weeks	12	20.0
39-40 weeks	20	33.3
40-41 weeks	11	18.3
Total	60	100

Table 6: Mean and Standard Deviation of Blood Pressure, Serum Uric acid and Foetal outcome

Variable	Number of mothers	Mean	Standard deviation
Systolic	60	146.3	7.12
Diastolic	60	95.67	6.21
Serum uric acid	60	5.25	1.64
APGAR 1 min	60	4.05	1.84
APGAR 5 min	60	6.49	1.19

Table 7: Distribution of Mothers according to Urine Albumin

Urine albumin	Number of mothers	Percentage
1+	16	26.7
2+	26	43.3
3+	16	26.7
4+	2	3.3
Total	60	100.0

Table 8: Distribution of Mothers according to Mode of Delivery

Mode of delivery	Number of mothers	Percentage
Caesarean section	50	83.3
Abnormal vaginal delivery	4	6.7
Normal vaginal delivery	4	6.7
Forceps delivery	2	3.3
Total	60	100.0

Table 9: Distribution of Mothers according to IUGR and IUD

IUGR & IUD	Number of mothers	Percentage
IUGR	27	79.4
IUD	5	14.7
Both IUGR & IUD	2	5.9
Total	34	100.0

Table 10: Relationship between 1 min APGAR and Serum Uric Acid

Serum uric acid	1 min APGAR Score				Chi square value	p value
	<5/10		>5/10			
	No	%	No	%		
≥6	17	94.4	1	5.6	1.80	0.1798
<6	34	80.9	8	19.1		

OR= 5.17

Table 11: Relationship between 5 min APGAR and Serum Uric Acid

Serum uric acid	5 min APGAR Score				Chi square value	p value
	<5/10		>5/10			
	No	%	No	%		
≥6	10	55.6	8	44.4	12.804	0.001
<6	5	11.9	37	88.1		

OR = 5.32

Table 12: Maternal complications

Complications	Mothers with Serum Uric Acid <6	Mothers with Serum Uric Acid >6	Total
Yes	7	4	11
No	11	38	49
Total	18	42	60
Chi square value	7.26		
p value	0.0071		Significant at 5%

OR=6.05

Table 13: Types of Maternal Complications of Pre-eclampsia

Serum uric acid level	Complication					Total
	DIC	HELLP	Ascites	Eclampsia	Abruption	
>6	0	1	2	2	2	7
<6	0	0	0	1	3	4
Total	0	1	2	3	5	11
Percentage	0	9.1	18.2	27.3	45.5	100

Table 14: Serum Uric Acid and Baby Weight

Serum uric acid level	Baby weight				Chi-square value	p value
	Number of women		Proportion of women			
	>2.5Kg	<2.5Kg	>2.5Kg	<2.5Kg		
<4.5	22	2	51.2	11.8	12.517	0.01
4.5-5.5	8	2	18.6	11.8		
5.5-6.5	6	6	14.0	35.3		
6.5-7.5	3	5	7.0	29.4		
7.5-8.5	4	2	9.3	11.8		
>8.5	0	0	0	0		
Total	43	17	100	100		

Significant at 0.001 level

Table 15: Stepwise regression analysis of predictive value of Serum Uric Acid

Serial No.	Step/Source	Cumulative R^2	^ R^2	Step t	P value
1	Maternal outcome	0.042	0.031*	1.421	0.42
2	Foetal	0.094	0.086*	4.424	0.01

Constant value = 21.541 * $p < 0.01$