THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (March–April 2017) 67(2):109–118
DOI 10.1007/s13224-016-0933-8

ORIGINAL ARTICLE

Estimation of Serum Uric Acid as an Indicator of Severity of Preeclampsia and Perinatal Outcome

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Received: 27 May 2016 / Accepted: 12 August 2016 / Published online: 9 September 2016

About the Author

Dr. Aparna Nair completed her MBBS degree in 2005 and MS (OBG) in 2009. She was placed third in her batch of students who successfully completed their post graduation. She has worked in multiple institutions across India post completion of her studies. She has a passion for teaching and is currently working as an Asst. Professor at a medical college in Bangalore. She has attended multiple camps in villages around Bangalore and has conducted awareness programmes in schools regarding menarche and menstrual cycles to increase awareness among vulnerable age children. Her areas of interest include hysteroscopy, laparoscopy, oncology, infertility. Working in a teaching institution has given her the opportunity to manage several rare and complicated (including medico-legal) cases like mullerian anomalies, adolescent oncology etc.

Abstract

Background Uric acid is a marker of oxidative stress tissue injury and renal dysfunction, hence a correlation hypothesized.

Objectives (1) To evaluate severity of preeclampsia with raised serum uric acid. (2) To evaluate perinatal outcome in preeclampsia with raised serum uric ccid.

Materials and Methods 50 pregnant women with severe preeclampsia and 50 normotensive women were included in the study and maternal serum uric acid was estimated in both the groups.

Results In the study group comprising of 50 cases of preeclampsia, there is a positive correlation ($r = 0.695$ & $+0.359$) between the variables in study group, and as the SBP or DBP increases, the MSUA concentration also increases. In control group, there is a negative correlation ($r = -0.083$ & -0.095). Perinatal complication was more in study group, 54 % were preterm compared to 4 % in control group also as MSUA value increased average gestational age decreased. Mean birth weight in study group was 1.8 kg study group of which 13 (26 %) babies were VLBW, 28 (56 %) were LBW, and 9 (18 %) babies had normal birth weight, in control group mean birth

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weight was 2.99 kg. There were 6 cases of ELBW babies in study group which were included in VLBW group for statistical calculation. The difference was found to be statistically significant ($p < 0.05$). In the study group, the MSUA concentration is found higher in LBW and VLBW babies compared to normal birth weight babies.

Conclusion There is a positive correlation between SUA & severity of preeclampsia, and a significant adverse fetal outcome is observed with raised MSUA in preeclamptic patients.

Keywords Maternal serum uric acid · Birth weight · Preeclampsia · Perinatal mortality

Introduction

Hypertension is defined as sustained blood pressure reading greater than 140/90 mm of Hg [1]. PIH is a common complication in 7–10 % of all pregnancies [2]. It is responsible for more than 50,000 maternal deaths yearly worldwide, 25 % fetal growth restriction and 15 % of preterm birth. It was reported in 1917 that uric acid elevation is a common clinical finding in women with clinically evident preeclampsia [2]. Since then the clinical utility of increased serum uric acid is actively debated. Uric acid is a marker of oxidative stress, tissue injury and renal dysfunction, hence a correlation with severe preeclampsia is hypothesized [3]. However, increased uric acid is an independent risk factor for cardiovascular diseases and is proposed to mediate altered vascular function and inflammation. Therefore, perhaps increased uric acid is a marker for severity of preeclampsia [4]. Uric acid is the end product of purine metabolism, synthesized by enzyme Xanthine oxidase [5–7]. During uncomplicated pregnancies, serum uric acid concentration decreases by 25–35 % in early pregnancies, but then increases throughout the pregnancy, primarily as the result of altered renal handling [8]. Renal handling of uric acid is complex and involves four sequential steps, namely 1. glomerular filtration, 2. reabsorption of about 98–100 % in proximal convoluted tubules, 3. secretion into the lumen of distal portion of proximal tubules and 4. further reabsorption in distal tubules. The net urinary excretion of uric acid is 6–12 % of amount filtered.

The reference interval for uric acid is 3.5–7.2 mg/dl (208–428 μmol/L) for men and 2.6–6.0 mg/dl (155–357 μmol/L) for women.

Reasons of Increased Uric Acid in Preeclampsia

1. Elevated uric acid level in preeclampsia is the result of a decrease in uric acid clearance that is secondary to disproportionate fall in glomerular filtration rate due to vasoconstrictors such as angiotensin II, nor epinephrine and endothelin [9, 10].
2. Preeclampsia is associated with increased free radical formation and elevated oxidative stress. Uric acid production is coupled with formation of reactive oxygen species when the Xanthine oxidase/dehydrogenase enzyme is in the oxidase form [11].
3. Elevated blood lactic acid levels interfere with uric acid excretion. Hyperlactacidemia is reported in PE, produced by hypoxic placenta [12].

Fetal Outcome in PIH

Preeclampsia and eclampsia are associated with intrauterine growth restriction, intrauterine hypoxia, intrauterine death and iatrogenic prematurity [13, 14]. Compromised uteroplacental circulation due to vasospasm is a major cause of increased perinatal mortality and morbidity associated with preeclampsia [4]. Fetal demises, birth asphyxia, meconium aspiration, neonatal hypoglycemia and hypothermia are all increased [15, 16].

Materials and Methods

Source of Data

The study was conducted for 2 years from September 2006 to August 2008. Data were collected from 100 patients from Department of Obstetrics and Gynaecology in Bowring & Lady Curzon Hospital and Vani Vilas Hospital attached to Bangalore Medical College and Research Institute. It included 50 pregnant women with severe preeclampsia as study and 50 normotensive pregnant women as controls. A prospective clinical observational study is carried out.

Study Group

Inclusion Criteria are 1. singleton pregnancy, 2. patients with gestational age of 28–40 weeks, 3. without other medical and surgical cause of hypertension, 4. severity of preeclampsia criteria a. diastolic blood pressure more than 110 mm hg, b. proteinuria >/= 3+ (3gm/l) and 5. perinatal outcome is measured under following parameters 1. birth weight, 2. gestational age and 3. perinatal mortality.

Exclusion Criteria are 1. multiple pregnancies, 2. chronic hypertension, 3. diabetes mellitus, 4. renal disorder, 5. liver disorder, 6. H/o antepartum hemorrhage, 7. H/o present or past gout and 8. H/o taking diuretics.

Control Group

The subjects included in this group were normotensive pregnant women with gestational age of 28–40 weeks, blood pressure of <140/90 mm hg and without medical comorbidities admitted for delivery.

A total of 100 cases meeting the inclusion and exclusion criteria were included in our study. A detailed clinical history was taken, and examination was done. The study protocol was approved by the ethical committee of the Bangalore Medical College and Research Institute, and written informed consent was obtained from each woman before inclusion in the trial. Blood pressure was measured with patient lying in the left recumbent position.

Estimation of urine albumin was done by fresh mid-stream clean catch urine using multistix reagent strip and is read as traces, +, ++, +++. ++++ depending on concentration of proteins. Estimation of serum uric acid was done by Trivedi & kabasakalian method with a modified trinder peroxidase method using TBHB. Normal value range −3.5 to −5.5 mg/dl.

Study Protocol

5 ml of venous blood was collected and analyzed within 24 h in our clinical laboratory for serum uric acid by modified trinder peroxidase method.

Method of Statistical Analysis

The following methods of statistical analysis have been used in this study. The Excel and Statistical Package for Social Science (SPSS Inc, Chicago) software packages were used for data entry and analysis.

1. Student's t test.
2. Proportions were compared using Chi-square test of significance.

In all the above tests, the "p" value of less than 0.05 was accepted as indicating statistical significance.

Results

In a study of 100 patients out of which 50 were normotensive (control) and 50 had PIH in study group. Table 1 shows comparison between cases and control with respect to age, parity, gestational age at delivery and maternal serum uric acid. Table 1 reveals that mean gestational age among study and control groups were 35.62 ± 3.4 wks (ranging from 28 to 40 weeks) and 38.08 ± 1.9 wks (ranging from 34 to 40 weeks MGA), respectively. Mean SUA concentration in study group is

Table 1 Comparison table for age, parity, gestational age and maternal serum uric acid

	Age					Parity			Gestational age					Maternal serum uric acid				
	Mean Age	SD	Min Value	Max Value	*p* value	Primi	Multi	*p* value	Mean	SD	Min	Max	*p* value	Mean	SD	Min Value	Max Value	*p* value
Case (50)	22.12	3.815	18	38	0.108	41 (82 %)	9 (18 %)	0.005	35.62	3.40	28	40	0.000	6.374	1.43	4	10.3	0.000
Control (50)	23.30	3.460	18	32		28 (56 %)	22 (44 %)		38.08	1.94	34	40		3.66	0.468	3	4.5	

Table 2 Mean comparison of systolic and diastolic blood pressure in study and control groups

	Systolic blood pressure					Diastolic blood pressure				
	Mean	SD	Min value	Max value	*p* value	Mean	SD	Min	Max	*p* value
Case (50)	166.7	18.63	140	240	0.000	114.3	9.10	110	150	0.000
Control (50)	115.4	5.37	110	126		75.16	5.82	60	82	

Table 3 Maternal morbidity in study group in view of, severity of PIH, HELLP and Eclampsia

	Severity of PIH		HELLP		Eclampsia	
	With impending signs	Without impending signs	Yes	No	Yes	No
Cases (50)	32	18	3	47	8	42

Table 4 Fetal Outcome

	Prematurity			Perinatal mortality			Birth weight				
	Pre Term	Term	*p* value	Live	Dead	*p* value	Mean	SD	Min	Max	*p* value
Case (50)	27 (54 %)	23 (46 %)	0.000	39 (78 %)	11 (22 %)	0.000	1877.00	593.35	600	3200	0.000
Control (50)	2 (4 %)	48 (96 %)		50 (100 %)	0 (0 %)		2990.00	326.55	1900	3600	

Table 5 Comparison of perinatal mortality according to gestational age

Gestational Age	Group	Perinatal mortality		
		Live	Died	Total
Preterm	Case	18	9	27
		66.6 %	33.3 %	100.0 %
	Control	2	0	2
		100.0 %	0 %	100.0 %
	Total	20	9	29
		68.9 %	31.03 %	100.0 %
Term	Case	21	2	23
		91.3 %	8.6 %	100.0 %
	Control	48		48
		100.0 %		100.0 %
	Total	69	2	71
		97.1 %	2.9 %	100.0 %

6.37 mg/dl, and in control is 3.6 mg/dl. The difference in MGA and mean SUA concentration between study and control groups was also found to be statistically significant ($p < 0.05$) (Table 1). Table 2 compares the systolic and diastolic blood pressure of the groups and difference was statistically significant.

Table 3 shows the maternal morbidity like severity of preeclampsia, HELLP syndrome & eclampsia. In Table 4, fetal outcome was compared. There were 27 (54 %) preterm deliveries in study group and only 2 (4 %) in the control group. Next perinatal mortality was significantly higher in study group, 11 (22 %) newborn expired in study and none in control group. The difference in the mean birth weight between study and control groups is found to be statistically significant ($p < 0.05$).

In the study group, 27 (54 %) were preterm out of which 9 (33.3 %) babies died and 2 (8.6 %) term babies died.

Of the total 39 live babies in study group, 23 (58.9 %) babies were IUGR babies. Out of the 39 (78 %) live babies in study group, 10 (25.6 %) babies had severe RDS when born, 9 (23.1 %) had mild RDS, and 20 (51.3 %) babies were healthy.

Table 5 shows distribution of birth weight of neonates into VLBW (1–1.5 kg + < 1 kg), LBW (1.5–2 kg), normal weight (>2 kg), of which 13 (26 %) of babies were VLBW, 28 (56 %) were LBW, and 9 (18 %) babies had normal birth weight in study group. There were 6 cases of ELBW babies in study group which were included in VLBW group for statistical calculation. The difference was found to be statistically significant ($p < 0.05$).

Table 6 shows the perinatal morbidity of infants in study ($n = 39$). 23 babies had IUGR and 10 had severe RDS. In the study group, the MSUA concentration is found higher in LBW and VLBW babies compared to normal birth weight babies, also MSUA concentration is higher in VLBW babies as compared to LBW babies. The difference between mean MSUA concentration in preterm and term groups in study group was found to be statistically significant ($p < 0.05$). Table 7 shows the correlation between

Table 6 Perinatal morbidity in study group (n = 39)

IUGR		RDS		
Yes	No	Severe	Mild	No problems
23 (58.9 %)	16 (41.02 %)	10 (25 %)	9 (23.1 %)	20 (51.3 %)

Table 7 Correlation chart between SUA & SBP & DBP

Group	Systolic blood pressure	Diastolic blood pressure
Case		
Uric acid		
Pearson correlation	0.695**	0.359*
Sig. (2-tailed)	0.000	0.011
N	50	50
Control		
Uric acid		
Pearson correlation	−0.083	−0.095
Sig. (2-tailed)	0.569	0.513
N	50	50

SBP, DBP and MSUA, in study group and control group. There is a positive correlation (r = 0.695 & +0.359) between the variables in study group and as the SBP or DBP increases the MSUA concentration also increases. In control group, there is negative correlation (r = −0.083 and −0.095).

Discussion

The ultimate goal of any protocol for management of preeclampsia must be maternal safety delivery of a healthy live mature newborn. As some amount of expectant management exists in all treatment protocols it would be advantageous to predict development of severe of PIH.

Five principle findings have been evolved from this study: (1) there is a positive correlation between SUA and both SBP and DBP, hence as the SUA concentration increased both systolic and diastolic blood pressure increased. (2) There is a significant increase in perinatal mortality in severe preeclamptic patients with hyperuricemia, more so in preterm group, compared to control group. (3) As shown in Table 8, the mean gestational age of delivery decreased significantly with increasing MSUA concentration in preeclamptic patients. (4) A significant increase in low birth weight, very low birth weight, extremely low birth weight babies with increasing MSUA concentration, with highest MSUA level in very low birth weight babies. (5) Perinatal morbidity (as increase in RDS, IUGR) is significantly increased in preeclamptic patients with hyperuricemia compared to control group.

Table 9 Comparison of present study to others about SUA & PIH

Studies	Control	Mild PIH	Severe PIH	Eclampsia
Present study	3.6		6.3	
Magnann et al. [17]	2.8–4.3	4–5.5	4.8–7.8	5.9–10.1
Powers et al. [2]	5.1 ± 1.2	5.3 ± 1.2	6.9 ± 1.4	

(All values of serum uric acid is in mg/dl)

Certain studies have been conducted to estimate value of SUA in predicting complications of PIH, like in a study by Wiltin et al. [18] MSUA concentration >8.1 mg/dl is associated with increased incidence of eclampsia, in preeclamptic patients. In our study, such value could not be calculated as it is a cross-sectional study and only one value of SUA was calculated. Table 9 compares the present study to other studies with respect to serum uric acid and severity of PIH.

In the present study group, 6 % patients had HELLP syndrome and 16 % patients had eclampsia, similar to a study by Robert et al. [19] were in patients with increased SUA concentration 2.8 % patients had HELLP syndrome.

As seen in Table 10, Powers et al. [2] conducted a prospective study where SUA was compared with mean birth weight and results were comparable to present study.

In our study distribution of neonates in the study group is more in LBW (56 %). When compared with MSUA concentration to neonatal birth weight in both groups, in

Table 8 Comparison of serum uric acid in terms of birth weight and gestational Age

	Birth weight							Gestational age						
		N	Mean	SD	Min	Max	p value		Number	Maternal serum uric acid	SD	Min	Max	p value
Case (50)	Very low	13	7.969	1.23	6.4	10.3	0.000	Preterm	27	7.119	1.38	4.8	10.3	0.000
	Low	28	6.025	1.01	4.2	8.6								
	Normal	9	5.156	0.80	4.0	6.3		Term	23	5.500	0.92	4.0	10.1	
Control (50)	Low	3	3.967	0.05	3.9	4.0		Preterm	5	3.520	0.90	3	4.0	0.485
	Normal	47	3.640	0.47	3.0	4.5		Term	45	3.67	0.40	3.1	4.5	

Table 10 Results by Powers et al

	Control	Hypertension & proteinuria	Hypertension & proteinuria & hyperuricemia	Hypertension & hyperuricemia
Mean birth weight	3.42 kg	3.2 kg	2.48 kg	3.17 kg
Mean serum uric acid	5.1 ± 1.2	5.3 ± 1.2	6.9 ± 1.4	7.3 ± 1.1

Table 11 Study by Robert et al

	Control	Hypertension, proteinuria	Hypertension, hyperuricemia	Hypertension, proteinuria, hyperuricemia
Birth weight centile	50	42.8	38.9	33.7

Table 12 Effect of hyperuricemia on gestational age

	Control	HP	HPU	HU
Gestational age at delivery(wks)	39.5	39	38.7	35.4
Percent of preterm	6.3 %	8.3 %	57.5 %	19.2 %

the study group as the MSUA concentration increased the mean birth weight in neonate decreased, This observation is similar to result by various other authors like August et al. [20] Robert et al., Magnnan et al.

In various other studies conducted they compared birth weight and birth weight centile in different category of PIH, like a study by Robert et al. [19] in Table 11.

As seen in Table 10, birth weight centile decreased with the presence of hyperuricemia. Also in the study by Robert et al. shown in Table 11 they noted the risk of having infant birth weight </=10th/5th centile increased with increase in SUA concentration.

The MGA of delivery in study group was 35.62 weeks, and in control group was 38.08 weeks, the difference is statistically significant ($p < 0.05$). Accordingly, more preterm birth occurred in the study group. When it is compared with MSUA concentration, highest MSUA concentration was in study preterm group and as the MSUA concentration increased the mean gestational age decreased. This study is comparable with studies of other authors like Magnann et al. found a positive correlation between increasing/raised SUA & IUGR & preterm birth. In Table 12, Robert et al. stated that with every one unit increase in SUA ź score it increased the odds of preterm birth by 2.43 fold and SGA by 1.8 fold.

According to Robert et al., the risk of preterm is increased in group of patients with hypertension proteinuria hyperuricemia and even in the absence of proteinuria, hyperuricemia is a significant risk factor for preterm birth. This is specified in Table 12.

The perinatal mortality in present study was 22 % study group and 0 % in control group, and the difference was found statistically significant ($p < 0.05$). In other study by Magnnan et al. [17], there is a positive correlation between increasing/raised SUA level & increased incidence of PNM, stillborn.

In the present study increased perinatal morbidity was observed in study group. This observation is similar to studies mentioned below.

1. Magnnan et al.—positive correlation with increased SUA.
2. Robert et al.—23.9 % associated with hypertension, proteinuria and hyperuricemia groups.
3. August et al.—17 % in preeclampsia group with SUA concentration 4.17 ± 0.9 mg/dl.

To conclude, for the past two decades, there have been conflicting reports in the literature regarding usefulness of MSUA estimation in preeclamptic women. The present study was carried out as an attempt to critically reappraise its role in evaluating the severity of preeclampsia and predicting the fetal outcome in preeclampsia patients.

Compliance with Ethical Statement Conflict of Interest Dr. Aparna Nair and Dr. Savitha C declare that they have no conflict of interest.

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

Appendix 1

CONSENT FORM

I have been explained to my entire satisfaction the nature of the study entitled "Estimation of Serum Uric Acid as an indicator of severity of Preeclampsia & Perinatal Outcome".

I am willing to give consent for my participation in this study. I am also aware of my right to opt for discontinuation from the study at any time without giving reasons to do so.

Signature of the Doctor:

Date:

Patient Signature:

Date:

Appendix 2

PROFORMA

Name: IP NO:
Age: DOA:
Occupation: DOD:
Address:

Chief Complaints: -

1. Months of amenorrhea
2. Pain abdomen
3. H/o swelling of lower limb, facial puffiness, etc.
4. H/o headache, blurring of vision, epigastric pain
5. Perception of fetal movement
6. H/o leak, bleed p/v

9. Obstetric H/o: -

1. Married life Consangutiy
2. Age of Marriage
3. Parity Index G P L A D
4. Obstetric Details T1

T2

T3

5. Booked/ Unbooked

10. Menstrual H/o-

1. LMP- EDD-
2. Age at menarche-
3. Past menstrual cycles-

11. Past H/o: -

1. Diabetes mellitus
2. Hypertension
3. Tuberculosis
4. Bronchial asthma
5. Gout
6. Renal disorder
7. Liver disorder
8. Epilepsy
9. H/o Surgery

12. Family H/o :-

1. Diabetes mellitus
2. Hypertension
3. Ischemic Heart Disorder
4. Renal Disorder
5. Liver Disorder
6. Gout

13. Personal H/o : -

1. Diet
2. Appetite
3. Weight
4. Sleep
5. Bowel Habits
6. Bladder Habits
7. Smoking
8. Alcohol

14. EXAMINATION: -

1. General Physical Examination: -

(i) Blood Pressure
(ii) Pulse Rate
(iii) Temperature
(iv) Respiratory rate
(v) Pallor
(vi) Icterus
(vii) Cynosis
(viii) Clubbing
(ix) Pedal edema
(x) Lymph node
(xi) Thyroid
(xii) Breast
(xiii) Spine
(xiv) Koilonychias

2. per Abdomen: –

(i) Uterine size
(ii) S.F.H
(iii) Fundal grip
(iv) Lateral grip
(v) Pelvic grip
(vi) F.H.S
(vii) Abdominal wall edema

3. per Vaginal Examination: -

(i) 1. Os
(ii) Cervix
(iii) Presenting part
(iv) Membrane
(v) Pelvis
(vi) Liquor

15. INVESTIGATION:-

(i) Hemoglobin
(ii) Bleeding time
(iii) Clotting time
(iv) Urine routine- micro
Sugar
Albumin
(v) Blood group
(vi) H.I.V
(vii) HbsAg
(viii) V.D.R.L.
(ix) Sr.Uric acid
(x) R.B.S.
(xi) Blood Urea
(xii) Sr.Creatinine
(xiii) Liver function test-
T.bilirubin
D.Bilirubin
SGOT
SGPT
T.Protein
Sr. Albumin
A: G ratio
LDH
Alkaline phosphatase
(xiv) Platelet count
(xv) N.S.T
(xvi) Ultrasound reports

16. DELIVERY NOTES: -

1. Mode of Delivery- a) Vaginally

b) L.S.C.S
Indication

17. PERINATAL OUTCOME: -

1. Birth weight-
2. Gestational age
3. Perinatal mortality

Appendix 3: Key to Master Chart

IP No	Inpatient number
GA	Gestational age in weeks
Obs index	Obstetric index
BP	Blood Pressure
MAP	bMean arterial pressure
NA	Not applicable
Primi	Primigravida
FTND	Full-term normal delivery
IUGR	Intrauterine growth restriction
IUD	Intra uterine death
NICU	Neonatal intensive care unit
NR NST	Non-reactive non-stress test
PIH	Pregnancy-induced hypertension
SUA	Serum uric acid
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MGA	Mean gestational age
HTN	Hypertension
PNM	Perinatal mortality
HELLP	Hemolysis elevated liver enzymes low platelet
RDS	Respiratory distress syndrome
LBW	Low birth weight
MSUA	Maternal serum uric acid

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