Maternal Serum Uric Acid as an Index of Perinatal Outcomes in Severe Preeclampsia

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Abstract: *Preeclampsia is a multisystem disorder characterized by gestational hypertension after the 20th week of gestation with proteinuria, is common and dangerous adverse event of pregnancy. Several studies reported relationship between uric acid concentrations and severity of disease in pregnant women. The objective of this study was to explore the relation between serum uric acid level and perinatal outcomes. A case–control study conducted in Sulaimani Maternity Teaching Hospital from January 2014 to July 2014. Included 100 pregnant women in third trimester with signs and symptoms of labour, who had no comorbid diseases. Grouped to 30 control without hypertension, 30 with pregnancy induced hypertension (PIH) and 40 with severe preeclampsia based on clinical and laboratory evaluation. SPSS v21 was used for obtain mean, standard deviation, frequency and percentage. One way ANOVA test used to obtain P value with consider <0.05 significant value. Results show serum uric acid mean and standard deviation (±SD) for control, PIH and severe preeclampsia groups were (5.83 ± 9.544), (4.35 ± 1.372) and (7.59 ± 0.508) respectively. The positive and significant (< 0.001) correlation coefficient was found between high serum uric acid level and oligohydramnios, low birth weight and low Apgar score. The highest level of serum uric acid was recorded in preeclampsia group and the lowest level was in PIH group. Significant and adverse perinatal outcomes relation were noted in the patients with high serum uric acid (>7 mg/dl); decreased amniotic fluid index (AFI), caused low birth weight and low Apgar score. In*
conclusion that severity of illness in pregnant preeclampsia cases can be estimated by serum uric acid level and high serum uric acid indicate high risk cases. Maternal serum uric acid is a useful index for estimate fetal health status and predict neonate outcomes.

Keywords: preeclampsia, uric acid, pregnancy induced hypertension (PIH), maternal serum uric acid.

1. INTRODUCTION

Preeclampsia is hypertension when Systolic BP≥140mm Hg and diastolic BP ≥ 90mmHg on at least two occasions
4 hours apart. Preeclampsia is a multisystem disorder after the 20th week of gestation with proteinuria cause maternal and fetal morbidity and mortality [1], in Lisonkova study they determined that preeclampsia identified in 3.1 per cent of all pregnancies [2]. Berg and colleagues (2003) reported that almost 16 per cent of 3201 maternal deaths were from complications of pregnancy-related Hypertension [3]. Preeclampsia is associated with uricemia [4].

Uric acid is minimally soluble and its concentration is maintained relatively low in healthy individuals (<6.0 mg/dL), increased uric acid in pregnant women is a marker of raised xanthine oxidase activity. This elevation of uric acid in women related to reduced glomerular filtration rate, increased tissue breakdown, decreased secretion and increased reabsorption [5]. In pregnant women, a high increase of uric acid influence on placental growth and development, resulting in compromised oxygen and nutrient delivery to the placenta [6].

Elevated uric acid concentrations were first noted in preeclamptic women in the late 1800s. Since that time, numerous studies have demonstrated a significant relation and we can use uric acid level as an indicator for severity of preeclampsia [7] and other studies showed a non-significant relationship between uric acid concentrations and severity of preeclampsia, they showed a lack of sensitivity and specificity to be used as diagnostic test [8-10]. Still, most of the studies concluded that validity of using uricemia as a preeclampsia predictor [11] and Corominas 2018 study suggest, combination usage of the uric acid and proteinuria [12].

The aim of this study to explore the relationship between serum uric acid level with perinatal outcomes and serum uric acid level can be used as an indicator of preeclampsia severity and fetus health status.

2. PATIENTS AND METHODS

Observational study with case-control method conducted at Sulaimani Maternity Teaching Hospital during the period from January 2014 to July 2014. A total number of 100 primigravida pregnant women at labour ward in the third trimester were included with characteristics; Primigravida, singleton pregnancy, gestational age (30 – 40 weeks) determined by LMP and early pregnancy ultrasound, vertex presentation and women in spontaneous labour and cases excluded if they had multiple pregnancies, *Diabetes mellitus*, chronic hypertension, history of crystal arthropathy (gout), thyroid problem, renal disease, obesity, meconium stained liquor, induction of labour, instrumental delivery and Malpresentation. After taking a detailed history, clinical examination and Blood pressure measurement

from patients file they divided to three study groups: 30 of them with normal blood pressure and no proteinuria, while the other 30 with pregnancy-induced hypertension (BP >140/90 mmHg without proteinuria) and the remaining 40 with severe preeclampsia [BP>160/110 mmHg with proteinuria (urine protein ≥ 2+ by dipstick measurement)]. For measurement of serum uric acid, 3 ml sample of maternal peripheral blood is collected directly in the tube, centrifuged for 10 minutes then the serum is analyzed in multi-analyte biochemistry panel.

Data collected by direct interview and from patients file for patient's history and tests, collected data analyzed by SPSS (Statistical Program for Social science) software version 21, quantitative data were described as a mean and standard deviation and qualitative variables were described as frequency and percentage. ANOVA test used to determine a relation between variables with P value < 0.05 considered statistically significant.

3. RESULTS

A total participates of 100 pregnant women who were admitted to Sulaimani Maternity Teaching Hospital included in period from January 2014 to July 2014, who were in spontaneous labour, separated in to 3 groups; Severe Preeclampsia (PE) were 40 cases, pregnancy-induced hypertension (PIH) 30 cases and control group were 30 pregnant women.

The age of the women in 3 groups ranged between 18 to 40 years old, the mean ages were, for the preeclampsia (PE) 28.35 ± 6.070, pregnancy-induced hypertension (PIH) 29.60 ± 6.42 and control groups 29.67 ± 5.561. Regarding body mass index (BMI) in all groups ranged between (16-26) kg/m2, mean were PE 22.75 ± 2.035, PIH 22.63 ± 1.938 and control 22.37 ± 1.991. The gestational ages for all groups ranged between (30-40) weeks, with mean PE 34.78 ± 2.675, for PIH 35.30 ± 2.507 and for control 35.30 ± 2.781. There was no significant relationship between this groups as shown in (table 1).

Table 1: Characteristics of the studied groups.

| Studied variables | Studied groups | | | P values |
	PE Mean ± SD	PIH Mean ± SD	Control Mean ± SD	
Age (years)	28.35 ± 6.070	29.60 ± 6.42	29.67 ± 5.561	0.582 (NS)
BMI	22.75 ± 2.035	22.63 ± 1.938	22.37 ± 1.991	0.725 (NS)
GA (weeks)	34.78 ± 2.675	35.30 ± 2.507	35.30 ± 2.781	0.628 (NS)

The mean ± SD of serum uric acid level was higher in the PE group (7.59 ± 0.508) while it was less in control group (5.83 ± 9.544) but it was lowest in the PIH group (4.35 ± 1.372). However, there was a statistically significant relation between groups with P-value= 0.031 (Table 2).

Table 2: Mean and standard deviation of Serum uric acid level among studied groups.

| Groups | SUA mg/dl | P value |
	Mean ± Std. Deviation	
PE	7.59 ± 0.508	0.031
PIH	4.35 ± 1.372	
Control	5.83 ± 9.544	

Majority of cases 69% were had a normal level (2-7 mg/dl) of maternal serum uric acid (SUA) and 76% had a normal range of amniotic fluid index (AFI). Most of neonate 57(57.6%) did not admit to NCU with one neonate death and from all 42 neonates in NCU only 7(16.7%) cases developed convolution.

Table 3: frequencies and percentages of different parameters.

	Frequencies	Percentages
Serum uric acid (SUA):		
2-7 mg/dl	69	69
>7 mg/dl	31	31
Total	100	100
Amniotic fluid index (AFI):		
Oligohydramnios	24	24
Normal	76	76
Total	100	100
Neonatal care unit (NCU):		
Yes	42	42.4
No	57	57.6
Total	99*	100
Convulsion in NCU:		
Yes	7	16.7
No	35	83.3
Total	42	100

* One neonatal death (intrapartum)

Maternal serum uric acid (SUA) level (2-7) mg/dl were found in 11(27.5%) cases, in all PIH 30 (100 %) cases and in control 28 (93.3%) cases while was > 7 mg/dl SUA found in 29 (72.5%) PE cases, only 2 (6.7%) cases in control and no cases in PIH and there was a highly significant difference between less and more than 7 mg/dl SUA between groups with p-value (<0.001) (Table 3).

Amniotic fluid index (AFI) volume adversely react with SUA level, cases with normal AFI (5-25 cm) were 64 (84.2%) cases with normal SUA level but in abnormal level of SUA were 12 (15.8%) cases, as so in abnormal AFI (< 5 cm) volume were 5 (20.8%) cases with normal level of SUA level but in abnormal level of SUA level were 19 (79.2%) cases and there was highly a significant relationship with p-value (< 0.001) (Table 4).

Vaginal delivery (VD) were higher in normal level of SUA 47 (82.5%) cases but in abnormal level of SUA were 10 (17.5%) cases however for caesarean

section(C/S) were approximately same for both 22 (51.2%) cases for normal and 21 cases (48.8%) cases for abnormal level of SUA nevertheless there was a highly significant difference with a p-value < 0.001(Table 4).

Most admitted 23 (54.8%) cases to neonatal care unit (NCU) were had a normal level of USA while 19 (45.2%) cases had abnormal level of SUA and 46 (80.7%) cases not admitted were had normal level of SUA while 11(19.3%) cases had abnormal level of SUA with highly significant differences (p-value 0.006).

NCU admitted cases were 42 cases, only 3 (13.1%) cases in the normal level of SUA developed convulsion while 4 (21.1%) cases developed convulsion. There were non-significant differences with a p-value 0.129 (Table 4).

Table 4: Relationship between maternal serum uric acid levels with maternal and neonatal outcomes

Variables	SUA (mg/dl)		P values
	2-7 N (%)	More than 7 N (%)	
Studied groups:			
Severe PE	11(27.5%)	29(72.5%)	
PIH	30(100%)	0(0.0%)	< 0.001
Control	28(93.3%)	2(6.7%)	
Amniotic fluid index (AFI):			
< 5 cm (abnormal)	5(20.8%)	19(79.2%)	< 0.001
5-25 cm (normal range)	64(84.2%)	12(15.8%)	
Mode of delivery:			
Vaginal delivery (VD)	47(82.5%)	10(17.5%)	<0.001
Caesarean section (C/S)	22(51.2%)	21(48.8%)	
Neonatal care unit (NCU):			
Yes	23(54.8%)	19(45.2%)	0.006
No	46(80.7%)	11(19.3%)	
Convulsion in NCU cases:	3(13.1%)	4(21.1%)	0.129

In the comparison of mean ± SD of Apgar score at 1st minute, Apgar score at 5th minute and birth weight between groups show that all were lowest in severe PE and highest in control group. There was a highly significant difference between the three groups in all outcomes (Table 5).

Table 5: shows mean and standard deviation of perinatal outcome and studied groups.

Studied groups	Severe PE	PIH	Control	P values
APGAR (1st minutes)	5.38 ± 1.95	6.70 ± 1.02	7.10 ± 1.60	< 0.001
APGAR (5th minutes)	6.78 ± 1.80	7.67 ± 1.64	7.97 ± 1.45	0.009
Birth weight (kg)	1.99 ± 0.26	2.63 ± 0.51	2.90 ± 0.70	< 0.001

High uric acid level lowing mean of AFI, birth weight, Apgar at 1st and in 5th minutes. Mean of these birth outcomes were higher in the normal level of uric acid (2-7 mg/dl) than mean in an abnormal level of uric acid (>7 mg/dl) and differences were highly significant for all of the birth outcomes (Table 6).

Table 6: shows relation of serum uric acid and perinatal outcomes

SUA mg/dl	2-7 mg/dl Mean ± SD	>7 mg/dl Mean ± SD	P values
AFI	9.2 ± 3.19	3.88 ± 2.50	< 0.001
Birth weight(kg)	2.69 ± 0.63	1.97 ± 0.27	< 0.001
Apgar 1st min	6.85 ± 1.35	5.17 ± 2.01	< 0.001
Apgar 5th min	7.70 ± 1.50	6.67 ± 1.91	0.002

4. DISCUSSION

This study conducted on 100 pregnant women admitted to Sulaimani Maternity Teaching Hospital, by case-control method where divided to 3 groups; 40 cases with preeclampsia (PE), 30 cases with pregnancy induced hypertension (PIH) and 30 cases control. To evaluate the level of maternal serum uric acid (SUA) in preeclampsia and its effect on perinatal outcomes.

The results of the current study demonstrate that mean of age (28.35) and gestation weeks (34.78) was lower in preeclampsia group than other groups we found same difference and near mean rate in Enaruna 2014 study[13], preeclampsia group age was (28.83) and gestation weeks mean (36.19) but in the present study BMI mean was (22.75) slightly higher in PE group compare to other groups we found the same result in Enaruna study but BMI mean was (26.42), this deference might relate to region of the study and all relation were non-significant in the current study and Enaruna study.

The results showed that mean of serum uric acid level and percentage of abnormal level of serum uric acid was higher in PE group compared with other groups with a statistically significant difference, this result was same with Patel Tjel (2014) study [14], AnkitaGawde (2014) study [15] and Lim and Frideman in 1998 study concluded that hyperuricemia associated with Preeclampsia and uric acid level mirror to the severity of Preeclampsia [10].

In normal pregnancy women rate of uric acid decrease up to 35% compare to non-pregnancy women [16], it produces an increase of glomerular filtration and reduces of reabsorption of uric acid by pregnant women kidney [17]. However, in the pre-eclampsia women there is impairment in the placenta caused by trophoblastic invasion and formation of the ischemic metabolite [18], this formation effect on peripheral vasoconstriction in glomeruli and glomerular endotheliosis in the result cause decrease of GFR and increase absorption of uric acid by proximal convoluted tubule that leads to elevated uric acid level in blood [19]. Studies show this increase of the uric acid effects on decreasing estrogen and repressed the activity of the angiotensin system [20].

The results of this study shows that pregnant women with abnormal SUA had less amount of amniotic fluid index (AFI) with a significant correlation. Studies concluded that Oligohydramnios or deficiency of amniotic fluid volume is increasing neonatal and maternal morbidity and mortality [21, 22] and Ladella 2017 who showed that AFI greater than 5cm decrease stay in NICU period [23]. Amniotic fluid volume can be

estimated by many techniques but common techniques are the four quadrants amniotic fluid index and the single largest vertical pocket [24]. However, many studies like Bachhav 2014 study concluded that AFI is a poor predictor for perinatal outcome still it is valuable screening test for predict fetus health status [25].

Caesarean section was highest in high SUA groups and vaginal delivery was highest in normal SUA group with significant correlation, we found the same result in Patel Tejal (2014) [14], Agrawal (2015) [26] and F. Yassaee (2003) [27]. The Koopmans (2009) study concluded that vaginal delivery mode in preeclampsia had better outcomes compare to Caesarean section for both maternal and neonatal [28].

Our results show that high uric acid pregnant women had a lower mean of Apgar score for 1st and 5th minutes and birth weight compare to normal uric acid group with a significant relationship, this concludes that high uric acid had adverse effects on neonatal outcomes. These results agree with Patel Tejal (2014) study [14], Singh (2014) study [29] and Shah DM (1996) [30] concluded that high uric acid patients have 4.2 relative risk to adverse outcomes, Shah DM suggested that uric acid can be used to predict neonatal morbidity and mortality outcome.

Our study concluded that severe preeclampsia cause adverse outcome to neonatal like low birth weight and low Apgar score at 1st and 5th minutes with significant relation, we found same results in Asma Ul Hosna (2008) and James M. Roberts (2005) who reported patients with severe preeclampsia associated with higher incidence of neonatal adverse outcome [31,7]. In this study, neonatal care unit (NCU) admission in hyperuricemia neonates were lower than normal uric acid neonates with significant relation, we found the same result in Singh (2014) study [29] and opposite result with Acien (1990) show that hyperuricemia neonates more admitted to hospital but both studies were non-significant [32]. Very few neonates in the current study developed convulsion with non-significant relation, might be related to the sampling method and our study more focused on other outcomes than convulsion. To determine this relation more studies with a bigger sample size and control of other cofounders.

Limitation of this study was a short time period that we cannot choose cohort study to follow children after birth for long period, also we had chosen few sample size, more analytic tests need to determine some outcomes with control of other factors for that we recommend separate studies for each neonatal outcomes.

5. CONCLUSION

Our study concluded that severity of illness in pregnant preeclampsia cases can be estimated by serum uric acid level and high serum uric acid indicate high risk cases. Maternal serum uric acid is a useful index for estimate fetal health status and predict neonate outcomes. Maternal uric acid increased perinatal morbidity and admission to neonatal care unit (NCU).

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