



Serum Uric Acid as a Predictor of Perinatal Outcome in Women with Pre-Eclampsia

Jwan Muhammad Zangana^{1*} and Awat Ibrahim Hamadamen²

¹ Assistant Professor Family Medicine, College of Medicine, Hawler Medical University, Erbil, Iraq

² College of Medicine, Hawler Medical University, Erbil, Iraq

*Corresponding e-mail: dr_jwanzangana@yahoo.com

ABSTRACT

Background and objectives: Pre-eclampsia is one of the medical complication of pregnancy and contributes significantly to maternal and perinatal morbidity and mortality. Hyperuricemia is often associated with pre-eclampsia. The objective of this study was to assess serum uric acid in group of women with pre-eclampsia and to evaluate its diagnostic effect on perinatal outcome. **Patients and methods:** This is a hospital-based cross-sectional study conducted in Maternity Teaching Hospital in Erbil city, Iraq. Convenient sample size of 200 participants pre-eclamptic pregnant women with ≥ 34 weeks of gestation in different level of hypertension were included. After getting informed consent from participant who were diagnosed with pre-eclampsia (hypertension and proteinuria), all socio-demographic information was collected from 1st June 2017 to 19th January 2018. Blood samples were obtained to assess serum uric acid besides other investigation routinely done and fetal outcome (birth weight, gestational age, intrauterine death, Apgar score, admission to neonatal care unit, intrauterine growth restriction and early neonatal death) was evaluated. **Results:** Serum uric acid was ≥ 6 mg/dL in 127 (63.5%) among all pre-eclamptic women. There was positive significant association between means of serum uric acid at different levels of hypertension with $p=0.000$ in ANOVA and χ^2 test. This study revealed significant association between increased level of serum uric acid and bad fetal outcome (birth weight, gestational age, intrauterine death, Apgar score, admission to neonatal care unit, intrauterine growth restriction and early neonatal death and Apgar score in 1st minute). **Conclusion:** This study revealed significant raised level of serum uric acid among pre-eclamptic women and significant effect on fetal outcome and perinatal morbidity and mortality.

Keywords: Serum uric acid, Fetal outcome, Pre-eclamptic women, Hypertension

Abbreviations: BP: Blood Pressure; GFR: Glomerular Filtration Rate; IUGR: Intrauterine Growth Restriction; IUFD: Intrauterine Fetal Death; NCU: Neonatal Care Unit; PE: Pre-eclampsia; XO: Xanthine Oxidase

INTRODUCTION

Hyperuricemia is a common finding in pre-eclamptic pregnancies. The elevation of uric acid in pre-eclamptic women often precedes hypertension, proteinuria and the clinical manifestations used to diagnose the disorder [1]. There are several potential origins for uric acid in pre-eclampsia; abnormal renal function, increased tissue breakdown, acidosis, and increased activity of the enzyme xanthine oxidase/dehydrogenase [2]. Rather than its role in pre-eclampsia during pregnancy, hyperuricemia is considered a risk factor for hypertension, cardiovascular and renal disease [2]. The severity of pre-eclampsia increases with increasing uric acid, questions whether uric acid may play a role in the pathophysiology of pre-eclampsia [3]. The association of hyperuricemia with pre-eclampsia has been known since 1971; the relationship of the degree of hyperuricemia and severity of disease has been known since 1934 [2]. The role of uric acid in the pathophysiology of pre-eclampsia is not clear whether it is a marker of disease or it actively takes part in the pathogenesis of disease [4,5].

Elevated uric acid concentrations were first noted in pre-eclamptic women in the late 1800s. Since that time numerous reports have demonstrated a relationship between uric acid concentrations and severity of disease [6,7], at the

same time it is one of the most consistent and earliest detectable changes in pre-eclampsia and has been cited as a better predictor of fetal risk than blood pressure [7], hyperuricemia was evident in 16% of women with gestational hypertension without proteinuria and 75% of women with clinically diagnosed PE. Hyperuricemia among pregnant hypertensive women was associated with an excess of adverse fetal outcomes. The rate of growth restriction and preterm birth was prevalent among hypertensive women with elevated concentration of uric acid even in the absence of proteinuria disorder. Uric acid elevation often precedes clinical manifestations of the disease including reduced glomerular filtration rate [7].

Hyperuricemia has historically been attributed to reduced renal clearance. Uric acid is filtered, reabsorbed, and secreted by the kidney. Hypovolemia, an early change in pre-eclampsia, increases uric acid reabsorption which could increase serum uric acid concentrations. However, increased uric acid precedes the reduction in plasma volume [8]. Increased uric acid production from maternal, fetal, or placental tissues through heightened tissues breakdown (i.e. increased substrate availability) and/or increased XO activity could also explain the increased concentration. The specific stimuli responsible for increased XO activity in pre-eclamptic women are unclear. The possible roles of placental ischemia-reperfusion injury, reduced antioxidant capacity and oxidative stress will be discussed below.

It is reported in several previous studies in European countries that is in normal pregnant women the level of serum uric acid is 25-35% decreased of than the level of uric acid of non-pregnant women [9]. However, the level of uric acid increased and come to normal level, it is proposed that there is raised glomerular filtration in pregnant women and reduced reabsorption of uric acid from proximal tubules of kidney during pregnancy [10]. In women with pre-eclampsia there is impaired trophoblastic invasion in the placenta and ischemic metabolite formation [11]. These ischemic metabolites are responsible for peripheral vasoconstriction in glomeruli and glomerular endotheliosis results in decreased GFR and increased uric acid net reabsorption from proximal convoluted tubule leading to increased level of serum uric acid [12].

This study was previously done in many developed countries had revealed similar findings [13-15]. However, several other studies showed that serum uric acid is a poor predictor of PE [16-18]. The development of methods to predict and prevent PE in early pregnancy is important for management of PE. Therefore, one of the most convenient screening tests for predicting PE is serum uric acid measurement.

Aim and Objectives

1. To estimate the serum uric acid levels in participant pregnant women with pre-eclampsia.
2. To evaluate the perinatal outcome in relation to the serum uric acid level in women presented with pre-eclampsia.

PATIENTS AND METHODS

This study was carried out at Maternity Teaching Hospital in Erbil city, which is capital of Kurdistan region in north of Iraq from 1st June 2017 to 19th January 2018. To achieve the aim of the study, cross-sectional design was adopted. An agreement from scientific committee of obstetric and gynecological department and ethical committee of college of medicine was obtained. A consent form was signed from patients and samples were collected. The proposed sample size was 200 pregnant women with ≥ 34 weeks of gestation with different severity of hypertension. After ensuring pre-eclampsia by measuring two readings of blood pressure in supine and sitting position and documenting proteinuria, blood samples were sent for measuring serum uric acid besides other routine investigations needed for pre-eclamptic women when they entered high risk unit. The uric acid is minimally soluble, and its concentration is maintained relatively low in healthy pregnant women (<6.0 mg/dL) [7].

The study sample was divided into two groups, the first group with serum uric acid level <6 mg/dL, the second group with serum uric acid level ≥ 6 mg/dL. Perinatal outcome including gestational age, mode of delivery, admission to neonatal care unit, birth weight, gender, early neonatal death, intrauterine death, intrauterine fetal restriction measured in both groups, other socio-demographic parameter include age, educational state, occupation, antenatal care was also recorded.

The inclusion criteria for all women who involved in current study were singleton pregnant women presented with hypertension $\geq 140/90$, proteinuria and gestational age ≥ 34 weeks, excluding who had history of gout, renal disease, cardiovascular disease, diabetic, multiple pregnancy, liver disease, congenital anomaly of fetus and bleeding disorders.

Statistical analysis was done by entering the data in to the computer using the statistical package for social sciences program (SPSS, version 23) for data analysis. The results were analyzed by using frequency of distribution, Chi-square, and $P \leq 0.05$ was considered as statistically significant [11]. Appropriate tables and graphs will be used for data representation.

RESULTS

Out of 200 pre-eclamptic pregnant women with a different degree of hypertension (mild, severe, eclampsia) there were (73) 36.5% with serum uric acid less than 6 mg/dL and (127) 63.50% with serum uric acid equal and more than 6 mg/dL as shown in Figure 1.

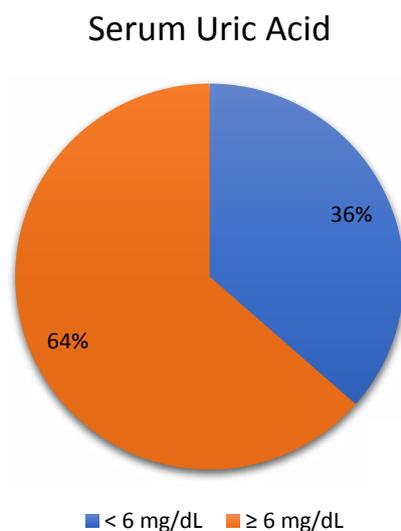


Figure 1 Percentage of uric acid among study group of pre-eclamptic women

The majority of participant pre-eclamptic women (80.5%) within age group 18-35, and nearly half of them 45% illiterate and 55% had primary and secondary education and 73% of them were homemakers, regarding the parity the highest level 46.5% of them having children (2-4), and 72.5% with antenatal care (ANC) as shown in Table 1.

Table 1 Distribution of sample according to sociodemographic criteria

Sociodemographic data		No.	%
Age in years	Less than 18	10	5
	18-35	161	80.5
	More than 35	29	14.5
Educational status	Illiterate	90	45
	Primary	80	40
	Secondary	30	15
Occupation	Homemaker	146	73
	Government Job	38	19
	Non-Government Job	16	8
Parity	0	35	17.5
	1	69	34.5
	2-4	93	46.5
	>4	3	1.5
ANC	No	145	72.5
	Regular	17	8.5
	Irregular	38	19
-	Total	200	100

Table 2 shows significant association among means of serum uric acid at different level of hypertension in pre-

eclamptic women. The highest level was found among eclamptic pregnant women. The mean \pm SD of serum uric acid in the study sample was 6.365 ± 1.77 in ANOVA test.

Table 2 Distribution of sample according to serum uric acid among different level of hypertension

Level of hypertension	Serum uric acid	95% Confidence Interval		P-value
	Mean \pm SD	Lower	Upper	
Mild-moderate	5.5231 \pm 1.66484	5.1696	5.8713	0.00
Severe	7.0245 \pm 1.54513	6.7234	7.3441	
Eclampsia	8.0556 \pm 0.63465	7.625	8.50	
Total	6.3652 \pm 1.77182	6.1281	6.5978	

Mild to moderate pre-eclampsia: BP is 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic and proteinuria is 300 mg/24 hours; or $\geq 1+$ (on 2 random urine samples, collected at least 4 hours apart). Severe pre-eclampsia: BP is ≥ 160 mmHg systolic and/or ≥ 110 mmHg diastolic (on 2 occasions at least 6 hours apart, while the patient is on bed rest) and proteinuria is 300 mg/24 hours; or $\geq 1+$ (on 2 random urine samples, collected at least 4 hours apart).

Table 3 shows significant association between the two groups level of serum uric acid and different level of hypertension among pre-eclamptic women in Chi-square test with p value 0.000, the highest percentage of serum uric acid revealed among eclamptic, then severe, and mild to moderate with percentage (100%, 80%, 42.55%) subsequently.

Table 3 Distribution of sample according to level of serum uric acid at different level of hypertension

Level of hypertension	Serum uric acid				Total	P-value
	<6 mg/dL	%	≥ 6 mg/dL	%		
Mild-Moderate	54	5.74	40	42.55	94	0.00
Severe	19	19.58	78	80.4	97	
Eclampsia	0	0	9	100	9	
Total	73	36.5	127	63.5	200	

Table 4 shows significant association between the two groups of level of serum uric acid and different perinatal outcome with highest percentage of (low birth weight 63.77%, admission to NCU 57.48%, caesarean section delivery 65.35%, preterm delivery 75.59) were found from 127 mothers with serum uric acid ≥ 6 mg/dL. Regarding the rate of other adverse perinatal consequences like intrauterine growth retardation 17.32%, intrauterine death 14.17% and early neonatal death 11.81%, were more common in group of pre-eclamptic women with serum uric acid ≥ 6 mg/dL in comparing to group of women with serum uric acid <6 mg/dL with a rate (5.47%, 4.1%, 2.73%) which were also statistically significant.

Table 4 Distribution of sample according to fetal outcome among different level of serum uric acid

Parameters	Variables	< 6 mg/dL (N (%))	≥ 6 mg/dL (N (%))	Total	Chi-square
Birth weight	< 2.5	36 (49.31)	81 (63.77)	117	0.045
	≥ 2.5	37 (50.68)	46 (36.22)	83	
Admission to NCU	Yes	31 (42.46)	73 (57.48)	104	0.041
	No	42 (57.53)	54 (42.51)	96	
Mode of delivery	NVD	49 (67.12)	44 (34.64)	93	0.00
	C/S	24 (32.87)	83 (65.35)	107	
Gestational age	<37 week	31 (42.46)	96 (75.59)	127	0.00
	≥ 37 week	42 (57.53)	31 (24.40)	73	
IUFD	yes	3 (4.109)	18 (14.17)	21	0.025
	No	70 (95.89)	109 (85.82)	179	
IUGR	Yes	4 (5.47)	22 (17.32)	26	0.016
	No	69 (94.52)	105 (82.67)	174	
Early neonatal death	Yes	2 (2.73)	15 (11.81)	17	0.025
	No	71 (97.26)	112 (88.18)	183	
-	Total	73 (36.50)	127 (63.50)	200	-

IUGR: Intrauterine Growth Restriction; IUFD: Intrauterine Fetal Death; C/S: Caesarean Section; NVD: Normal Vaginal Delivery

Table 5 shows significant negative correlation relationship r^2 between mean serum uric acid and Apgar score at 1st with $P=0.001$ and non-significant correlation with Apgar score at 5 minutes with $P=0.07$.

Table 5 Correlation between serum uric acid and Apgar score at 1st and 5 minutes

Variables	Mean	Standard Deviation	r^2
Uric acid level	6.3653	1.77182	0.001
Apgar score at 1 m	3.38	0.88856	
Uric acid level	6.3653	1.77182	0.07
Apgar score at 5 m	6.715	1.44715	

Apgar: A=appearance, P=pulse, G=grimace, A=activity, R=respiration

There was non-significant association between serum uric acid and Apgar score at 1st minute and at 5th minute as shows in Table 6.

Table 6 Association between serum uric acid and Apgar score at 1st and 5th minute in χ^2 test

APGAR score		Serum Uric Acid		Total	P-value
		<6 mg/dL	≥ 6 mg/dL		
1 st minute	<5	73	126	199	0.443
	≥ 5	0	1	1	
5 th minute	<7	44	80	124	0.703
	≥7	29	47	76	
Total		73	127	200	-

DISCUSSION

Perinatal complications were correlated with hypertensive disorders of pregnancy. In this study, the maternal serum uric acid level is found to be one of the prognostic factor in determining perinatal outcome. The current study showed that serum uric acid was elevated more than the normal level 6 mg/dL in a rate 63.5% among a sample of pre-eclamptic pregnant women with different degree in severity of pre-eclampsia, and the association between serum uric acid and hypertension was significantly elevated ($P=0.000$) on ANOVA and χ^2 test with mean \pm SD of serum uric acid level was (5.5231 ± 1.66484) in mild to moderate hypertensive, (7.0245 ± 1.54513) in severe cases and (8.0556 ± 0.63465) in eclamptic group then 6.3652 ± 1.77182 for the whole pre-eclamptic women of study sample, this result were lower than the result of studies done in Bangladesh and Pittsburgh [7,18] which revealed that elevated serum uric acid in a rate of 75%, 74.6% among pre-eclamptic women respectively, confirming the evidence that elevated uric acid is another component of the pre-eclamptic syndrome which was recognized many years ago [19]. Hyperuricemia is one of the most consistent and earliest detectable changes in pre-eclampsia and has been cited as a better predictor of fetal risk than blood pressure [7,18].

Regarding the sociodemographic criteria in current study sample revealed that the majority of women who involved in this study from age group (18-35) representing 80.5% of the whole sample which is representative of normal reproductive age in Islamic developing countries such as Iraq due to early marriage and early pregnancy which is in keeping with the religion, tradition and culture. The result was paralleled by a study that done at Magee women hospital in Pittsburgh [18] in terms of educational level which included 45% illiterate and 40% women with primary education level, with occupations been homemakers and Government employment in 73%, 19% respectively.

Other eligible criteria like parity of women in database clarified that 17.5% were nulliparous, 81% were from group with parity (1-4) and only 1.5% were grand multipara women and 72.5% with no ANC which is consistent with the result of study in Bangladesh and Pittsburgh and by Yassae [7,18,20], but higher than result of a similar study conducted in Dhaka city [21,22].

Non-pregnant population with hyperuricemia is an independent predictor of other physical diseases like cardiovascular, renal diseases among general population and subjects with chronic hypertension, elevated uric acid level in maternal blood, probably due to decreased renal urate excretion is frequently found in women with pre-eclampsia. Plenty numbers of studies were conducted to find out the relationship between elevated uric acid level and pre-eclampsia among pregnant women [21].

Pre-eclampsia has been defined as a triad of hypertension, edema, and proteinuria. A rising serum uric acid is now recognized as an early feature of pre-eclampsia and its measurement greatly increases the accuracy of diagnosis and helps to differentiate this disorder from essential and other chronic forms of pre-existing hypertension complicating pregnancy [15,23].

Association of serum uric acid level with fetal outcome in current study showed that out of 127 pre-eclamptic women with hyperuricemia. About 75.6% of them were delivered preterm, 40 neonates were admitted 18 (45%) were IUFD and 22 (55%) were IUGR which inconsistent with result of study that done in India which revealed 79.4% with IUGR and 14.7% with IUFD from 34 women with IUFD and IUGR [9], at the same time 17.32 out of all hypouricemic pre-eclamptic women were IUGR while 14.17% were with IUFD echoing the result parallel to result of study that done in Bangladesh and by Yassae [7,18].

Regarding the mode of delivery of neonate among pre-eclamptic women with hyperuricemia, 65.35% of them delivered by caesarean section and this result was less than result of study that done in India which was 80% [21].

Birth weight of neonate was significantly associated with serum uric acid of their pre-eclamptic mother, with 63.77% with birth weight less than 2.5 kg which is in accordance with results of the Indian study [20].

Regarding the admission to NCU, this study revealed that there was 57.5% of pre-eclamptic women with ≥ 6 mg/dL there neonates admitted NCU with significant association between serum uric acid and admission to NCU, but at there was negative significant correlation between mean of serum uric acid and mean of Apgar score of neonate at 1st minute while there was non-significant correlation at 5 minute in r^2 test but by χ^2 there was non-significant association at two times and this inconsistency with result of study that done in India [24] that revealed significant association between Apgar score and serum uric acid at 5 minutes.

As a result of all previous adverse effects of hyperuricemia on neonates, early neonatal mortality rate was increased. Seventeen babies died within 1st week of their life, 15 of them had pre-eclamptic mothers with hyperuricemia which explains the effect of higher serum uric acid level on the fetus and on their health condition.

CONCLUSION

The measurement of serum uric acid is thus of great diagnostic and prognostic value for fetus. This study shows that estimation of serum uric acid level in pregnancies complicated by pre-eclampsia and eclampsia help to assess the severity of illness, and to identify those fetuses that are likely to have perinatal mortality and morbidity which may help us to improve the outcome.

DECLARATIONS

Conflict of Interest

The authors have disclosed no potential conflicts of interest, financial or otherwise.

REFERENCES

- [1] Powers, Robert W., et al. "Uric acid concentrations in early pregnancy among preeclamptic women with gestational hyperuricemia at delivery." *American Journal of Obstetrics & Gynecology*, Vol. 194, No. 1, 2006, pp. 160-e1.
- [2] Johnson, Richard J., et al. "Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease?" *Hypertension*, Vol. 41, No. 6, 2003, pp. 1183-90.
- [3] Kang, Duk-Hee, et al. "Uric acid, endothelial dysfunction and pre-eclampsia: searching for a pathogenetic link." *Journal of Hypertension*, Vol. 22, No. 2, 2004, pp. 229-35.
- [4] Slemons, J. Morris, and L. Jean Bogert. "The uric acid content of maternal and fetal blood." *Journal of Biological Chemistry*, Vol. 32, No. 1, 1917, pp. 63-69.
- [5] Stander, H.J., and J.F. Cadden. "Blood chemistry in preeclampsia and eclampsia." *American Journal of Obstetrics and Gynecology*, Vol. 28, No. 6, 1934, pp. 856-71.
- [6] Voto, Liliana Susana, et al. "Uric acid levels: a useful index of the severity of preeclampsia and perinatal prognosis." *Journal of Perinatal Medicine-Official Journal of the WAPM*, Vol. 16, No. 2, 1988, pp. 123-26.

- [7] Roberts, James M., et al. "Uric acid is as important as proteinuria in identifying fetal risk in women with gestational hypertension." *Hypertension*, Vol. 46, No. 6, 2005, pp. 1263-69.
- [8] Gallery, Eileen DM, Stephen N. Hunyor, and Akos Z. Györy. "Plasma Volume Contraction: A Significant Factor in Both Pregnancy-Associated Hypertension (Pre-Eclampsia) and Chronic Hypertension in Pregnancy." *QJM: An International Journal of Medicine*, Vol. 48, No. 4, 1979, pp. 593-602.
- [9] Bainbridge, Shannon A., and James M. Roberts. "Uric acid as a pathogenic factor in preeclampsia." *Placenta*, Vol. 29, 2008, pp. 67-72.
- [10] Cheung, Katharine L., and Richard A. Lafayette. "Renal physiology of pregnancy." *Advances in Chronic Kidney Disease*, Vol. 20, No. 3, 2013, pp. 209-14.
- [11] Pennington, Kathleen A., et al. "Preeclampsia: multiple approaches for a multifactorial disease." *Disease Models & Mechanisms*, Vol. 5, No. 1, 2012, pp. 9-18.
- [12] Jeyabalan, Arundhati, and Kirk P. Conrad. "Renal function during normal pregnancy and preeclampsia." *Frontiers in Bioscience*, Vol. 12, No. 1, 2007, pp. 2425-37.
- [13] Aram, Sh, and A. Khalilian. "The Role of Increased Uric Acid in Predicting Pre-eclampsia at The Gestational Age of 24-28 Weeks." *Medical Laboratory Journal*, Vol. 1, No. 1, 2007, pp. 0-0.
- [14] Kharb, Simmi. "Uric acid and ascorbic acid levels in pregnancy with Preeclampsia and Diabetes." 2010.
- [15] Dekker, G.A., and Baha M. Sibai. "Early detection of preeclampsia." *American Journal of Obstetrics & Gynecology*, Vol. 165, No. 1, 1991, pp. 160-72.
- [16] Conde-Agudelo, Agustin, Roberto Ledesma, and José Belizán. "Evaluation of methods used in the prediction of hypertensive disorders of pregnancy." *Obstetrical & Gynecological Survey*, Vol. 49, No. 3, 1994, pp. 210-22.
- [17] Williams, Keith P., and France Galerneau. "The role of serum uric acid as a prognostic indicator of the severity of maternal and fetal complications in hypertensive pregnancies." *Journal of Obstetrics and Gynaecology Canada*, Vol. 24, No. 8, 2002, pp. 628-32.
- [18] Akter, Saida, Sharmin Sultana, and Seema Rani Dabee. "Association of hyperuricaemia with perinatal outcome in pregnancy induced hypertension." *Journal of Bangladesh College of Physicians & Surgeons*, Vol. 32, No. 3, 2014, p. 124.
- [19] Chesley, Leon C. *Hypertensive disorders in pregnancy*. Appleton-Century-Crofts, 1978.
- [20] Yassaee, F. "Hyperuricemia and perinatal outcomes in patients with severe preeclampsia." *Iranian Journal of Medical Sciences*, Vol. 28, No. 4, 2015, pp. 198-99.
- [21] Sultana, Razia, et al. "Association of serum uric acid with preeclampsia: a case control study." *Delta Medical College Journal*, Vol. 1, No. 2, 2013, pp. 46-50.
- [22] Cotter, Amanda M., et al. "Increased fetal DNA in the maternal circulation in early pregnancy is associated with an increased risk of preeclampsia." *American Journal of Obstetrics & Gynecology*, Vol. 191, No. 2, 2004, pp. 515-20.
- [23] Dekker, G.A., and Baha M. Sibai. "Low-dose aspirin in the prevention of preeclampsia and fetal growth retardation: rationale, mechanisms, and clinical trials." *American Journal of Obstetrics and Gynecology*, Vol. 168, No. 1, 1993, pp. 214-27.
- [24] Ramana Priya, K. Jeyapriya and N.S. Kannan. "Accuracy of serum uric acid predicting complication of preeclampsia." *International Journal of Current Research and Review*, Vol. 8, No. 5, 2016, pp. 13-21.