

Maternal Serum Uric Acid Level during Pregnancy: A Biomarker for Preeclampsia

*RUKHSHAN KHURSHID, *ADINA SHAMSI, **IRUM FAYYAZ, *MUDDASIR ZIA

ABSTRACT

Background: Pre-eclampsia is a frequent obstetrical problem responsible for adverse effects on pregnancy outcome.

Aim: To find role of serum uric as an early predictor of preeclampsia.

Methods: A case control study was conducted on 30 pre-eclamptic women and 20 age matched women with normal pregnancy. Patients were taken from Department of Obstetrics and Gynecology, Sir Ganga Ram Hospital Lahore, from January 2015 to December 2016. Pre-eclampsia was diagnosed by pregnancy with gestational age >20 weeks, with blood pressure $\geq 140/ \geq 90$ mm Hg and 24-hour urinary protein ≥ 300 mg. Blood samples were collected for estimation of serum uric acid. Serum uric acid was measured by Autoanalyzer using standard kit of Merck.

Results: Mean age of normal pregnancy group was 28.43 ± 4.11 with mean gestational age was 30.90 ± 3.9 weeks. Mean age of pre-eclampsia group was 29.07 ± 5.54 with mean gestational age was 28.70 ± 4.0 weeks. Level of serum uric acid was increased in pre-eclampsia group as compared to level of serum uric acid of group of normal pregnant women and it showed a highly significant difference ($P < 0.001$). Serum uric acid as a biomarker showed 65% sensitivity and 95% specificity with 95% positive predictive value.

Conclusion: It is concluded that age may be an independent risk factor for developing preeclampsia. Serum uric acid level may be a biomarker of preeclampsia and also may help to monitor the disease.

Keywords: Preeclampsia, serum uric acid, biomarker.

INTRODUCTION

Pre-eclampsia is the third frequent cause of maternal death and it complicates ~ 5-7% of pregnancy¹. Its prevalence rate in Pakistan is 19%. It is also associated with fetal morbidity and mortality².

Pre-eclampsia is considered as "a disease of hypothesis" and its exact reason is weakly understood. However it is proposed that endothelial dysfunction is mainly associated with pathophysiology of preeclampsia lead to increased risk of morbidity and mortality in mother and child³. The link between endothelial dysfunction and inflammation, oxidative stress and the hypercoagulable state is complex in the disease of preeclampsia as these condition may augment the effect of each other, resulting an increased vascular damage⁴.

Pre-eclampsia is multisystem disorder in pregnant women and distinguished by the development of proteinuria and hypertension, impaired liver function and raised serum uric acid after 20 weeks of gestation⁵. It is proposed that increased serum uric acid is related with hypertension, renal disease and adverse cardiovascular events in the non-pregnant women

and endothelial dysfunction, inflammation and unfavorable fetal outcomes in pregnant women^{6,1}. Endothelial dysfunction may lead to breakdown of trophoblast, cytokine release and ischemia, results a raised level of uric acid⁷.

In early pregnancy, serum uric acid fall to < 3 mg/dl due to the uricosonic effects of estrogen and increase in renal blood flow. Lately it increases during the third trimester, reaching levels of 4 to 5 mg/dl by term⁸. The damaging effects of uric acid are to decreased nitric oxide bioavailability and enhanced superoxide generation⁹.

An increased level of uric acid in preeclamptic women is not only a indicator of disease severity but it also have a direct role with the pathogenesis of the disease as uric acid unfavorably effect both placenta and maternal vasculature⁶. Increased level of serum uric acid may lead hypertension by an increase in salt sensitivity and proliferation of vascular smooth muscle¹⁰ and proteinuria¹¹.

Hypertension was reported to account complications for 15% of pregnant women. Complications of preeclampsia include an increased risk of acute renal failure, abruptio placentae, cardiovascular problems and maternal mortality¹².

In Pakistan the rate of eclampsia is high. Early detection, proper monitoring and treatment of pre-eclampsia is necessary in preventing maternal mortality. Our study aimed to confirm that maternal

*Department of Biochemistry, Fatima Jinnah Medical University and **CMH Medical College, Lahore.
Correspondence to Dr. Adina Shamsi, Associate Professor,
Email: adina.shamsi@gmail.com cell: 0321-8818082

serum uric acid level during pregnancy can be used as a biomarker for Preeclampsia and increased level of serum uric acid levels can be associated with the severity of Preeclampsia. A biomarker which is cheap and may be used to save the valuable lives of fetus and mother.

Present study was designed to find out role of serum uric as an early predictor of preeclampsia.

MATERIALS AND METHODS

A case control study was conducted on 30 pre-eclamptic women and 20 age matched women with normal pregnancy. Patients were taken from Department of Obstetrics and Gynecology, Sir Ganga Ram Hospital Lahore, from January 2015 to December 2016. Letter of consent was taken from each subject. Study was approved by Ethical Committee of Sir Ganga Ram Hospital Lahore.

Pre-eclampsia was diagnosed by pregnancy with gestational age >20 weeks, with blood pressure $\geq 140/ \geq 90$ mm Hg noted on two times 6 hours apart and 24-hour urinary protein ≥ 300 mg. Pregnant women with pre-existing hypertension, renal disease, cardiovascular disease, diabetes mellitus or any endocrinopathies were excluded from the study.

Blood samples were collected for estimation of serum uric acid. Serum uric acid was measured by Autoanalyzer using standard kit of Merck.

Statistical analysis was performed using SPSS. 18. Variables were expressed as mean \pm SD. Comparison of parameters were carried out by student 't' test. $P < 0.05$ was considered statistically significant. Sensitivity and Specificity, positive and negative predictive value of serum uric acid as a biomarker of disease was calculated.

RESULTS

Age distribution in study subjects is tabulated as table 1. It was observed that mean age of normal pregnancy group was 28.43 ± 4.11 with mean gestational age was 30.90 ± 3.9 weeks. Mean age of pre-eclampsia group was 29.07 ± 5.54 with mean gestational age was 28.70 ± 4.0 weeks.

Comparison of level of serum uric acid in study groups is tabulated as table 2. Mean level of serum uric acid was increased in pre-eclampsia group as compared to level of serum uric acid of group of normal pregnant women and it showed a highly significant difference ($P < 0.001$).

Serum uric acid as a biomarker based on sensitivity, specificity, positive predictive value and negative predictive value was calculated (Table 3). It was observed that sensitivity was 65%, specificity was 95%, positive predictive value was 94% and negative predictive value of uric acid was 60%.

Table 1: Age distribution in study subjects

No of cases in parenthesis	Values are expressed as mean \pm SD	
	Normal pregnancy group (20)	Preeclampsia group (30)
Age (years)	28.43 \pm 4.11	29.07 \pm 5.54
Gestational age (weeks)	30.90 \pm 3.9	28.70 \pm 4.0

Table 2: Comparison of level of serum uric acid in study groups

	Mean level of Uric acid(mg/dl)	Standard Deviation
Normal pregnancy group	4.39	0.72
Pre-eclampsia group	7.29	1.24

P value <0.001

Table 3: Serum uric acid as a Biomarker

Sensitivity	65%
Specificity	95%
Positive predictive value	94%
Negative predictive value	60%

DISCUSSION

Pre-eclampsia is a pregnancy precise, multisystem syndrome differentiated by decreased organ perfusion resulting to vasospasm and coagulation cascade activation. This syndrome has been related to multiple factors. However, exact cause of preeclampsia is not known^{13,14}.

Mean age of pre-eclampsia group was 29.07 ± 5.54 with mean gestational age was 28.70 ± 4.0 weeks. There is mild difference between the mean age and gestational weeks of normal pregnant women and of pre-eclamptic group. A study found that pre-eclampsia is reported in both younger and the middle aged women¹⁵. A study also stated that rate of pre-eclampsia was decreased in women with age <30 years and it increased in women with age 30-34 years¹⁶. In addition some studies found that maternal age found to be an independent risk factor for early development of preeclampsia and impaired growth of fetus^{17,18}.

Our study is in accord with a study who found that preeclampsia develops before 33 weeks of gestation increased the risk of adverse maternal and perinatal outcome¹⁹. It is stated that early-onset of pre-eclampsia, with <34 gestational weeks, may be associated with placental pathology. However, gestational age ≥ 34 weeks may present late onset preeclampsia which may be triggered by intrinsic pathology involving overcrowding of microvillus. It is suggested that oxidative stress proteins change the maternal response via regulating many growth factors and preventing early onset of preeclampsia²⁰.

Mean level of serum uric acid was increased in pre-eclampsia group as compared to level of serum uric acid of group of normal pregnant women and it showed a highly significant difference ($P < 0.001$).

It is reported that in normal pregnant women the level of serum uric acid is 25-35% decreased of than the level of uric acid of non-pregnant women⁶. 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 pregnancy²¹.

In women with pre-eclampsia there is impaired trophoblastic invasion in the placenta and ischemic metabolite formation⁷. These ischemic metabolite are responsible for peripheral vasoconstriction in glomeruli and glomerular endotheliosis results in decreased GFR and increased uric acid net reabsorption from proximal convulated tubule leading to increased level of serum uric acid²².

A study found that raised uric acid reabsorption, increased sympathetic activity, repressed the activity of angiotensin system and decreased the level of estrogen²³. Some studied suggested that in pre-eclampsia increased level of serum lactate may reduced the secretion of uric acid through renal tubules²⁴. Though some studies show that uric acid may itself have a pathogenic role in Preeclampsia resulting in a vicious cycle of disease²⁵. However, the role of serum uric acid as a marker of preeclampsia is not confirmed¹⁰.

Serum uric acid as a biomarker based on sensitivity, specificity, positive predictive value and negative predictive value showed it has high positive predictive value and high specificity.

Uric acid level >6 mg/dl in the third trimester showed that the chance of developing Preeclampsia is 94%. According to a study in preeclampsia high levels of uric acid, may be resulting from the body's effort to manage with oxidative stress²⁵.

Limitation: Levels of serum uric acid in women with first and second trimester of pregnancy were not estimated. It is therefore not clear that the level of serum uric acid was raised in acute phase of disease or it may slowly rise from the initial stage of pregnancy.

CONCLUSION

It is concluded that age may be an independent risk factor for developing preeclampsia. Serum uric acid level may be a biomarker of preeclampsia and also may help to monitor the disease.

REFERENCES

- Vafaci H, Dalile M, Hashemi S A. Serum concentration of calcium, magnesium and zinc in normotensive versus preeclampsia pregnant woman. *Iran. J. Reprod. Med* 2015;13(1): 23-26
- Aziz R, & Mahboob T. Preeclampsia and lipid profile Pak T Med 2007; 23 (1): 5-7

- LaMarca B. Endothelial dysfunction; an important mediator in the Pathophysiology of Hypertension during Preeclampsia. *Minerva Ginecol.* 2012 Aug; 64(4): 309–320.
- Garovic VD, & August P. Preeclampsia and the Future Risk of Hypertension: The Pregnant Evidence *Curr Hypertens. Rep* 2013; 15(2): 10-13
- Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi JM. Preeclampsia: pathophysiology, diagnosis, and management. *Vasc Health Risk Manag.* 2011; 7: 467–474.
- Bainbridge SA, Roberts JM. Uric Acid as a Pathogenic Factor in Preeclampsia. *Placenta* 2008; 29(Suppl A): S67–S72.
- Pennington KA, Schlitt JM, Jackson DL, Schulz LC, Schust DJ. Preeclampsia: multiple approaches for a multifactorial disease. *Dis Model Mech.* 2012 Jan; 5(1): 9–18.
- Johnson RJ, Kanbay M, Kang D, Lozada LG. Uric acid: A Clinically Useful Marker to Distinguish Preeclampsia from Gestational Hypertension. *Hypertension* 2011;58(4):548–549.
- Papezikova I, Pekarova M, Lojek A, Kubala L. The effect of uric acid on homocysteine-induced endothelial dysfunction in bovine aortic endothelial cells. *Neuro. Endocrinol, Lett* 2009; 30(Suppl 1):112-5.
- Roberts JM, Bodnar LM, Lain KY, Hubel CA, Markovic N, Ness RB, Powers RW. Uric Acid Is as Important as Proteinuria in Identifying Fetal Risk in Women With Gestational Hypertension. *Hypertension* 2005; 46: 1263-1269
- Powers RW, Bodnar LM, Ness RB, Cooper KM, Gallaher MJ, Frank MP. Uric acid concentrations in early pregnancy among preeclamptic women with gestational hyperuricemia at delivery. *Am J Obstet Gynecol* 2006;194:160-164
- Kattah Ag, Garovic VD. The Management of Hypertension in Pregnancy. *Adv Chronic Kidney Dis.* 2013 May; 20(3): 229.
- Skjaerven R, Wilcox AJ, Lie RT. The interval between pregnancies and the risk of preeclampsia. *N Engl J Med* 2002; 346:33-8.
- Hernandez-Diaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. *BMJ*2009;338:b2255
- Zhang J, Zeisler J, Hatch MC, Berkowitz G. Epidemiology of pregnancy-induced hypertension. *Epidemiol Rev*1997;19:218
- Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis *BMJ* 2013;347:f6564
- Miranda M, Swamy G, Edwards S, Maxson P, Gelfand A, James S. Disparities in maternal hypertension and pregnancy outcomes: evidence from North Carolina, 1994–2003. *Public Health Rep.* 2010;125:579–587
- Lamminpaa R, Julkunen KV, Gissler M, Heinonen S. Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland 1997–2008. *BMC Pregnancy Childbirth.* 2012; 12: 47.
- English FA, Kenny LC, McCarthy FP. Risk factors and effective management of preeclampsia. *Integr Blood Press Control.* 2015; 8: 7–12.
- Redman CW, Sargent IL, Staff AC. IFPA Senior Award Lecture: making sense of pre-eclampsia – two placental causes of preeclampsia? *Placenta.* 2014;35(Suppl):S20–S25.
- Cheung KL, Lafayette RA. Renal Physiology of Pregnancy. *Adv Chronic Kidney Dis.* 2013 May; 20(3): 209–214.
- Jayabalan A and Conrad KP. Renal function during normal pregnancy and preeclampsia. *Front Biosci.* 2007 Jan 1;12:2425-37.
- Mumford SL, Dasharathy AZ, Pollack AZ, Perkins NJ, Mattison DR, Cole SR. et al. Serum uric acid in relation to endogenous reproductive hormones during the menstrual cycle: findings from the BioCycle study. *Hum Reprod.* 2013 Jul; 28(7): 1853–1862.
- Bobulescu IA and Moe OW. Renal Transport of Uric Acid: Evolving Concepts and Uncertainties. *Adv Chronic Kidney Dis.* 2012 Nov; 19(6): 358–371.
- Negi R, Pande D, Karki K, Khanna RS, Khanna HD. Oxidative stress and preeclampsia. *Advances in Life Sciences* 2011;1(1):20-23.

