The Clinical Utility of Non Protein Nitrogenous Substances in Pre-Eclampsia and Eclampsia

*Dr. P.V.Satyanarayana,**Dr R.K. Padalkar, **Dr. S S Bhagat, , **R .A. Ghone, **S. M. Patil

*Department of Biochemistry, Kakatiya Medical College, Warangal, (AP), India. **Department of Biochemistry , PDVVPF's Medical College, Ahmednagar,

Address for Correspondence : PDVVPF's Medical College, Ahmednagar, (MS), India.

Abstract :

Background : Modern obstetrics, hypertensive disorders of pregnancy are understood to a clinical abnormalities ranging from minimal elevation in blood pressure to severe hypertension with multi organ dysfunction.

Aim : The goal of study was to scrutinize impact of serum urea, creatinine, uric acid in patients with pre-eclampsia and eclampsia.

Objectives : The objective of study to estimate the non-protein nitrogenous substances in pre-eclampsia and eclampsia compared with normal pregnant women.

Study design : In present case control study 60 pre-eclampsia and 60 eclampsia patients were estimated and compared with 60 normal pregnant women. The serum urea estimated by diacetyl monoxime method, uric acid by uricase method and serum creatinine by alkaline picrate method .Result: significant elevations were found in the levels of serum urea, creatinine, and uric acid ($p<0.001$) in patients when compared with controls. These effects may be due to generalized reduction of organ perfusion leading endothelial cell activation, vasospam and microthrombi formation or it may be due to increased reabsorption, decreased secretion or both.

Key Words : Renal tubular function, Non-protein nitrogenous substances, Pre-eclampsia, and Eclampsia.

Introduction : Pre-eclmpsia & eclampsia has been called the diseases of theories. It is relatively common entity & it has been the subject of a large body of research. Preeclampsia is a pregnancy-specific, multisystem disorder that is characterized by the development of hypertension and proteinuria after 20 weeks of gestation[1]. The criteria that define pre-eclampsia have not changed over the past decade [2]. These are onset at >20 weeks' gestational age of 24-hour proteinuria $\geqslant$ 30 mg/day or, if not available, a protein concentration $\geqslant$ 30 mg in a minimum of two random urine samples collected at least 4–6 hours but no more than 7 days apart, a systolic blood pressure .140 mmHg or diastolic blood pressure $\geqslant$ 90 mmHg as measured twice, using an appropriate cuff, 4–6 hours and less than 7 days apart, and disappearance of all these abnormalities before the end of the 6th week postpartum. Nonetheless, some presentations of pregnancy-related hypertension combined with clinical or laboratory abnormalities or intrauterine growth restriction should also be considered as potential pre-eclampsia [3,4].

Women with mild pre-eclampsia generally have no symptoms. However, women with severe pre-eclampsia & eclampsia may have sign and symptoms such as renal insufficiency like decreased urinary volume, enhanced serum creatinine concentration, upper abdominal pain, elevated liver enzymes, headache, visual disturbances, exaggerated tendon reflexes, convulsions, hematological disturbances and disturbances in bone –mineral metabolism [5,6,7].

The risk factor for pre-eclampsia is chronic kidney disease, which may unmask underlying renal pathologies [8]. Creatinine, urea, and uric acid are non-protein nitrogenous metabolites that are cleared from the body by the kidney following glomerular filtration. Hence, their determination in serum during pregnancy is of a major importance to diagnose kidney function especially at women with preeclampsia signs [8].

Hyperuricemia is considered to be the marker of severity of disease [8,9]. Urea, which is the catabolic product of ammonia and an important marker to assess the kidney functions, seems to be raised in preeclampsia & eclampsia[10,11]. Creatinine that is another important marker to assess kidney functions had role in preeclampsia remain controversial. Few studies observe insignificant change in creatinine levels [12,13].

With this background knowledge, we have investigated the role of non-protein nitrogenous substances, which may be the markers of renal functions in preeclampsia & eclampsia.

Materials & Materials : The present work was cunducted in the Department of Biochemistry,

Mahatma Gandhi Memorial College & Hospital, Warangal (A.P.) and Department of Biochemistry, PDVVPF, s Medical College, Ahmednagar, Maharashtra. Prior to start the study, local institutional ethical clearance was obtained and utmost care was taken during experimental procedure according to the Declaration of Helsinki 1964.

Study type : Hospital Based Case-Control Study.

This study has been performed on total 180 subjects who include 60 normal pregnant women act as healthy controls and 60 pre- eclampsia & 60 eclampsia patients from the age group 20-36 years were included in the study.

After informed consent, 60 eclampsia & 60 women diagnosed to have preeclampsia defined as BP greater than 140/90 mm of Hg and proteinuria of 300mg or greater on minimum two occasions and 60 women (age matched) with normal pregnancy were taken as controls. The exclusion criteria for patients were already hypertensive before 20 weeks of gestation or suffering from diabetes, asthma, heart disease, kidney disorders, liver disorders auto immune disorder, twin pregnancy, or on such medications that may alter the diagnosis of true preeclampsia. Blood pressure measurements were done by using a sphygmomanometer and proteinuria analysis was performed using standard procedures.

After obtaining a written consent form from all the subjects who were included in the study and by giving detail information of study, blood samples were collected from controls and patients. Total 5ml blood was withdrawn aseptically from the antecubital vein from each subject in a plain container. The samples were centrifuged at 3000 rpm for 10 min to separate serum. Lipaemic and icteric samples were discarded.

Serum uric acid was measured by Uricase method [14], Serum urea by Diacetyl Monoxime method [15], and creatinine levels were measured by using Alkaline Picrate method [16] using commercial kits. Analyses of all the parameters were estimated by using UV visible Spectrophotometer (Systronix).

Statistical Analysis : The statistical analysis was carried out by using the SPSS (Statistical Package for Social Sciences) statistical software, version 17.0 for Windows. The Student's 'z' test were applied for the significance and the results were expressed in mean ± SD. p values ($p<0.001$) were considered as significant.

Results : A total of 169 patients were evaluated for the study. After applying inclusion and exclusion criteria, total of 120 patients were eligible for the study.

Table-1 : Shows the baseline demographic clinical characterization of normal pregnant women, pre-eclampsia, & eclampsia patients.

Sr. No	Variables	Controls (n = 6 0)	Pre-eclampsia women (n=60)	Eclam-psia women (n=60)	P value <
1.	Age in years	28.1±09.13	29.4±8.01	26.48±9.73	0.001*
2.	Systolic Blood Pressure (mm of Hg)	114.3±4.2	179.80±8.54	175.42±6.75	0.001*
3.	Diastolic Blood Pressure (mm of Hg)	79.20±6.92	106.60±8.14	102.28±4.83	0.001*
4.	Serum Urea (mg/dl)	17.73±1.73	26.13±2.87	25.32±2.96	0.001*
5.	Serum Uric acid (mg/dl)	4.3±0.6	5.99±0.95	6.62±0.81	0.001*
6.	Serum Creatinine (mg/dl)	1.03±0.4	1.5±0.7	1.4±0.5	0.001*

Table -1 shows the baseline characteristics of all the subjects.

Values were expressed in mean with standard deviation (Mean±SD).

*Indicates statistically significant ($p<0.001$)

n=Number of patients.

Discussion : The term preeclampsia is disorder related to hypertension during pregnancy. It is one of the most potential complications contributing to preterm labour, perinatal mortality, maternal mortality, intra uterine growth retardation, low birth weight infants, and many such related problems.

Consequently, keeping this view in mind the study was endeavored to comprehend the role of non protein nitrogenous substances also called renal markers like uric acid, urea, and creatinine in preeclampsia & eclampsia.

In the present study, we had illustrated drastic increase in Systolic blood pressure, Diastolic blood pressure in preeclampsia eclampsia along with abnormal elevated levels of uric acid, creatinine and urea in both the groups when compared with the normal pregnanceis.

In our study, there was significant elevatoin in concentration of serum urea ($p<0.001$) in preeclampsia & eclampsia when compared with the normal

pregnancies. Our results are in line with the various researchers such as Hidajet Paçarizi et al, Tausif Zar et al [17,19]. It may be due to excretion of urea is dependent on Renal Blood Flow (RBF) and is the result of glomerular filtration, but less tubular reabsorption. The urea reabsorption takes place in proximal tubule and the inner medulary collecting duct. Hypovolemia, which leads to high angiotensin II and an angiotensin II hypersensitive state such as pre-eclampsia, efferent arteriolar resistance and filtration, is increased. This process allows normal glomerular filtration fraction when RBF is decreased. The increased filtration fraction leads rise in protein concentration and oncotic pressure within the efferent arteriole, enhancing fluid reabsorption from the proximal tubule along with urea transport, which follows water reabsorption. So, Angiotensin II promotes direct tubular reabsorption of water, and in turn, urea may be the reason for elevated levels observed in preeclamptics [18,19,20].

One more reason is the occurrence of microangiopathic haemolysis, which is related to the injury of endothelium in the group with pre- eclampsia changes. As a consequence, urea synthesis in liver would be increased as well as the incapability of kidneys to excrete urea from blood with such a high concentration may explain to some extent about urea [18,19,20,21].

We had found significantly enhanced level of serum uric acid in patients with preeclampsia & eclampsia when compared with the normal pregnancies. Our results are collaborated with the other investigators Pasaoglu H et al, Kharb S. et al, Saha A. et al, which shows significantly elevated levels of uric acid in preeclampsia & eclampsia [22,23,24].

Uric acid the end product of purine metabolism synthesis which may be increased, because of death and damage of trophoblastic cells in proliferation or by increased reabsorption and decreased excretion of uric acid and physiologic response to hypovolemia, [24, 25]or may be due to increased production from maternal, fetal or placental tissues breakdown and may be due to increased xanthine oxidase (XO) activity but, the reason behind increased XO activity in pre-eclamptic women are unclear [25]. Uric acid also has inflammatory action mediation of pro-inflammatory cytokines. The scientist Gulati R et al was observed that, Pre-eclamptic women have increased concentration of circulating TNF- which was positively correlated to circulating uric acid concentrations [26]. The increased frequency of preterm birth and growth restriction was present in hypertensive women with elevated concentration of uric acid even in the absence of proteinuria [27].

These evidences suggest that, elevated levels of uric acid even in absence of proteinuria can be considered as a risk factor for developing preeclampsia [28].

Our study observed that, significant changes ($p<0.001$) in levels of creatinine in both groups when compared with the controls. it may be due to decline in glomerular filtration rate can attributed to renal damage caused by pre-eclampsia. Glomerular endotheliosis leads to impairment in permeability of glomerular capillary walls. This is most likely predominant cause of hypofiltration in pre-eclampsia [29].

The study stands in contrast with studies of Mohamed Abdulfatah Abdulmunem et al, and Salako BL et al. [12,13] who observed insignificant change in creatinine level in two groups.

Conclusion : The essence of the current study lies in the fact that, the serum urea & uric acid measurements may be the preeminent markers of the diagnosis as well as severity of pre-eclampsia & eclampsia and will be a useful index for the management of the same. In all cases of toxemias of pregnancy, the estimation was undertaken for uric acid levels. Regular evaluation of GFR can gives idea about ongoing renal damage. This will be helpful for timely diagnosis, assessments, & treatment that further trim down the complications related to diseases.

References :

1. Witlin AG, Sibai BM. Magnesium sulfate therapy in preeclampsia and eclampsia. Obstet Gynecol 1998;92:883-89.
2. Pottecher T, Luton D. Prise en Charge Multidisciplinaire de laPrééclampsie. Issy Les Moulineaux, France: Elsevier Masson SAS;2009.
3. Carty DM, Delles C, Dominiczak AF. Preeclampsia and future maternal health. J Hypertens. 2010;28:1349–1355.
4. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33:130–137.
5. Cnossen JS, Post JAV, Mol BWJ, Khan KS, Meads CA, Riet G. Prediction of pre-eclampsia: a protocol for systematic reviews of test accuracy. BMC Pregnancy and Childbirth. 2006; 6:29.
6. Juha R, William EW, Michael K, Leila R. Bone and Mineral metabolism. In Burtis CA, Ashwood

ER, Bruns DE. Editors. Tietz text book of clinical chemistry and molecular diagnostics, Philadelphia: W.B Saunders 5th edn. 2012; 1733-1801.

7. Lamb EJ and Price CP. Kidney Function Tests In. Burtis CA, Ashwood ER, Bruns DE. Editors. Tietz text book of clinical chemistry and molecular diagnostics 5th edn: Philadelphia: W.B Saunders 2014; 669-707.
8. Lalitha Devi Seerla, Syed Abdul Jaweed, Jyothinath Kothapalli. Is Non-protein Nitrogenous Compounds Have Role in Preeclampsia. National Journal of Laboratory Medicine. 2014 Sep, Vol 3(3): 23-26.
9. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41:1183–90. [PubMed: 12707287].
10. C. W. G. Redman, J. Beilin, and j. Bonnar. Renal function in preeclampsia. J. Clin. Path., 29 10, 91-94.
11. Hidajet Paçarizi, Luljeta Begolli, Shefqet Lulaj, Zana Gafurri. Blood urea nitrogen/creatinine index is a predictor of prerenal damage in preeclampsia. Journal of Health Science. 2012: 2, 61-65.
12. Mohamed Abdulfatah Abdulmunem. "The Values of Plasma Uric acid, Urea, Creatinine and Electrolytes in Diagnosis of Preeclampsia." Thesis. Sudan University of Sciences, 2005.
13. Salako BL, Odukogbe AT, Olayemi O, Adedapo KS, Aimakhu CO, Alu FE, Ola B. Serum albumin, creatinine, uric acid and hypertensive disorders of pregnancy. East Afr Med J. 2003, 80:424-428.
14. Carl A Burtis, Edward R Ashwood, David E Bruns. TIETZ Clinical Chemistry & Molecular Diagnostics. Elsevier Publications 4th Edition 2006; pp-798-799.
15. Carl A Burtis, Edward R Ashwood, David E Bruns. TIETZ Clinical Chemistry & Molecular Diagnostics. Elsevier Publications 4th Edition 2006; pp-802-803.
16. Carl A Burtis, Edward R Ashwood, David E Bruns. TIETZ Clinical Chemistry & Molecular Diagnostics. Elsevier Publications 4th Edition 2006; pp-803-805.
17. Hidajet Paçarizi, Luljeta Begolli, Shefqet Lulaj, Zana Gafurri. Blood urea nitrogen/creatinine index is a predictor of prerenal damage in preeclampsia. Journal of Health Science. 2012: 2, 61-65.
18. Annabel CM, Brown MA. Could uric acid have a pathogenic role in pre-eclampsia? Nature Reviews Nephrology. 2010, 6: 744 – 748.
19. Tausif Zar, Orly F Kohn, Andre A Kaplan. Fractional Excretion of Urea in Preeclampsia A Clinical Observation. Iranian Journal Kidney Disease. 2011;5:398-403.
20. Kaplan AA, Kohn OF. Fractional excretion of urea as a guide to renal dysfunction. Am J Nephrol. 1992;12:49-54.
21. Hayashi M, Ueda Y, Hoshimoto K, et al. Changes in urinary excretion of six biochemical parameters in normotensive pregnancy and preeclampsia. Am J Kidney Dis. 2002;39:392-400.
22. Pasaoglu H, Bulduk G, Ogus E, Pasaoglu A, Onalan G. Nitric Oxide, Lipid Peroxide and Uric Acid Levels in Preeclampsia and Eclampsia. Tohoku J. Exp. Med. 2004, 202: 87- 92.
23. Kharb S. Uric Acid and Ascorbic Acid Levels in Pregnancy with Preeclampsia and Diabetes. Webmed Central Biochemistry 2010, 1: WMC00718.
24. Saha A. Role of nitric oxide, angiogenic growth factors, and biochemical analysis in preeclampsia. Indian J Biochem & Biophysics. 2013, 50: 462-66.
25. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Truong L, Harris R, Johnson RJ. A role for uric acid in the progression of renal disease. J Am Soc Nephrol. 2002; 13:2888–97.
26. Vince GS, Starkey PM, Austgulen R, Kwiatkowski D, Redman CW. Interleukin-6, tumour necrosis factor and soluble tumour necrosis factor receptors in women with pre-eclampsia. Br J Obstet Gynaecol. 1995; 102:20–25.
27. Shannon A. Bainbridge, James M. Roberts. Uric Acid as a Pathogenic Factor in Preeclampsia. Placenta. 2008, 29: S67–S72.
28. Zhang J, Zeisler J, Hatch MC, Berkowitz G. Epidemiology of pregnancy- induced hypertension. Epidemiol Rev. 1997; 19:218-32.
29. Lafayette RA, Druzin M, Sibley R, Derby G. et al. Nature of Glomerular dysfunction in pre-eclampsia. Kidney International 1998;54:1240-1249.