International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2021; 5(4): 112-115
Received: 11-05-2021
Accepted: 16-06-2021

Dr. Maturu Sudha Kumari
Associate Professor, Department of Obstetrics and Gynaecology, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram, Andhra Pradesh, India

Corresponding Author:
Dr. Maturu Sudha Kumari
Associate Professor, Department of Obstetrics and Gynaecology, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram, Andhra Pradesh, India

An observational study on the association of biomarkers such as maternal C-reactive protein and serum uric acid with preeclampsia in Andhra Pradesh

Dr. Maturu Sudha Kumari

DOI: https://doi.org/10.33545/gynae.2021.v5.i4b.1061

Abstract
Preeclampsia is one of the major conditions causing maternal morbidity and mortality throughout the world. Hyperuricemia due to oxidative stress is known to be associated with deleterious effects on endothelial function, oxidative metabolism, platelet adhesiveness and aggregation. C-reactive protein is an acute phase reactant protein, plays a role in eliciting the inflammatory response characteristic of preeclampsia. The present study was conducted in the Department of Obstetrics and Gynecology, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram (Dist.), Andhra Pradesh, India, which included pregnant women with preeclampsia taken as experimental group consisting of n=22 cases and n=22 matched normal pregnant women in the third trimester enrolled were taken as control group. Clinical history and blood was collected to assess C-reactive protein and uric acid levels. The serum C-reactive protein and uric acid levels were found significantly higher in preeclampsia cases than normal pregnant subjects. Uric acid and C-reactive protein levels were 5.06±1.84 mg/dL and 7.98±7.2 mg/dL respectively in the study group (cases) compared to 3.42±1.58 mg/dL and 6.43±4.18 mg/dL respectively in controls. There was a positive correlation between CRP and mean arterial pressure and also between C-reactive protein and serum uric acid. Serum uric acid and C-reactive protein may be feasible to be used as biomarkers for identifying women at risk of preeclampsia and hence, can be considered as supportive diagnostic tools in preeclampsia.

Keywords: C-reactive protein, hypertension, preeclampsia, serum uric acid

Introduction
Hypertensive disorders complicating pregnancy are common and form one of the deadly triad, along with hemorrhage and infection; that contribute greatly to maternal morbidity and mortality. Indeed hypertensive disorders remain among the most significant and intriguing unsolved problems in obstetrics [1].

The hypertensive disorders of pregnancy include hypertension that antedates pregnancy, chronic hypertension, and gestational hypertension occurring uniquely during pregnancy. When the gestational hypertension is accompanied by new-onset proteinuria, the disorder is termed as preeclampsia (PE) and when not associated with proteinuria, it is called transient hypertension of pregnancy. If the woman with chronic hypertension also manifests evidence of preeclampsia, this is classified chronic hypertension with superimposed preeclampsia. Eclampsia is the occurrence of seizures in women with preeclampsia [2].

Preeclampsia (PE) is a multisystemic, pregnancy-specific disorder, which may cause maternal and neonatal morbidity and mortality. The global incidence of preeclampsia has been estimated at 5-14% of all pregnancies [3, 4].

In India, the incidence of preeclampsia is reported to be 8-10% of the pregnancies [5]. It is an elevated blood pressure more than 140/90 mm of Hg on two separate occasions, taken six hours apart, within a period of one week and evidence of proteinuria which develops after 20 weeks of gestation. The specific cause for this syndrome remains unclear despite the intense investigation. It has been reported that an altered Lipid profile [6]. Leukocyte activation [7], Enhanced inflammatory response [8] and Oxidative stress [9] in maternal circulation are frequently associated with development of this disorder.

Among all these factors, though immunologic factors have long been considered to be key players in preeclampsia, the endothelial cell dysfunction and inflammation are considered to have a crucial role in pathophysiological mechanism of preeclampsia [10].

An inflammatory response is usually accompanied by increasing concentrations of proinflammatory cytokines, acute-phase proteins and may also involve leukocyte activation. It has been suggested that elevated levels of CRP in accordance with its proposed function may reflect the inflammatory response characteristics of preeclampsia. The value of CRP level reflects the severity of endothelial cell injury which is one of the responsible factors for developing or initiating the preeclampsia.
It is speculated that circulating xanthine dehydrogenase / xanthine oxidase (XO) can bind to endothelium and lead to local oxidative injury [11]. Hyperuricemia is a common finding in preeclamptic pregnancies. The cause of hyperuricemia in preeclampsia has been attributed to either a decreased excretion or to an increased production of uric acid. Decreased uric acid clearance, reflected by altered tubular function has been documented, while Fay [12] proposed an increased breakdown of purines in the placenta as a possible explanation for the overproduction of uric acid.
The present study was conducted to determine the levels of C-reactive protein and serum uric acid levels in preeclampsia pregnant women and to determine the severity by the association among CRP, uric acid concentration, BMI and blood pressure.

Material and Methods

The present study was carried out in the Department of Obstetrics and Gynaecology, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram (Dist.), Andhra Pradesh, India for a period of eighteen months.
The patients attending the hospital outpatient department or admitted in the Dept. of Obstetrics and Gynaecology were selected for the present study according to the specific criteria like pregnant women in the third trimester of gestation between 28-40 weeks, who were diagnosed as having preeclampsia on the basis of clinical history, examination, systolic blood pressure >140mmHg and diastolic blood pressure >90mmHg.
The sample size of the present study consisted 44 (n=44) cases of which 22 (n=22) diagnosed preeclamptic pregnancy considered as Experimental group, 22 (n=22) cases healthy normal pregnant women comparable gestational age in the 3rd trimester were chosen as controls from the general population.

Inclusion criteria of the subjects in the study included

- Experimental study group subjects: Pregnant women in third trimester of gestation between 28 – 40 weeks, who were diagnosed as having preeclampsia on the basis of clinical history, examination, systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg.
- Control group subjects: Apparently healthy singleton pregnant women in the third trimester (28– 40 weeks).

Exclusion criteria of the subjects in the study included

- Patients with multiple gestation
- Patients in active labor
- Patients with essential hypertension , history of acute or chronic liver diseases
- Patients on drugs affecting coagulation or taking corticosteroids
- Patients with DM or Gout or Hypothyroidism or Hyperthyroidism
- Patients having chronic inflammatory disorders like Rheumatoid Arthritis, Tuberculosis, Osteoarthritis, Inflammatory Bowel Disease.
- Patients on drugs like Diuretics, Salicylates, Ethambutol, Pyrizinamide
- Patients on magnesium supplementation or other metal containing medications
- Chronic Alcoholics
- Chronic Kidney Diseases
- Patients with cardiovascular diseases
- Fetal infections or fetal congenital abnormalities
- Women with chorioamnionitis
- Women with premature rupture of membranes
- Women with active sexually transmitted diseases
- Women with severe anaemia (Hb < 6g/dL)

Ethical Committee approval was taken from the Institutional Ethical Committee Board and permission was obtained from the HOD of the department to conduct the study, informed consent was taken from all participants before initiating the study.

Diagnosis of Preeclampsia

Systolic blood pressure greater than 140 mmHg or a rise of at least 30 mmHg; diastolic blood pressure >90mmHg or a rise of at least 15 mmHg (measured on two occasions at least 6 hours apart); proteinuria of 300 mg or more in 24 hours urine collection or protein concentration of 1 gm/dl (on two occasions of at least 6 hours apart), or ≥2+ in mild preeclampsia and >3+ in severe preeclampsia by dipstick method. Those patients whose 24 hours urine sample examination revealed single plus (+), two plus (++) and three plus (+++) by dipstick method were categorized as mild, moderate and severe preeclampsia.

Data and Sample collection

After a thorough history taking and clinical examination, the procedure was explained to the subjects and an informed consent was taken from all participants before initiating the study. Body Mass Index (BMI) was calculated for all the subjects. Blood pressure and proteinuria in the subjects were noted. 3ml of venous blood sample (fasting) was collected from antecubital vein following aseptic precautions and assessment of serum uric acid and C-reactive protein was done.

Statistical Analysis

Statistical analysis was performed by the SPSS program for Windows, Version 17.0 (SPSS, Chicago, Illinois) and Continuous Variables are presented as mean ± SD and categorical variables are presented as absolute numbers and percentage. Statistical formulae like chi-square test, independent sample t-test, Pearson's correlation were used wherever found suitable and necessary and accordingly interpretations were made.

Results

The statistical data of continuous variables (Mean and SD) for Maternal age (years), gestational age (weeks), Body mass index (kg/m^2), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), serum uric acid (mg/dL), C-reactive protein (mg/L), proteinuria (%) of experimental (n=22) group and control (n=22) group are presented in Table 1.

Table 1: Descriptive Statistics of individual clinical data of control group (n=22) and experimental group (n=22) group

Clinical parameters		Experimental (Preeclampsia) Group (n=22)	Control group (n=22)
		Mean ± SD	Mean ± SD
Maternal age (years)		28.8 ± 5.2	24.8 ± 4.6
Gestational age (week)		31.8 ± 3.2	32.6 ± 2.8
Body mass index (kg/m2+)		25.2 ± 1.8	22.4 ± 2.6
Systolic blood pressure (mmHg)		164.26 ± 27.64	120.50 ± 9.37
Diastolic blood pressure (mmHg)		104.36 ± 13.34	78.86 ± 8.42
Serum uric acid (mg/dL)		5.06 ± 1.84	3.42 ± 1.58
C-reactive protein (mg/L)		7.98 ± 7.2	6.43 ± 4.18
Proteinuria (%)	• >+++	• 64.00	• --
	• +	• --	• 46.00

Maximum number of subjects in the experimental group belongs to age group of 31 - 35 years (46%) and maximum number of subjects in the control group belongs to age group between 21 - 25 years (41%). It is observed that mean age in control group is 24.8 ± 4.6 (years), whereas in preeclampsia group is 28.8 ± 5.2 (years).

In the experimental preeclampsia study group, maximum number of patients had severe proteinuria i.e., >+++ (64%) and in the control group maximum number of subjects had mild (+) proteinuria (46%) which is considered as physiologically normal. However, moderate proteinuria (++) was observed both in the experimental and control groups. The statistically significant difference of proteinuria was observed between preeclampsia experimental group and control group.

The comparison of mean ± SD (mmHg) of blood pressure between the preeclampsia experimental study group and control group showed highly statistically significant difference. The mean ± SD of systolic as well as diastolic blood pressure levels were much higher in preeclamptic pregnant women recording 164.26 ± 27.64 mmHg, 104.36 ± 13.34 mmHg respectively when compared to systolic as well as diastolic blood pressure levels in normal pregnant control subjects recording 120.50 ± 9.37 mmHg and 78.86 ± 8.42 mmHg respectively.

The mean serum uric acid level in study group was observed to be 5.06 ± 1.8 (%), much higher than the control group i.e. 3.42 ± 1.58 mg (%) and the difference was statistically significant. The mean serum CRP level in the experimental study group subjects is much higher (7.98±7.2 mg/l) compared to that of control group subjects (6.43±4.18 mg/l) however, was not statistically significant.

The mean values of serum uric acid and CRP levels always remained higher in experimental study group than that of the control group subjects. The mean values of both serum uric acid and CRP levels in experimental study group were nearer to their respective upper limits of normal range.

There was a strong positive correlation observed between serum uric acid and blood pressure (systolic and diastolic) and was statistically highly significant. A positive correlation is also observed between serum uric acid and serum CRP level.

Discussion

Hypertensive disorders of pregnancy which frequently manifest as preeclampsia continues to exert an enormous toll in developing countries like India and also in western society. Despite progress in its prevention, detection and treatment, it continues to be the leading cause of maternal death. Research over last decade proved the role of oxidative stress and inflammation in pathophysiology of preeclampsia. Oxidative stress, xanthine oxidase activity and inflammation are important contributors. Various traditional and newer biomarkers were suggested for diagnosis and prognosis of preeclampsia.

Preeclampsia is a complication of pregnancy, constituting a major cause of maternal and foetal morbidity and mortality. Several aetiologies have been implicated in the development of preeclampsia including abnormal trophoblast invasion of uterine blood vessels and immunological intolerance between feto-placental and maternal tissues.

The triad of severe preeclampsia is often described as a combination of hypertension, edema and proteinuria. Proteinuria is the last sign to develop [13, 14]. Although salt and water retention are common features of preeclampsia. In the current study, the mean blood pressure (mmHg) was significantly higher in preeclampsia compared to normal controls similar to the findings reported by Powers *et al.* and Baksu *et al.* [15, 16].

In the current study, the levels of serum uric acid are significantly higher in the experimental study group compared to the control group. During pregnancy, maternal serum uric acid levels initially falls, with a subsequent rise as the pregnancy period reaches near term [17]. The elevated serum uric acid levels due to decreased renal urate excretion is frequently found in women with preeclampsia [18]. Soluble uric acid impairs nitric oxide generation in endothelial cells inducing endothelial dysfunction [19].

Besides the reduced clearance hyperuricemia in preeclampsia may be due to increased uric acid production caused by trophoblast breakdown, cytokine release and ischemia. Uric acid can promote endothelial dysfunction, damage and inflammation, which leads to oxidation.

It has also been reported that rise in uric acid level in preeclampsia is secondary to placental damage leading to purine catabolism and increased production of uric acid. In our study, the increased uric acid level in preeclampsia cases shows positive correlation with serum CRP level. This is supported by the findings of Ingec *et al.* [20], where it has been reported that increase in uric acid level in preeclampsia is secondary to placental damage leading to purine catabolism and production of uric acid. A positive correlation is found between the serum uric acid level and blood pressure.

Limitations of our study and Addition of our study to the existing knowledge

Limitations of the present study are sample size was too small due to which I did not correlate the parameters with different gestational age groups. We did not estimate the severity of preeclampsia and its complications.

Further studies on a larger sample size however, is needed to substantiate our findings before firm conclusion can be drawn on the utility of these parameters for the diagnostic assessment of preeclampsia. Serum uric acid and CRP could be considered as a supportive diagnostic tool in preeclampsia along with conventional markers. Therefore, early diagnosis or recognition of the onset of preeclamptic changes can help to curb and

control the situation, limiting the undesirable results.

Conclusion

Uric acid and CRP level can be measured before the development of preeclampsia or early in pregnancy in order to identify and monitor the patients at risk of preeclampsia and thus to provide the best prenatal care for these women and their babies.

References

1. Cunningham FG, Leveno KG, Bloom SL, Hauth JC, Gilstrap III LC, Wenstrom KD. Hypertensive disorders in pregnancy. Williams Obstetrics. 22nd Edition. Mc Graw Hill 2005, 761-785.
2. Report of National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000;183(1):s1-s22.
3. Villar J, Betran A, Gulmezoglu M. Epidemiological basis for the planning of maternal health services. WHO/RHR. 2001;111:298-298.
4. Khedun S, Moodley J, Naicker T, Maharaj B. Drug management of hypertensive disorders of pregnancy, Pharmacology & therapeutics 1997;74(2): 221-258.
5. Pushparaj JL, Subramanyam G. Preeclampsia, dyslipidemia, atherogenesis, lipid profile, placental ischemia, cardiovascular disease. Dyslipidemia in Preeclampsia-Risk Factor for Future Maternal Cardiovascular Diseases 2012, (187).
6. Catarino C, Rebelo I, Belo L. Fetal Lipoprotein Changes in Pre-Eclampsia. Acta Obstetricia ET Gynecologica Scandinavica 2008;87(6):628-634.
7. Lok CA, Jebbink J, Nieuwland R. Leukocyte Activation and Circulating Leuckocyte-Derived Microparticles in Preeclampsia. American Journal of Reproductive Immunology 2009;61(5):346-359.
8. Borzychowski A, Sargent I, Redman C. Inflammation and Pre-Eclampsia. Paper Presented At Seminars In Fetal And Neonatal Medicine, 2006.
9. Bernadi F, Guolo F, Bortolin T, Petronilho F, Dal-Pizzol F. Oxidative stress and Inflammatory Markers in Normal Pregnancy and Preeclampsia. Journal of Obstetrics and Gynaecology Research 2008;34(6):948-951.
10. Kharb S, Gulati N, Singh V, Singh G. Lipid Peroxidation Andvitamin E Level S In Preeclampsia. Gynecologic and Obstetric Investigation 1998;46(4):238-240.
11. White CR, Darley-Usmar V, Berrington WR. Circulating Plasma Xanthine Oxidase Contributes To Vascular Dysfunction In Hyper cholesterolemic Rabbits. Proceedings of the National Academy of Sciences 1996;93(16):8745-8749.
12. Fay RA. Uric Acid in Pregnancy and Preeclampsia: An Alternative Hypothesis. Australian and New Zealand Journal of Obstetrics and Gynaecology 1990;30(2):141-142.
13. Mandal KK, Singh YP, Das A, Devi NS, Singh NN. Serum Uric Acid and C - reactive protein In Preeclampsia 2015;14(2):16-23.
14. Macgillivray I, Campbell DM. The Relevance of Hypertension and Oedema in Pregnancy. Clinical and Experimental Hypertension 1980;2(5):897-914.
15. Powers RW, Dunbar MS, Laivuori HM, Harger GF, Lykins DL, Roberts JM. Maternal Plasma Homocysteine Concentrations Are Not Increased In Twin Pregnancies. Hypertension in Pregnancy 2005;24(1):49-58.
16. Baksu A, Taskın M, Goker N, Baksu B, Uluocak A. Plasma Homocysteine In Late Pregnancies Complicated With Preeclampsia and In Newborns. American Journal of Perinatology 2006;23(01):031- 036.
17. Lind T, Godfrey K, Otun H, Philips P. Changes In Serum Uric Acid Concentrations During Normal Pregnancy. Bjog: An International Journal of Obstetrics & Gynaecology. 1984;91(2):128-132.
18. Kang DH, Finch J, Nakagawa T. Uric Acid, Endothelial Dysfunction and Pre-Eclampsia: Searching For a Pathogenetic Link. Journal of Hypertension. 2004;22(2):229-235.
19. Khosla UM, Zharikov S, Finch JL. Hyperuricemia Induces Endothelial Dysfunction. Kidney International 2005;67(5):1739-1742.
20. Ingec M, Borekci B, Kadanali S. Elevated Plasma Homocysteine Concentrations in Severe Preeclampsia and Eclampsia. The Tohoku Journal of Experimental Medicine 2005;206(3):225-231.