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Original Research Article

A comparison of serum levels of uric acid, c-reactive protein and nitric oxide in preeclampsia patients and normal healthy pregnant females

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ABSTRACT

Background: Preeclampsia is a human pregnancy specific multisystem disease of unknown etiology. It is a major cause of maternal mortality, morbidities, perinatal deaths, preterm birth and intrauterine growth restriction. It was aimed to find the role of Uric Acid, CRP and Nitric Oxide in preeclampsia by comparing their levels with normal pregnant females. As its etiology is unknown, so it's early detection and its follow up is required to prevent maternal and fetal complications.

Materials and Methods: A case control study was conducted in the Department of Biochemistry and Department of Obstetrics and Gynaecology, UPUMS Medical College and Hospital, Saifai, Etawah, Uttar Pradesh, India. The study group includes 50 normal healthy pregnant females and 50 preeclampsia patients who were between 20 - 40 years of age and more than 20 weeks of gestation.

Results: There was significantly ($p < 0.0001$) raised serum uric acid, C-reactive protein and decreased nitric oxide levels in preeclampsia patients as compared to normal healthy pregnant females.

Conclusion: It concludes that high serum levels of uric acid, C-reactive protein and low levels of nitric oxide shows their important role in pathogenesis of preeclampsia. Their serum levels can be considered as an indicative markers for disease and its severity of preeclampsia to prevent maternal and fetal complications.

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1. Introduction

Preeclampsia is a human pregnancy specific multisystem disease of unknown etiology that is defined by the onset of hypertension (Blood Pressure $\geq 140/90$ mmHg) on 2 separate occasions that are at least 6 hours apart and newly detected proteinuria (≥ 300 mg in 24 hours urinary collection), at a period of >20 weeks of gestation in a previously normotensive and non-proteinuria women.¹ Prevalence of preeclampsia in developing countries ranges from 1.8% to 16.7%.² According to National Health Portal 2016 prevalence of hypertensive disorders of pregnancy was 7.8%, out of which preeclampsia contribute 5.4% of

the study population in India.³ It is an important public health problem both in developing and developed countries contributing to maternal and fetal morbidity and mortality.¹ It is a major cause of maternal mortality, morbidities, perinatal deaths, preterm birth and intrauterine growth restriction.⁴

It occurs mainly due to the abnormal cytotrophoblastic invasion into the spiral arteries, utero-placental hypoperfusion, an imbalance between increased synthesis of vasoconstrictors and decreased production of vasodilators, increased oxidative stress and endothelial dysfunction.¹

1.1. Risk factors for preeclampsia

1. Pregnancy-associated factors

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- (a) Chromosomal abnormalities
- (b) Hydatidiform mole
- (c) Hydrops fetalis
- (d) Multifetal pregnancy
- (e) Oocyte donation or donor insemination
- (f) Structural congenital anomalies
- (g) Urinary tract infection

2. Maternal-specific factors

- (a) Age greater than 35 years
- (b) Age less than 20 years
- (c) Black race
- (d) Family history of preeclampsia
- (e) Nulliparity
- (f) Preeclampsia in a previous pregnancy
- (g) Specific medical conditions: gestational diabetes, type I diabetes, obesity, chronic hypertension, renal disease, thrombophilias
- (h) Stress

3. Paternal-specific factors

- (a) First-time father
- (b) Previously fathered a preeclamptic pregnancy in another woman.⁵

The diagnostic criteria were revised in 2013 and 2014: it is defined as new onset hypertension developing after 20 weeks of gestation and the coexistence of a minimum of one of the following new onset conditions:

1. Proteinuria: demonstrated by the ratio of proteinuria/creatinine above 0.3mg/mg, or by urine dipstick test equal to or above 1+, or by 24hrs proteinuria above 300mg/24h OR
2. Maternal end-organ dysfunction (including renal, hepatic, hematological, or neurological complications) OR
3. Uteroplacental dysfunction reflected in fetal growth restriction (FGR).⁶

Uric acid is the end product of purine degradation catalyzed by the enzyme xanthine oxidase in liver.⁷ It is a marker of oxidative stress, tissue injury and renal dysfunction,⁸ also has antioxidant properties as well as it contributes as free radical scavenger in human serum.⁷ Uric acid plays an important role in vascular damage and oxidative stress.⁹

Under pathological conditions, there may be an increase in the production of radicals or a deficiency of superoxide dismutase, with a consequent increase in circulating reactive oxygen species. An increase in reactive oxygen species generation has been suggested to contribute to vascular remodelling, apoptosis and proliferation of vascular smooth muscle.¹⁰

C-reactive protein is a biochemical marker which is an objective and sensitive index of inflammatory

activity in body.¹¹ Inflammation is considered as an important contributor in the pathogenesis of preeclampsia. In preeclampsia, the systemic maternal inflammatory response is enhanced and it is also characterized with more generalized intravascular inflammatory reaction.³ C-reactive protein can be considered as a marker in antenatal to monitor or predict the preeclampsia and its progression of severity.¹²

Nitric Oxide (NO) which is a potent vasodilator plays an important role in relaxing smooth muscles and helps in the vasodilation of maternal blood flow. It also plays a significant role in fetoplacental blood flow and quiescence of the uterus before parturition.¹³ In preeclampsia, vascular endothelial dysfunction occurs which can cause hypertension with its increased production of vasoconstrictor agents such as plasma endothelin or reduced release of vasodilator such as nitric oxide. Reduced level of nitric oxide can be used as marker for preeclampsia.¹⁴

2. Materials and Methods

The case control study was conducted with institutional ethical committee approval in Department of Biochemistry and Department of Obstetrics and Gynaecology of Uttar Pradesh University of Medical Sciences Medical College and Hospital, Saifai, Etawah, U.P., India. The present study comprised 100 pregnant females out of which 50 were preeclamptic patients and 50 were normotensive pregnant females, after taking their written consent. All subjects were between 20-40 years of age and >20 weeks of gestation. The exclusion criteria includes pregnant females with active labour, History of diabetes mellitus, cardiovascular diseases, liver disease, renal disease, endocrine disorder, essential hypertension, seizure disorder, severe anemia. Evaluation of parameters was done in laboratory of Biochemistry Department by photometry and ELISA. Statistical analysis was performed using statistical software: Statistical Package for Social Sciences (SPSS) version 23. The data was summarized as arithmetic means and standard deviation (Mean $\pm$ SD) along with mode. Difference between variables of two groups were compared using the Student's t-test (unpaired t-test). $P < 0.05$ was considered as statistically significant.

3. Result

Table 1: List of the study parameters and their units

S.No.	Parameter	Unit
1.	Uric acid (UA)	mg/dL
2.	C-reactive protein (CRP)	mg/L
3.	Nitric oxide (NO)	μ mol/L

Table 2: Showing the status of biochemical parameters in normal healthy pregnant females and preeclampsia patients

Study Group		UA (mg/dL)	CRP (mg/L)	NO (μ mol/L)
Normal Healthy Pregnant Females (n=50)	Min	2.3	0.7	58.09
	Range			
	Max.	6.4	11	103.7
	Mean $\pm$ SD	3.99 $\pm$ 0.89**	3.18 $\pm$ 2.13**	80.49 $\pm$ 10.14**
	SE	0.13	0.3	1.43
	Mode	3.4	4.2	78.8
	Min	3.5	1.5	51.66
Preeclampsia Patients (n=50)	Range			
	Max.	10	21.1	89.93
	Mean $\pm$ SD	6.26 $\pm$ 1.31**	7.62 $\pm$ 3.41**	69.13 $\pm$ 9.47**
	SE	0.19	0.48	1.33
	Mode	5.9	8.9	62.2

Unpaired 't' test

Values expressed as Mean $\pm$ SD, SD= Standard deviation, SE= Standard Error, Mode, **P<0.0001, NS = Non-significant

This study shows that, Serum Uric Acid level was significantly ($p<0.0001$) raised in preeclampsia patients with mean value of 6.26 ± 1.31 (mg/dL) and mode of 5.9 (mg/dL). Mean value of 3.99 ± 0.89 (mg/dL) and mode of 3.4 (mg/dL) was found among normal healthy pregnant females. Serum C-Reactive Protein level was significantly ($p<0.0001$) raised in preeclampsia patients with mean value of 7.62 ± 3.41 (mg/L) and mode of 8.9 (mg/L). Mean value of 3.18 ± 2.13 (mg/L) and mode of 4.2 (mg/L) was found among normal healthy pregnant females. Serum Nitric Oxide level was significantly ($p<0.0001$) low in preeclampsia patients with mean value of 69.13 ± 9.38 (μ mol/L) and mode of 62.2 (μ mol/L). Mean value of 80.49 ± 10.14 (μ mol/L) and mode of 78.8 (μ mol/L) was found among normal healthy pregnant females. (Table 2)

4. Discussion

More than one & half of subjects, cases (80%) & (72%) of controls were between 20-30 years. Rest 20% of cases and 28% of the controls were between the 31-40 years.

Serum Uric acid was studied and found to be significantly ($p<0.0001$) raised among preeclampsia patients (6.26 ± 1.31 mg/dL) compared to the normal healthy pregnant females (3.99 ± 0.89 mg/dL). These values are corresponded to the several studies out of which one was led by Sushma Goad et al¹⁵ in which it was found that mean serum uric acid levels in the preeclampsia patients was 7.01 ± 0.58 and control samples was 3.41 ± 0.62 ($P = 0.001$) which was significantly higher in preeclampsia patients compared with controls. The findings suggest that raised level of uric acid may contribute to pathophysiology of preeclampsia. In preeclampsia, uric acid levels could be useful indicator of fetal complication.

Similarly, in the study done by Pramanik T et al,¹⁶ uric acid levels was significantly higher ($p<0.05$) in preeclamptic patients (6.27 ± 1.37) compared to their healthy pregnant women (4.27 ± 0.61). The study indicated that preeclampsia

is associated with elevated serum uric acid level which could be used as biochemical indicator of preeclampsia in pregnant women. In preeclampsia, uric acid level has found to be increased and to correlate with maternal and fetal morbidity, but always has been assumed to be a reflection of disease rather than a cause and it has antioxidant properties that serve to protect from oxidative stress, but it also appears to contribute directly to endothelial dysfunction by its proinflammatory effects, as well as to hypertension during preeclampsia.¹⁵

Serum C-reactive protein was studied and found to be significantly ($p<0.0001$) increased among preeclampsia patients (7.62 ± 3.41 mg/L) compared to the normal healthy pregnant females (3.18 ± 2.13 mg/L). These values were corresponded to the several studies out of which one was led by Mohan Lal Meena et al,¹¹ in which they wanted to find out association of C-reactive protein with preeclampsia. In the study, C-reactive protein concentration was found to be significantly higher ($p<0.001$) in preeclamptic patients (15.4 ± 2.37) than in normal pregnant women (2.68 ± 0.9). The study concludes that C-reactive protein level is raised in preeclampsia than normal pregnancy, thus serum C-reactive protein level can be used as a utility parameter for the assessment of preeclampsia.

In the study done by Zaima Ali et al,¹⁷ C-reactive protein levels were significantly high (p -value < 0.001) in the preeclamptic group with a median value of 8.8 (0.3 - 25.5) as compared to 5.4 (0.24 - 9.8) mg/L in the normotensive women. It concludes that elevated c-reactive protein levels in preeclamptic pregnant women is a part of an exaggerated maternal systemic inflammatory response and correlates with low fetal birth weight.

Serum Nitric oxide, was studied and found to be significantly ($p<0.0001$) decreased among preeclampsia patients (69.13 ± 9.38 μ mol/L) compared to the normal healthy pregnant females (80.49 ± 10.14 μ mol/L). These values are corresponded to the several studies out of which one was done by Jong Weon Choi et al¹⁸ which was aimed

to investigate the changes in nitric oxide production during & after normal pregnancy & in pregnancies complicated by preeclampsia. The study shows significantly ($p < 0.01$) lower serum nitric oxide concentration in preeclamptic women (43.1 ± 12.7 microM) than those in the gestation age-matched normal pregnant women (249.7 ± 51.3 microM). It concludes that nitric oxide biosynthesis increases with advancing gestation during normal pregnancy & decreases in preeclampsia.

In the study done by Salma Akter et al,¹⁹ serum nitric oxide levels were significantly ($p < 0.05$) lower in preeclampsia patients (18.37 ± 3.64 mol/L) as compared to normal pregnant women. It concludes that decrease nitric oxide levels as proxy indicator can be used as marker for preeclampsia.

5. Conclusion

It was concluded that high serum levels of uric acid, C-reactive protein and low levels of nitric oxide shows their important role in pathogenesis of preeclampsia. Their serum levels can be considered as an indicative markers for severity of preeclampsia to prevent maternal and fetal complications.

6. Conflicts of Interest

The authors declares that there is no conflict of interest regarding the submission and publication of the manuscript and its potential implications.

7. Source of Funding

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