

# Biomedical Markers and Antioxidant Vitamins in Preeclampsia and Normal Pregnancy

**Shinde Uma, Rane SA, Prabhu Teja, \*Yi Ching Ling**

Department of Biochemistry and Clinical Nutrition, \*Department of Obstetrics & Gynecology, Seth G.S. Medical College, K.E.M. Hospital, Parel, Mumbai 400012 (India), \*Topiwala National Medical College, Bai Yamunabai Laxman Nair Charitable Hospital, Mumbai Central, Mumbai 400008

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## ABSTRACT

The preeclampsia (PE), the gestational hypertension, is a major condition affecting the pregnant women and the new borne all over the world. With paucity of the conclusive knowledge of its origin and progress it is essential to focus on early diagnosis and timely treatment. The study of the important biochemical parameters would offer clues for the causes or the progress of the PE. The altered parameters could be used as the biomarkers of PE and its progress. The present study aimed at the evaluation of these metabolites viz. urea, uric acid, creatinine and the liver enzymes (AST, ALT & ALP) in PE patients and in normal healthy pregnant women.

Oxidative stress plays important role during PE. The evaluation of status of electrolytes and the antioxidant vitamins in PE patients was carried out to get the clues about progressive disorders. The PE patients exhibited uremia, hypercreatininemia along with elevated enzymes levels. But insignificant changes in electrolytes were seen. The statistically significant reduction was observed in levels of vitamin A and vitamin C contents. These results would help to analyse the alterations in various metabolisms which can be linked to PE condition.

**KEY WORDS:** creatininemia, oxidative stress, preeclampsia, uremia, uric acid

## INTRODUCTION:

Preeclampsia (PE), the gestational hypertensive disorder is a major cause of maternal and foetal morbidity and mortality<sup>[1,2]</sup>. The incidence rate of the disorder is 3-10% globally and about 6% in India<sup>[3]</sup>. It is a major cause of maternal death throughout the world and is accompanied by substantial perinatal morbidity and mortality. It is also responsible for other disorders in pregnancy like small for growth age (SGA), intrauterine growth restriction (IUGR), preterm labour and delivery. The effects of oxidative stress also seem to be having role in pathophysiology of preeclampsia and free

radical induced birth defects<sup>[3]</sup>. The aetiology of the pathophysiology of the disorder is still elusive. Therefore the search for the causative factors and an effective preventive therapy have been the major focus of the current research.

The aim was the identification of the changes in various metabolic processes as they might provide the clues for the development of PE and its progress. The current study evaluated the status of important metabolites like plasma urea, uric acid and creatinine along with the liver enzymes Aspartate transaminase (AST), Alanine transaminase (ALT) and Alkaline phosphatase (ALP) in PE patients and in normal pregnant women. Serum uric acid and creatinine were the important metabolites known to be elevated as reported by many research studies<sup>[2,4]</sup>. The liver enzyme-activities were also known to be elevated during pregnancy, preterm labour and delivery<sup>[5]</sup>.

The presence of oedema in PE patients led to the analyses of electrolytes levels in the PE patients<sup>[1,6]</sup>. It has been reported that oxidative stress

### Corresponding Author:

**Dr S.A. Rane**

Associate Professor,  
Department of Biochemistry  
Seth GS Medical College,  
KEM Hospital, Parel Mumbai- 400012  
Phone No.: 9930105732  
E-mail: drsarane@gmail.com



play important role during the normal pregnancy and during the gestational hypertensive disorders leading to pathological condition with multi-organ involvement<sup>[1,7]</sup>.

Effects of oxidative stress were seen in pathophysiology of preeclampsia, hydatidiform mole, free radical induced birth defects and other situations such as abortions<sup>[2,8]</sup>. The most common antioxidant assessed were vitamin A, vitamins C and vitamin E<sup>[9]</sup>. These are the required antioxidant micronutrients that are obtained from the diet that are present in measurable quantities in blood but cannot be synthesized by the body. Such antioxidants selected were vitamin A carotenes ( $\alpha$ -carotene,  $\beta$ -carotene, lycopene), oxy-carotenoids (lutein, zeaxanthin, cryptoxanthin), retinols, ascorbic acid (vitamin C) and vitamin E (total tocopherol including  $\alpha$ -tocopherols). The blood samples were assessed to judge any increased need of the same. This might be suggestive to nutritional supplementation to reduce the chances of PE & its progress and to provide prophylactic effect if possible.

## MATERIALS AND METHODS:

Pregnancy is a metabolic stage involving development of placenta and foetus. Preeclampsia (PE) is the hypertension associated with pregnancy observed after 20 weeks of gestation<sup>[2,3,10]</sup>.

The clinically confirmed Preeclamptic patients of 18 years to 40 years (with BP  $\geq$  140/90 mm of Hg (Systolic/Diastolic B.P.) and proteinuria (+2)), admitted in the wards of Department of Obstetrics and Gynecology, T.N. Medical College, Nair Hospital, Mumbai-400008, formed the test group (Number =90). The normotensive pregnant women (attending OPDs of Department of Obstetrics & Gynecology of the same Hospital) were the controls (Number: 90 matched age-wise). The patients with bone deformities, cancerous conditions and any endocrinological disorders were excluded from the studies.

The Research study had been approved by The Institutional Ethics Board of Topiwala National Medical College, B.Y.L. Nair charitable Hospital, Mumbai Central, Mumbai, India. The participants were voluntary and the Informed Consent was obtained (in English, Marathi & Hindi) from all participants.

The blood samples of the PE patients and the Controls were collected and analysed for the biochemical parameters i.e. Creatinine, Urea, Uric

Acid, the electrolytes (Na, K and chlorides) AST, ALT and Alkaline Phosphatase using Autoanalyzer AU400. Estimation of the Vitamin A, Vitamin C and Vitamin E were performed using the colorimetric Methods, i.e. by Carr-Price method<sup>[11]</sup>, 2-6-Dichlorophenol Indophenol method<sup>[12]</sup> and Emmerir Enjel methods respectively<sup>[13]</sup>.

The statistical analysis was carried out with help of standard formulae and SPSS software.

## RESULTS:

Preeclampsia (PE), the disorder of gestational hypertension, is observed in third trimester of pregnancy and is a major cause of morbidity & mortality for the pregnant mother and the child worldwide<sup>[2,3,4]</sup>. The present study carried out comprehensive study of the biomolecules in PE patients and in normal pregnant women. It would lead to fix the abnormalities in various metabolisms during the onset of PE.

The normal uric acid levels observed in the PE group (Table 1, Figure 1) indicated the low socio-economic strata of the patients and the increased clearances of the normal excretory products. The serum uric acid, urea and creatinine levels have been suggested as important parameters in women with preeclampsia to monitor severity of PE and to aid management of these women. Hyperuricemia has been one of the characteristic findings in preeclampsia but observations of current studies do not support it. The present study indicated the statistically significant elevation in serum urea and creatinine contents but no such elevation in uric acid contents. The heterogeneity in levels of uric acid of PE cases had been supported by the earlier studies,<sup>[22,23]</sup> Metabolism of Uric Acid would be least affected in the early stages of preeclampsia.

The results of present study indicated rise in urea and creatinine levels, 34% & 70% respectively. The parameter Uric acid did not show any significant changes in PE group, but 34% and 70% increments were observed in Urea and creatinine contents of PE group (Table 1, Figure 1). Substantial heterogeneity was observed by different research groups<sup>[5,7,8,9]</sup>.

Similarly elevated levels of AST, ALT and ALP were observed in PE cases (178%, 180% and 101% respectively) (Table 2, Figure 2). The higher ALP activity has been reported to be associated in third trimester and in parturition as was also supported by those of the control group<sup>[1,5]</sup>. The higher activity of ALT & AST enzymes were indicative of changes in

**Table 1 :** Mean serum levels (mg/dl) of the metabolites in preeclamptic patients and in the control group.

Parameters(mg/dl)	PE	Control	p- value	% Increase(+) / Decrease (-)
Uric Acid	4.5 ± 1.09	4.3 ± 1.390	NS	-
Urea	26.78 ± 1.08	19.7 ± 1.08	<0.01	(+) 34.0
Creatinine	1.70 ± 0.22	0.70 ± 0.301	<0.01	(+)70.0

**Table 2:** Mean Serum enzymes levels (IU/l) in preeclamptic (PE) Patients and in the control group.

Parameter(IU/L)	PE	Control	p- value	% Increase (+) / Decrease(-)
Alanine Aminotransferase	82.675 ± 16.66	29.43 ± 7.49	<0.001	(+) 180
Aspartate Aminotransferase	61.57 ± 14.248	24.53 ± 7.205	<0.001	(+) 178
Alkaline Phosphatase	173.68 ± 46.40	83.16 ± 18.74	<0.01	(+) 101

**Table 3 :** Mean Serum electrolyte levels (mEq/l) in preeclamptic patients and in the control group.

Parameters	PE	Control	p value
Sodium	137.2 ± 3.73	138.4 ± 2.97	NS
Potassium	4.12 ± 0.307	4.25 ± 0.49	NS
Chlorides	100.4 ± 3.14	100.7 ± 3.12	NS

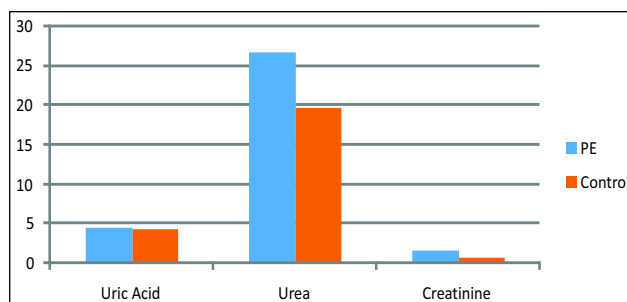
**Table 4 :** Serum antioxidant –Vitamins (mg/dl) in preeclamptic patients and in the control group

Parameters	PE	Control	p value	% Increase (+) / Decrease (-)
Vitamin A (mg/dl)	2.047 ± 0.015	4.3 ± 0.67	<0.001	(-) 50
Vitamin C (mg/dl)	1.59 ± 0.340	1.5 ± 0.26	NS	-
Vitamin E (mg/dl)	0.74 ± 0.227	1.1 ± 0.11	<0.01	(-) 30

liver metabolism or increased endothelial permeability of their parent organs. There are other references stressing the importance of ALP in predicting the severity of the PE disorder<sup>[5]</sup>.

The levels of sodium (Na), potassium (K) and chlorides were assessed from these groups. The assessment of antioxidant vitamins i.e. vitamin A, vitamin C and vitamin E, was also thought to be supportive in the study. It would be very helpful to judge the increased utilization of the same to reduce the oxidative stress.

The levels of serum electrolytes in the test group were not found to be differing statistically from those of normal pregnant women of Control group.

**Figure 1 :** Important metabolites in PE and normal pregnancy.

(Table 3, Figure 3). Despite of observation of an occasional oedema in PE cases, the present study

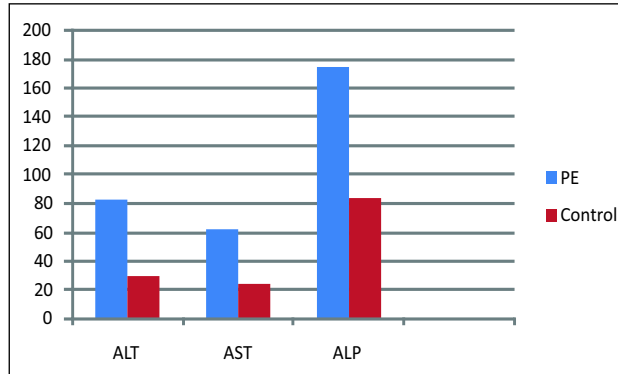


Figure 2 : Liver enzymes in PE and normal pregnancy.

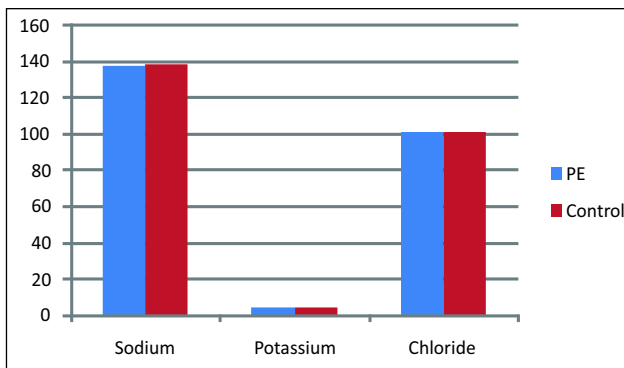


Figure 3 : Electrolytes in PE and normal pregnancy.

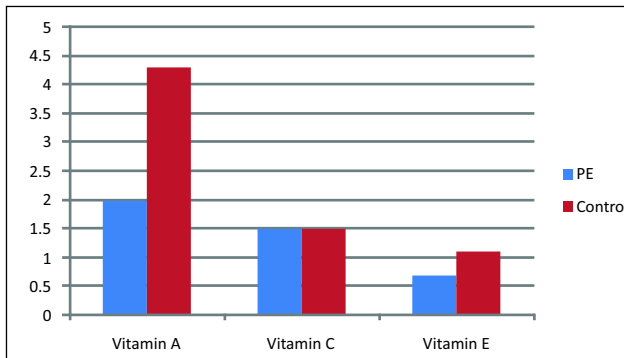


Figure 4 : Antioxidant vitamins in PE and normal pregnancy.

failed to observe such changes reflected in the electrolyte levels of PE and Control groups. Substantial heterogeneity was observed by different research groups<sup>[6,7,8]</sup>.

The elevation in sodium and potassium levels were observed by some research groups. In abnormal pregnancy- conditions viz pre-eclampsia, it is suggestive of the crucial role for the natural nutritional antioxidants.

The study of status of total Vitamin A (Retinol, Retinoic acid & Retinal), Vitamin C (Ascorbic acid) and Vitamin E (Tocopherols) would help to assess any excess utilization of the same. (Table 4 and Figure 4)<sup>[14,15,16]</sup>.

The significant reduction in levels of Vitamin A and Vitamin E was observed in the present study. Decrease in contents of Vitamin E was also reported earlier<sup>[17]</sup>. But statistical significant decrease of Vitamin A was seen in PE cases first time, indicating higher utilization of the same during the disorder.

The statistically insignificant decrease in serum contents of Vitamin C was observed in PE women when compared with that of control.

## DISCUSSION :

The normal pregnancy leads to changes in the haemodynamics and the fuel metabolisms in pregnant women to ensure ready availability of the fuel molecules for the development of the placenta and foetus. These metabolic adaptations support the growth and development of the foetus. Preeclampsia (PE), the disorder of gestational hypertension observed after 20 weeks of gestation (along with proteinuria) is a major cause of morbidity and mortality for the pregnant mother and the foetus in its advanced stage. The pathogenicity and aetiology of the disorder are still elusive<sup>[1,2,3]</sup>.

The comparative assessment of the important biochemical parameters of pregnant women ( normal and with PE ) was aimed at the alterations during the hypertensive state.

The uremia, and hypercreatininemia observed in the present study would be due to the reduced clearance of these metabolites (Urea and creatinine) secondary to reduced glomerular filtration rate, increased reabsorption and decreased secretion might be the reasons for elevated serum levels of Urea and Creatinine in women with pre-eclampsia (2,4). The pathophysiologic mechanisms of pre-eclampsia comprising of increased trophoblastic tissue shedding, endothelial dysfunction, and reduced blood flow in the foeto-maternal unit have also been hypothesised as the underlying cause of uremia and hypercreatininemia in this condition .

There is significant rise in the activity of enzymes viz AST, ALT and ALP. The elevated levels of ALP,AST and ALT in serum of PE group allowed the differentiation of PE group and normal group. Similar results were reported by Dacaj et al<sup>[5]</sup>.

The interested antioxidant micronutrients electrolytes and vitamins that are obtained from the

diet and dietary supplements and that are present in measurable quantities in blood, but cannot be synthesized by the body. Such antioxidants included tocopherols (vitamin E), carotenes ( $\alpha$ -carotene,  $\beta$ -carotene, lycopene), oxy-carotenoids (lutein, zeaxanthin, cryptoxanthin), retinol (vitamin A), and ascorbic acid (Vitamin C). The pathophysiology of preeclampsia and SGA (Small for Gestational Age) are incompletely understood, but endothelial dysfunction was indicated to play a role in both conditions. The oxidative stress, caused by increased production of free radicals and insufficient antioxidant defences, is a known cause of endothelial dysfunction, and may thus be causally related to preeclampsia, SGA and similar consequences<sup>[17]</sup>.

These results supported the views that preeclampsia depleted natural antioxidants and suggested that the reduced levels of vitamin A in such women experiencing hypertension of pregnancy, would place them at an increased risk for mother and child health. The status of Vitamin A was hardly assessed in PE cases<sup>(6,9)</sup>. Insignificant changes were reported in the status of vitamin C and vitamin E levels of PE group, but vitamin A levels were significantly affected. The supplementation of vitamin A would be more effective in PE group, along with vitamin C, that would reduce the risk of PE, Intra Uterine Growth Restriction (IUGR) and their consequences.

Hypertension, renal disease, lupus, and older age are known to be associated with endothelial dysfunction and are risk factors for these conditions<sup>[18,19]</sup>. In preeclampsia, the electrolytes and the antioxidant-vitamins would get disturbed. Similar studies have indicated that the markers of oxidative damage are elevated and antioxidant vitamin levels are lowered in patients of preeclampsia.

An eclampsia, the advanced stage of preeclampsia is associated with HELLP syndrome, where the functions of liver, kidney are very abnormal. Considering PE as an intermediate stage between normal pregnancy followed by normal birth of the child and extreme hypertensive stage with highly risky pregnancy and risky parturition. The abnormal parameters in PE lead the clues for abnormal metabolisms also help to provide the clues to treat or maintain the PE patients till the delivery.

## CONCLUSION:

A pregnancy with gestational hypertension led to alterations in various metabolisms during the growth and development of the placenta and fetus. The study would help not only to ascertain changes in

the metabolisms but also to indicate the possibility of dealing with the deficiency of any electrolytes or the antioxidant vitamins. The metabolic alterations in the PE group indicated uremia and creatinemia, elevated activity of AST, ALT and ALP along with deficient levels Vitamins A and Vitamin E. This led to the possibility of the intervention i.e supplementation of the deficient vitamins. It would help to reduce the severity of the disorder by inducing the maintenance the integrity of endothelial lining of uterus. This may thereby reduce the chances of uncontrolled gestational HT leading to eclampsia & its lethal consequences.

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