

## A Case Control Study of Changes in Levels of Serum Calcium and Uric Acid in Preeclamptic Women in Visakhapatnam Region, Andhra Pradesh-India

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**Abstract :** The present study aims to find significant association of serum calcium and serum uric acid levels in women with preeclampsia. **METHOD:** Fifty (50) preeclamptic women (cases) and forty (40) normal pregnant women (controls) were included in the study to compare serum calcium and serum uric acid levels among them. **RESULTS:** The serum calcium level in preeclamptic women was significantly lower with  $7.74 \pm 0.84$  mg/dL when compared to normal pregnant women with  $9.35 \pm 0.83$  mg/dL with a statistically significant 'p' value of  $< 0.001$ . The serum uric acid in preeclamptic women was significantly higher with  $6.22 \pm 0.62$  mg/dL when compared to healthy pregnant women with  $4.26 \pm 0.85$  mg/dL with a statistically significant 'p' value of  $< 0.001$ . **CONCLUSION:** Hypocalcemia and hyperuricemia are associated with preeclampsia.

**Keywords -** Serum calcium, serum uric acid, preeclampsia.

### I. Introduction

Preeclampsia is one of the most common causes of maternal and fetal morbidities and mortalities<sup>1</sup>. Its incidence is 4-8% of pregnancies. Preeclampsia is a disorder of pregnancy characterized by high blood pressure and excretion of a large amount of protein in the urine<sup>2</sup>. Preeclampsia usually begins after 20 weeks of pregnancy in a normotensive woman. Blood pressure is defined as high when it is greater than 140mm Hg systolic or 90mm Hg diastolic at two separate times, more than four hours apart in a woman after 20 weeks of pregnancy<sup>3</sup>. Risk factors for preeclampsia include obesity, prior hypertension, older age and diabetes mellitus. It is more frequent in primi and in multiple pregnancy. The pathophysiological mechanism is characterized by a failure of the trophoblastic invasion of the spiral arteries, leading to maladaptation of maternal spiral arterioles. This is associated with an increased vascular resistance of the uterine artery and a decreased perfusion of the placenta. In severe preeclampsia there may be red blood cell breakdown, a low blood platelet count, impaired liver function, kidney dysfunction, swelling, shortness of breath due to fluid in lungs and visual disturbances.

On the physiological basis, calcium plays an important role in muscle contraction and regulation of water balance in cells. Calcium has relaxant effect on pregnant uterus<sup>4</sup>. Calcium homeostasis is an important aspect of maternal and fetal physiology during gestation, since fetal bone mineralization requires adaptive adjustments in maternal calcium regulation. Calcium is deposited in the fetal skeleton at the rate of 200 mg/day. Women double their urinary excretion of calcium during pregnancy. Alteration in calcium metabolism is involved in the pathogenesis of hypertension. The hypercalciuria of pregnancy is due to a combination of increased gastrointestinal absorption of calcium and an increased glomerular filtration rate. Change of plasma calcium concentration leads to the alteration of blood pressure. Preeclamptic women show markedly lower levels of daily urinary calcium excretion and fractional excretion of calcium, than found in either normal pregnant women or woman with chronic or transient hypertension of pregnancy. In women with severe preeclampsia there is significantly lower levels of 1,25dihydroxy vitaminD<sub>3</sub> [1,25 (OH)<sub>2</sub>D<sub>3</sub>] compared with normal pregnant women. Also higher levels of parathyroid hormone (PTH) is observed in preeclamptic women. A primary reduction in 1,25(OH)<sub>2</sub> D<sub>3</sub> or a calcium-deficient diet lowers absorption of calcium from the intestine, resulting in a decrease in serum-ionized calcium. Low serum ionized calcium causes an increase in PTH. Finally, the increased PTH leads to increased calcium reabsorption in distal tubules resulting in hypocalciuria. Ionized-calcium levels are either low or normal in preeclampsia. Abnormalities in cellular calcium metabolism in platelets, have been reported in preeclampsia. Increased intracellular free calcium in platelets reflects increased platelet activation and a defect in vascular smooth muscle cells and lymphocytes.

Uric acid is the end product of purine metabolism. 5% uric acid is bound to plasma proteins in blood and is completely filtered by the glomerulus. About 90% of the uric acid is then reabsorbed in the early proximal tubule and secreted (about 50% of the filtered urate, via the S2 segment of the proximal tubule). Finally it undergoes post-secretory reabsorption in the last segment of the proximal tubule<sup>5</sup>.

Hyperuricemia results from decreased renal excretion that occurs as a consequence of preeclampsia but this result is due to increased production secondary to tissue ischemia and oxidative stress. Decreased renal clearance and the increase in uric acid levels is attributed to the decrease in glomerular filtration rate. Thus, hyperuricemia plays a pathogenic role by contributing to vascular damage and hypertension<sup>6</sup>. Therefore, the modification of calcium and uric acid metabolism during pregnancy could be one of the potential causes of preeclampsia.

## **II. Materials And Methods**

Fifty (50) pregnant women diagnosed with preeclampsia were taken as cases and forty (40) normal pregnant women were taken as controls in the present study from the department of Obstetrics and Gynaecology, King George Hospital, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India.

**Inclusion Criteria:** Pregnant women with the following criteria:

1. Gestational age  $\geq$  28 weeks with a single fetus
2. Blood pressure of at least 140/90 mm Hg measured on two occasions each 6 hours apart
3. Proteinuria of at least 300mg / 24 hours or at least 1 + on dip stick testing<sup>1</sup>.

**Exclusion Criteria:**

1. Patients with a history of chronic or transient hypertension,
2. History of renal-disease (or) cardiovascular disease, thyrotoxicosis, hemophilia, diabetes mellitus,
3. Multiple pregnancies.

**Estimation Of Serum Calcium:**

**Method:** Orthocresophtholein complexone method.

**Principle:** At alkaline pH, calcium binds with Orthocresophtholein complexone to form a bluish purple complex. The intensity of the colour formed is proportional to calcium concentration at 578 nm and interference from Mg is overcome by presence of 8 hydroxyquinoline in the reagent which binds free magnesium.

**Procedure:** 5 ml of blood is taken in a test tube, serum is separated by centrifugation. Test is done for calcium estimation. Normal range is 8.7 – 11 mg/dl.

**Estimation Of Serum Uric Acid**

**Method:** Estimation of serum uric acid was done by Uricase – POD method.

**Principle:** In the assay, uricase catalyzes the conversion of uric acid to allantoin, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and carbon dioxide. The H<sub>2</sub>O<sub>2</sub> then in the presence of horse radish peroxidase (HRP) reacts with 4-aminoantipyrine and DHBS (3,5 – dichloro – 2 hydroxy benzene sulfonic acid) to generate red quinoneimine complex, which is measured calorimetrically at 505 nm or with green filter.

**Procedure:** 5ml of blood is taken in a test tube, serum is separated by centrifugation. Test was done by uricase – POD method. Optical densities were measured colorimetrically. Values were obtained by standard curve. Normal range = 2.4 – 5.7 mg/dl

## **III. Results And Observation**

The present study comprises of fifty (50) cases of preeclamptic women and forty (40) normal pregnant women as controls. The serum calcium in cases was significantly lower with  $7.742 \pm 0.846$  mg/dl (mean  $\pm$  SD) when compared to controls with  $9.357 \pm 0.837$  mg/dl (mean  $\pm$  SD) with a statistically significant 'p' value of  $<0.001$ . The serum uric acid in cases was significantly higher with  $6.220 \pm 0.628$  mg/dl (mean  $\pm$  SD) when compared to controls with  $4.260 \pm 0.85$  mg/dl (mean  $\pm$  SD) with a statistically significant 'p' value of  $<0.001$ .

## **IV. Discussion**

In the present study, fifty (50) pregnant women with preeclampsia were studied for serum calcium and uric acid. Forty (40) normal pregnant women were taken as controls for comparison. In all cases and controls serum calcium and uric acid levels were measured by appropriate methods. Calcium homeostasis needs to be maintained in pregnancy because its deficiency leads to a state of convulsions. Preeclamptic woman showed markedly lower levels of daily urinary calcium excretion. Primary deficiencies in calcium intake and serum 1,25(OH)<sub>2</sub>D<sub>3</sub> levels decrease serum ionized calcium causing hypocalciuria. This is due to action of increased levels of PTH at kidney which in turn leads to increased calcium reabsorption in distal tubules. The lowering of

serum calcium or the increase of intracellular calcium can cause an elevation of blood pressure in preeclamptic women. This is due to the constriction of smooth muscles in blood vessels and subsequent increase in vascular resistance. This effect of calcium on blood pressure is explained by the influence of calcitrophic hormones on intracellular calcium.  $1,25(\text{OH})_2\text{D}_3$  stimulates calcium influx in vascular smooth muscle cells.  $1,25(\text{OH})_2\text{D}_3$  exerts a repressor effect, promotes contraction and increases peripheral vascular resistance and thus contribute to vascular damage and hypertension.

In the above study it was found that serum calcium levels have decreased in cases with  $7.7\pm 0.84$  mg/dl when compared to normal pregnant woman with  $9.35\pm 0.83$  mg/dl with a statistically significant p value of  $<0.001$ . The values in the present study are in accord with the study of Calcium –Panthumapol C et al in 2007 in Taksin hospital in Bangkok<sup>7</sup>. The study states that hypocalcemia was observed in preeclamptic women.

Uric acid has deleterious effects on endothelium, oxidative metabolism and platelets. Serum uric acid level slowly decreases until sixteen (16) weeks of pregnancy secondary to plasma volume expansion, increased renal clearance and uricosuric effect of estrogen. In the second trimester, the uric acid level remains stable and then increases during third trimester because of increased catabolism or production.

In preeclampsia the increase in uric acid levels correlate with maternal and fetal mortality and morbidity. Elevated serum uric acid levels in preeclamptic women is due to decreased renal urate excretion. The cause of hyperuricemia is due to decreased renal clearance and increased placental production of uric acid. This occurs secondary to placental ischemia and increased trophoblastic shedding. Thus, hyperuricemia induce endothelial dysfunction by its pro-inflammatory effects and contribute to vascular damage causing hypertension in pregnancy. The reason for increased uric acid in development of hypertension is yet to be elucidated, but it plays a significant role because its levels correlate with plasma renin activity<sup>8</sup>.

The mean serum uric acid level in preeclamptic women was more than normal pregnant women. The serum uric acid levels in preeclamptic women was significantly higher with  $6.22\pm 0.62$  mg/dl when compared to normal pregnant woman with  $4.26\pm 0.85$  mg/dl with a statistically significant p value of  $<0.001$ . The values of the present study were in consistence with studies of Bain bridge S et al in 2008<sup>9</sup> and Taefi A et al in 2008<sup>10</sup>. Thus the elevations in circulating uric acid in preeclamptic women contribute to the pathogenesis of the disorder, through attenuation of normal trophoblast invasion and spiral artery vascular remodeling.

## V. Conclusion

In preeclampsia the abnormalities of serum calcium and uric acid are due to renal defects. Low serum calcium and high uric acid levels could be a useful indicator of the maternal and fetal complications in preeclampsia. These biochemical markers would allow early identification of patients at risk of preeclampsia and thus help in providing adequate prenatal care and reduce the maternal mortality.

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