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Original Research Article

Essential Minerals and Lipid Levels in the Etiopathogenesis and Severity of Preeclampsia

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Abstract: Hypertensive disorders of pregnancy remain a major health issue for women and their infants. A transient and potentially dangerous complication of pregnancy is Preeclampsia. Despite intensive research being undertaken worldwide, the etiology of pregnancy induced hypertension is still unknown. Various studies have claimed that lipid abnormalities and alteration in the serum levels of essential minerals like sodium, potassium, calcium and magnesium have relevant roles in the etiopathogenesis and severity of preeclampsia. So this study was aimed to determine the role of serum lipid levels and minerals in the pathogenesis and severity of preeclampsia. In this study serum lipid profile (which includes total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol, HDL cholesterol) and minerals (sodium, potassium, total calcium, magnesium) were measured in 30 women in the third trimester of pregnancy with mild preeclampsia , 20 women in the third trimester of pregnancy with severe preeclampsia and compared statistically with 50 healthy age and sex matched normotensive women in the third trimester of pregnancy by Student t-test and Anova in SPSS version 17.0. In lipid levels serum triglycerides, total cholesterol and LDL-C were all found to have significant positive correlation, while HDL-C were found to be negatively correlated with the severity of preeclampsia. Among the essential minerals, serum sodium, calcium and magnesium levels showed significant negative correlation with the severity of preeclampsia but serum potassium was found to have no significant relationship in preeclamptic women and normal pregnant women. From the above study it is concluded that dyslipidemia and reduced mineral levels might contribute for the development of preeclampsia. So early detection and appropriate supplementation may reduce the incidence and severity of preeclampsia.
Keywords: preeclampsia, lipid profile, electrolytes, calcium, magnesium, triglycerides

INTRODUCTION:

Hypertension is a global problem and it complicates about 10% of all pregnancies worldwide [1]. Hypertensive disorders complicating pregnancy includes a spectrum of conditions- preeclampsia, eclampsia, preeclampsia superimposed on chronic hypertension, chronic hypertension and gestational hypertension [2]. One of the most common complications is preeclampsia and is the leading cause of maternal and perinatal morbidity and mortality, with an estimated 50,000-60,000 preeclampsia related deaths per year worldwide [3]. Preeclampsia is not simply hypertension arising in pregnancy but is a multisystem disorder that can affect virtually every organ and body system [4].

Preeclampsia is characterized by a triad of high blood pressure (≥140 mmHg), edema and proteinuria occurring after 20 weeks of pregnancy [5]. Since multiple hypotheses have been put forward to explain its occurrence, it has been stated as the “diseases of theories”. The widely accepted theory is the failure of trophoblastic invasion of spiral arteries which leads to maladaptation of blood vessels, increased vascular resistance and reduced placental perfusion [6]. The exact etiology and pathogenesis still remains a mystery despite numerous studies. Various studies have shown that maternal serum lipid levels and various mineral levels play a significant role in the etiopathogenesis of preeclampsia. Dyslipidemia in early pregnancy is associated with an increased risk of preeclampsia. Several studies have shown that endothelial dysfunction

is related to hyperlipidemia. Endothelial dysfunction in preeclampsia leads to oxidative stress which is well established. This increase in oxidative stress is the cause for its association with dyslipidemia [7]. Many studies have explained that altered lipid levels may be predisposing to preeclampsia but the results are inconclusive.

The increased incidence of preeclampsia in developing countries suggested that malnutrition might be a risk factor in the etiology of preeclampsia. The altered levels of the essential minerals have been reported in several studies. One of the prime treatments of high blood pressure in preeclampsia is dietary restriction of sodium, which suggests the role of these minerals in the pathogenesis of preeclampsia [8, 9]. Several studies state that alteration in the metabolism of calcium and magnesium could be one of the causes of preeclampsia. With this background information this study was designed to determine the association of serum lipid profile and essential minerals in the pathogenesis and severity of preeclampsia.

MATERIALS AND METHODS:

The study protocol was approved by the Institutional Ethical Committee and informed consent was obtained from the controls and patients. 100 cases were included in this study, of which 50 were preeclamptic patients and 50 normal pregnant women as controls. These patients attended the antenatal outpatient department of the RSRM hospital, Chennai.

CASES REPORT:

The study population comprised of 50 women in the third trimester of pregnancy with preeclampsia (Group 1). Preeclampsia was diagnosed according to American College of Obstetrics and Gynaecology (ACOG) criteria - a blood pressure higher than 140/90 mm of Hg, edema and proteinuria > 300 mg/24 hours or 1+ dipstick method after 20th week of gestation. The patients with blood pressure >140/90 mmHg and <160/110 mmHg without proteinuria were included in mild cases. And patients with blood pressure 160/110 mmHg, proteinuria and presence of headache, visual disturbances, upper abdominal pain, oliguria and thrombocytopenia were included in severe cases.

They were subdivided into 2 subgroups depending upon the severity of prreeclampsia.

Group 1A: 30 women in the third trimester of pregnancy with mild preeclampsia.

Group 1B: 20 women in the third trimester of pregnancy with severe preeclampsia.

CONTROL SUBJECTS:

Controls comprised of 50 healthy normotensive women in the third trimester of pregnancy.

Exclusion Criteria:

Patients with history of hyperuricemia, diabetes mellitus, renal diseases, hypertension, cardiovascular illness, and symptomatic infectious diseases were excluded from all the study groups.

Sample Collection and Processing:

Under aseptic precautions, about 5ml of venous blood sample was collected after 12 hours of fasting. The blood was allowed to clot and the serum was separated by centrifugation. The samples were analysed for Serum Sodium and Potassium - Ion Selective Electrode, Total Calcium by O-cresolphthalein complex one method, Magnesium by Calmagite dye method, Triglycerides by GPO-PAP method, Total cholesterol and HDL cholesterol by Phosphotungstic acid and CHOD-PAP method and LDL-cholesterol and VLDL-cholesterol were calculated by Friedwald's formula.

Statistical Analysis:

The statistical analysis was done in SPSS version 17.0. The results were expressed as mean ± SD and analyzed by Student t-test and Anova . p value < 0.05 was considered significant.

RESULTS:

Blood pressure of control and pre-eclamptic patients are shown in table 1. Serum electrolytes and lipid levels are summarized in Tables No. 2, 3.

The average blood pressure of women with mild preeclamptic was 142.68 ± 4.23/91.90 ± 3.92 and severe preeclampsia was 162.12 ± 9.28/105.12 ± 5.64 at the time of admission. The normotensive pregnant women were age matched and had an average blood pressure of 114.32 ± 4.53/74.47 ± 5.23.

The levels of serum sodium, potassium, Calcium and Magnesium in the study groups were shown in Table No. 2. Serum Sodium was found to be significantly reduced ($p<0.05$) in preeclamptic women (133.28±7.1) when compared to normotensive women (138.06±6.45). Sodium decreases gradually with progression of preeclampsia i.e, from mild (134.9±7.36) to severe (130.85±6.07) preeclampsia.

Table 1: Blood Pressure Levels In Various Study Groups

CRITERIA	GROUP I (PREECLAMPSIA) (n=50)		GROUP II CONTROL (n=50)
	GROUP IA MILD PE (n=30)	GROUP IB SEVERE PE (n=20)	
Systolic Bp (mm of Hg)	142.68 ± 4.23	162.12 ± 9.28	114.32 ± 4.53
Diastolic Bp (mm of Hg)	91.90 ± 3.92	105.12 ± 5.64	74.47 ± 5.23

Values are expressed as mean ± SD, PE –preeclampsia.

Serum Potassium was found to have no significant relationship (p=0.85) between preeclamptic and normal pregnant women. Serum Calcium was found to be significantly reduced (p<0.05) in preeclamptic women (8.43±0.55) when compared to normotensive pregnant women (9.18±0.89). Serum Magnesium was also found to be significantly decreased (p<0.05) in preeclamptic women (1.04±0.38) when compared with normotensive pregnant women (2.07±0.72) and with progression of preeclampsia magnesium was found to be gradually decreasing i.e, from mild 1.14 ± 0.39) to severe (0.88 ± 0.29) preeclamptic woman.

Table 2: Serum Electrolytes in Various Study Groups

	GROUP I (PREECLAMPSIA) (n=50)	GROUP IA MILD PE (n=30)	GROUP IB SEVERE PE (n=20)	GROUP II CONTROL (n=50)
Sodium (mEq/L)	133.28 ± 7.10	134.9 ± 7.36	130.85 ± 6.07	138.06 ± 6.45
Potassium (mEq/L)	3.91 ± 0.82	3.98 ± 0.82	3.80 ± 0.74	3.934 ± 0.73
Calcium (mEq/L)	8.43 ± 0.55	8.50 ± 0.51	8.32 ± 0.60	9.18 ± 0.89
Magnesium (mEq/L)	1.04 ± 0.38	1.44 ± 0.39	0.88 ± 0.29	2.07 ± 0.72

Values are expressed as mean ± SD, PE – preeclampsia.

On comparing serum Lipid profile between the study groups, serum Total Cholesterol was significantly increased (p<0.05) in preeclamptic women (231±45.57) when compared with normotensive women (199.68±36.14) as shown in Table No. 3.

Table 3: Serum Lipid Profile In Various Study Groups

	GROUP I (PREECLAMPSIA) (n=50)	GROUP IA MILD PE (n=30)	GROUP IB SEVERE PE (n=20)	GROUP II CONTROL (n=50)
Total Cholesterol (mg/dl)	231 ± 45.57	219.93 ± 46.50	247.6 ± 39.64	199.88 ± 36.14
Triglycerides (mg/dl)	246.32 ± 66.84	232.9 ± 51.77	266.45 ± 81.98	173.32 ± 33.39
Very low density Cholesterol (mg/dl)	49.27 ± 13.37	46.59 ± 90.37	53.29 ± 16.40	32.46 ± 6.49
Low density Cholesterol (mg/dl)	132.88 ± 43.08	132.8 ± 43.07	155.86 ± 41.66	120.03 ± 36.44
High density Cholesterol (mg/dl)	39.66 ± 6.36	40.46 ± 5.99	38.45 ± 6.86	48.36 ± 9.95

Values are expressed as mean ± SD, PE– preeclampsia.

In our study serum triglycerides is increased significantly ($p<0.01$) with preeclamptic pregnant women (246.32±66.84) when compared with normotensive pregnant women (173.32±33.9) which correlates well with progression of the disease, that it gradually increases in concentration from mild (232.9±51.77) to severe (266.45±81.98) preeclampsia. Serum LDL-C is significantly elevated ($p<0.05$) in preeclamptic (132.88±43.08) when compared with normotensive pregnant women (120.03±36.44). LDL-C gradually increases from mild (132.8±43.07) to severe preeclampsia (155.86±41.66). Serum HDL-C was found to be significantly reduced in preeclamptic women (39.66±6.36) when compared with normotensive pregnant women (48.36±9.95).

DISCUSSION:

Preeclampsia is a multicausal disorder, with numerous theories postulated to explain its etiology and pathogenesis. The long known hypothesis is its association with abnormal placentation and impaired placental perfusion. But, intrauterine growth retardation which is also characterized by poor placentation does not necessarily lead to preeclampsia. This has led to the concept of involvement of maternal predisposing factors along with placental disorder in the pathophysiology of preeclampsia [10].

The other recently accepted hypotheses are immune maladaptation, genetic hypothesis and the hypothesis of imbalance between generation of oxidative radicals and the scavengers in favour of oxidative stress. Among these the most popular theory nowadays is the theory of oxidative stress [11]. This increase in oxidative stress is associated with abnormal lipid levels. The abnormal lipid profile that occurs during preeclampsia may play a vital role in endothelial dysfunction.

In our study serum total cholesterol, triglycerides and LDL-C were significantly elevated and serum HDL-C was significantly reduced in preeclamptic women when compared to normotensive pregnant women. Previous studies have documented that lipid level is altered in normal pregnancy, i.e. hypertriglyceridemia occurs especially in the third trimester when compared to nonpregnant women. This was also found in our study control group where there is increased triglyceride level (173.32±33.9). Estrogen is considered as the principal modulator of hypertriglyceridemia as pregnancy is associated with hyperestrogenism. The endogenous biosynthesis of triglycerides is induced by estrogen, which is carried by VLDL-C and this is modulated by hyperinsulinism associated with pregnancy [12]. Serum triglyceride level was also significantly increased in preeclamptic a woman who was in accordance with the findings of many studies. Increased triglycerides in preeclampsia get deposited in uterine spiral arteries and leads to endothelial dysfunction, through the generation of small dense LDL. Small dense LDL induces the synthesis of thromboxane by endothelial cells thereby promoting vasoconstriction. It is also indicated that small dense LDL are more susceptible to modification by oxidative stress forming increased oxidized LDL, which supports the hypothesis that oxidative stress play a major role in the etiopathogenesis of preeclampsia. Increased triglyceride levels may also be associated with hypercoagulability [2, 13].

The activity of hepatic lipase is increased and that of lipoprotein lipase is decreased during pregnancy [14]. Increased hepatic lipase activity is responsible for enhanced triglyceride synthesis in liver and decreased lipoprotein lipase activity leads to decreased catabolism in adipose tissue, whereas placental VLDL receptors are upregulated resulting in increased triglycerides in the maternal circulation [15]. Similar to other studies serum total cholesterol was significantly elevated in preeclamptic women; however some studies have documented no alteration in total cholestrerol.

In the present study serum LDL-C was significantly increased in preeclamptic women when compared to normotensive pregnant women. A significantly higher level of beta-lipoprotein was also reported by many researchers in third trimester of gestational proteinuric hypertension. VLDL-C was also significantly increased in preeclamptic women who may be attributed to increased endogenous hepatic biosynthesis of triglycerides [16]. In our study serum HDL-C was found to be negatively correlated with preeclampsia, the mechanism of which is not clearly known, may be probably due to insulin resistance that occurs in preeclampsia. Low levels of HDL-C may also compromise its prime function of reverse cholesterol transport.

Nutritional deficiencies occur commonly during pregnancy due to increased demand. This is more frequently observed in developing countries with a diet deficient in essential vitamins and minerals [17]. Previous studies have documented the role of essential minerals like sodium, potassium, calcium and magnesium in the pathogenesis of preeclampsia but the results are controversial. Serum sodium level was found to be significantly reduced in preeclamptic women in our study. This may be because of altered sodium

transport across cell membrane leading to increased sodium accumulation in extravascular spaces and decreased sodium levels in plasma. The decreased intrarenal production of cyclic GMP, endothelin and PGE2 may have implications in sodium retention, hypertension, intrarenal thrombosis and vasospasm resulting in abnormal placental vasculature leading to the development of preeclampsia. Some studies reported that there was significant increase in sodium levels in preeclampsia and other studies have demonstrated normal sodium levels. So there is a varied observation in various population studies with respect to sodium level. Hence the role of sodium in the etiopathogenesis of preeclampsia remains equivocal [18, 19]. The "peripheral arterial vasodilation hypothesis" of sodium and water retention in pregnancy and its implications for the pathogenesis of preeclampsia-eclampsia explain that with increased endothelial damage, sodium retention and increased sensitivity to angiotensin lead to hypertension, oedema and proteinuria, the diagnostic triad of preeclampsia-eclampsia [20].

In our study, there was no significant difference in the potassium levels in preeclamptic women as compared to normotensive women although some studies have reported low potassium levels. The extrusion of sodium load in erythrocytes is by Na/K pump and Na/K co-transport. In pregnancy induced hypertension the net sodium extrusion occurs at an abnormal low rate by the Na/K co-transport. PIH may be an early sign of abnormality in the transport of sodium and potassium across the vascular smooth-muscle cell membrane, which is responsible for the maintenance of blood pressure [21, 22].

Calcium is an important element which plays a crucial role in the function of cardiac and vascular smooth muscles. During pregnancy metabolism of calcium is altered which contributes to increased vascular sensitivity in preeclampsia. In the present study serum total calcium level was decreased significantly in preeclamptic women when compared to normotensive pregnant women. This decrease in calcium level in preeclampsia may be due to suboptimal absorption of calcium by intestines because of reduction in 1, 25 – dihydroxy vitamin D. Subsequently it leads to increase in parathyroid hormone, resulting in increase of intracellular calcium level leading to increased vascular smooth muscle contraction thereby increasing the blood pressure [18, 23]. Renal handling of calcium in preeclampsia is also abnormal. In preeclampsia, the fractional excretion of calcium is reduced markedly, leading to hypocalciuria, which is in contrast to hypercalciuria that occur in normal pregnancy [24]. In a randomized controlled study conducted by Bucher HC et al on the effect of calcium supplementation in pregnancy induced hypertension, have concluded that supplementation of calcium may lead to significant reduction in systolic and diastolic blood pressure in preeclampsia [25].

In our study there is a significant decrease in serum Magnesium in preeclamptic patients. Magnesium influences the blood pressure by altering the transport of calcium and it's binding to the membrane and organ cells. Magnesium also causes peripheral vasodilation that result in fall in blood pressure. It induces the synthesis of prostacyclin, a potent vasodilator from the endothelial cells. In addition, magnesium depletion increases the vasoconstrictor effect of angiotensin II and nor-adrenaline [18, 26]. So hypomagnesemia that occurs in preeclampsia may contribute to vasospasm and increase in blood pressure.

CONCLUSION:

From the above study it may be concluded that dyslipidemia that occur in preeclampsia may lead to oxidative stress which may have a significant role in the development of endothelial dysfunction eventually contributing to the pathogenesis of preeclampsia. Our study also shows the significant alteration in the essential minerals, sodium, calcium and magnesium that may contribute to the development of preeclampsia. Also for diagnosis and assessing the severity, none of these can be used as an independent risk factor. But together all these can be used in assessing the severity of preeclampsia. Supplementation of essential minerals in pregnancy may decrease the risk of developing preeclampsia. Further studies are required to know the effect of supplementation of essential minerals during pregnancy and the development of preeclampsia.

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