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Iron Status in Preeclampsia – A Study from South India

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Abstract:
Preeclampsia is one of the major causes of maternal and fetal morbidity and mortality. Though the etiology is obscure, studies indicate the role of increased oxidative stress due to endothelial dysfunction in preeclampsia. The aim of this study was to find out iron status parameters in preeclamptics and their comparison to normotensive pregnancies. This study was done in a medical college hospital in South India. 60 women with preeclampsia and 60 normotensive pregnant women were analyzed for serum iron, ferritin and hemoglobin levels. Pregnancy outcome in both groups were compared. Data were expressed as Mean ± Standard Deviation. Comparison of serum levels of the elements was performed by Independent t test and Chi square test and P value of < 0.05 was considered as statistically significant. Mean serum iron and ferrtin levels in preeclamptics were significantly higher compared to normotensives whereas hemoglobin levels did not show much difference. Also preeclamptic women were older, with higher BMI and lower birth weight compared to normotensives. The higher serum iron and ferritin levels might play an important role in the etiopathogenesis of preeclampsia. Therefore, pregnant women with higher serum iron and ferritin levels should be investigated for preeclampsia. Iron status of pregnant women should be assessed before giving iron supplements as these may cause more harm than benefit.
Key Words: *Preeclampsia, Serum Ferritin, Serum Iron, Hemoglobin*

INTRODUCTION

Preeclampsia is one of the most leading causes of maternal mortality and morbidity in developing countries. It is a systemic disease that affects about 5 – 7 % of all pregnancies and is the most common, yet least understood disorder of pregnancy. (1)The development of hypertension and proteinuria and/or edema after 20th week of gestation is described as preeclampsia and if convulsion or coma is added it is named as eclampsia. (2) The patho physiological mechanism is characterized by failure of the trophoblastic invasion of the spiral arteries which may be associated with an increased vascular resistance of the uterine artery and a decreased perfusion of the placenta. (3) It may be associated with complications like visual disturbances, oliguria, eclampsia, hemolysis, elevated liver enzymes, thrombocytopenia, pulmonary edema and fetal growth restriction. (4) Early detection and prompt management helps in reducing the complications of this condition. Despite its prevalence and severity, the patho physiology of this multisystem disorder is still poorly understood and its etiology has not yet been fully elucidated. (5) Globally an estimated 2, 87,000 women died during childbirth in 2010, of which India accounted for approximately 19%. (6)

The greatest impact of preeclampsia is in developing countries where it accounts for 20 – 80% of the strikingly increase maternal mortality. (7) It is one of the commonest medical disorders diagnosed by Obstetricians in clinical practice. (8) Due to this, methods to reduce the risk of hypertensive disorders in pregnancy have received considerable attention. Research is focusing on prevention rather than treatment. Iron may also have a role in the patho physiology of preeclampsia.

A number of reports indicate that blood levels of lipid peroxidation products are elevated in women with preeclampsia relative to normal pregnancy. It has been suggested that lipid peroxidation may play a role in the etiology of the disease. Iron promotes lipid peroxidation. (9) Iron species released from ischemic placenta by destruction of red blood cells can initiate the process of lipid peroxidation to cause endothelial cell damage of preeclampsia. (10) Also there is evidence that oxidative stress occurs in preeclampsia. Transitional metals especially iron which are abundant in the placenta are important in the production of free radicals.(9) Iron or iron species could be a factor in generation of oxidative stress in preeclampsia .(10) Recent studies in pregnant women have shown that an elevated maternal serum ferritin, iron concentration and abnormal transferrin metabolism can occur in association with pregnancy induced hypertension and eclampsia.(11) Only few studies have investigated the relationship of iron parameters in preeclampsia. The current study is undertaken to evaluate iron status and its possible contributory role in oxidative stress in pre eclampsia

MATERIALS AND METHODS

This was a case control study which was a part of a larger study done to know the levels of various elements in women with preeclampsia. The study was conducted in the department of obstetrics in a

medical college hospital in Mangalore, Karnataka, India. 120 pregnant women beyond 32 weeks of gestation were included in the study. 60 pregnant women with preeclampsia were taken as cases and an equal number of pregnant women without preeclampsia matched for gestational age, parity, anthropometrics and socioeconomic status were taken as controls.

Pre-eclampsia was diagnosed in those who had a blood pressure of 140/90 or more on two occasions each 6 hours apart associated with proteinuria of at least 300 mg per 24 hours or at least 1+ on dipstick testing. Severe pre-eclampsia was defined as a blood pressure of 160/110 mm Hg or above measured on two occasions each 6 hours apart. The repeat measurement of blood pressure was done in the hospital after adequate rest. There were no dropouts in the study. Among the 60 cases, 7 had severe pre-eclampsia. There were no cases of eclampsia.

Informed consent was taken from all the subjects included in the study. Ethical committee clearance was obtained from the institution.

Women with history of chronic hypertension, renal disease, cardiovascular disease, liver disease, diabetes, thyroid and other endocrine disorders, multiple gestations, hydatidiform mole and other secondary causes of hypertension, malignancy, hematological disorders etc were excluded from the study. Also women with history of smoking, alcohol and other drug consumption which might affect the blood pressure were excluded from the study. Iron supplements were not given to both cases and controls. Women with anemia and those with recent blood transfusion were not included in the study. A detailed family and medical history were taken. A complete clinical examination was done in all the subjects. Systolic and diastolic blood pressure was carefully recorded. Urine analysis was done in all subjects to measure the degree of proteinuria. Blood was taken from the ante cubital vein using a sterile needle and syringe in the morning after overnight fasting. Estimation of hemoglobin percent, serum ferritin and serum iron concentration was done. Hemoglobin was estimated by Cyanmet Hemoglobin method, serum ferritin and iron were estimated by kit method. Data was expressed as Mean ± Standard Deviation. Data analysis was done by SPSS version 20. Comparison of serum levels of the elements between the two groups was performed by Independent t-test and Chi-square test and p-value of < 0.05 was considered as statistically significant.

RESULTS

The study enrolled 120 pregnant women with similar demographic characteristics. The clinical characteristics of the participants are shown in [Table/Fig-1]. Among the controls, 75% were booked having regular antenatal check up where as only 35% among the hypertensive women were booked. ($P < 0.001$) The mean age of women with pre-eclampsia was higher than normotensive controls. (27.45 ± 4.33 yrs Vs 25.87± 3.11yrs p-value 0.023). The gestational age was significantly higher in the normotensives compared to preeclamptics. (36.9 ± 0.9 Vs 38.21

± 0.85 p < 0.001).The mean BMI [Body Mass Index] was significantly higher in pre-eclamptics than normotensives. (27.07± 3.07 kg/m2 Vs 24.9 ±2.32 kg/m2 p <0.001) The systolic and diastolic blood pressure was significantly higher in cases compared to controls. Table/Fig-2 shows the outcome of labor in cases and controls. The rate of cesarean section was higher among cases (56.7% Vs 25.8% p < 0.001). The fetal birth weight was lower in preeclamptics. (2.61±0.53 kg Vs 2.98 ±0.36 kg p-value <0.001)

Table/Fig-3 shows the comparison of iron parameters in both the groups. There was no much difference in the hemoglobin and hematocrit levels in the cases and controls. Serum ferritin levels were significantly higher among cases compared to controls (29.96±10.63 Vs 16.78±7.86 g/l) which were statistically significant. (P<0.05) Also serum iron was significantly higher (P<0.001) in preeclamptics compared to normotensives. (79.38±4.37 Vs 48.70±2.79)

DISCUSSION

In spite of numerous studies, the etiology of preeclampsia has not been fully elucidated. It has been dubbed the 'disease of theories' because of the multiple hypotheses has been proposed to explain its occurrence. Numerous studies on etiology and biochemical variables in preeclamptic women have been carried out throughout the world. Among them alteration of iron status is identified as a risk factor for pathogenesis of preeclampsia by some researchers. (12) Although the pathophysiology of preeclampsia remains undefined, placental ischemia or hypoxia is widely regarded as a key factor. (8) Inadequate trophoblast invasion leading to incomplete remodeling of the uterine spiral arteries is considered to be a primary cause of placental ischemia. (10) When tissues become ischemic, reactive oxygen species such as superoxide and hydrogen peroxide are produced, but neither of these is reactive enough to initiate cellular damage directly. (8) However, in the presence of catalytic amounts of transition metal ions, particularly iron, which may arise in the ischemic placenta by destruction of red blood cells from thrombotic, necrotic and hemorrhagic areas, these species can generate the highly reactive hydroxyl radical by Fenton chemistry. (4) This radical can initiate the process of lipid peroxidation which, if uncontrolled may result in endothelial cell damage. (8)

OR Excess iron is postulated as causal factor in the oxidative stress in its radical form, which might be involved in pathogenesis of preeclampsia. (8)

Normal women have a decrease in serum iron and ferritin during the third trimester of pregnancy as their stores of iron are depleted because of fetoplacental demand and required expansion of red cell mass. Elevated level of serum iron is observed in preeclamptics as compared to normal pregnant women. (9)

The metabolism of the serum iron and iron binding proteins, ferritin and transferrin is abnormal in women with preeclampsia. Increased

serum iron promotes lipid peroxidase activity and induces endothelial cell damage. Increase serum ferritin exacerbates hypertension and eclampsia. (11) Lower ferritin level during 28-30 weeks of pregnancy would be associated with lower incidence of preeclampsia. (13) Iron and markers of iron status have been reported to be abnormal in preeclampsia. Elevated hemoglobin rather than anemia in pregnancy was linked to underlying conditions like preeclampsia. (14)We did not find much difference in the hemoglobin concentration among cases and controls. We found high levels of serum ferritin and iron among preeclamptics compared to controls which was statistically significant. Similar findings were reported by Rayman et al, Siddiqui etal and also by Sultana et al, in a study from Bangladesh. (10, 2, 12)Taheripanah and Farkush found significantly high serum ferritin levels in preeclamptics and they observed that evaluation of ferritin can be helpful in the identification of high risk subjects and diagnosis of preeclampsia before obvious clinical findings presented. (11) Similarly, study by Zafar showed a significantly higher serum ferritin levels in preeclampsia than in normal pregnancy. (9) The rationale of routine iron supplementation in non anemic women is questionable. Also, routine investigation of serum iron status of pregnant women with high risk for preeclampsia as part of antenatal checkup may help to establish diagnosis of preeclampsia before appearance of its clinical manifestations and unnecessary use of iron in non anemic women can be avoided.

CONCLUSION

In this study we observed significantly higher levels of serum ferritin and iron in women with preeclampsia compared to normotensive women. So, it can be concluded that increased levels of serum iron and ferritin may play a role in the pathogenesis of preeclampsia. Therefore, iron status of pregnant women should be assessed before giving iron supplements as these may cause more harm than benefit.

Clinical Parameters	Cases (n=60)	Controls (n=60)	Significance level(P value)
Booked Pregnancy	35%	75%	<0.001*
Age (years)	27.45 ±4.33	25.87 ± 3.11	0.023*
Gestational age (weeks)	36.9± 0.9	38.21 ± 0.85	<0.001*
BMI (kg/m2)	27.07± 3.07	24.9 ± 2.32	<0.001*
Systolic BP (mm Hg)	155.50±12.18	108±6.50	<0.001*
Diastolic BP(mm Hg)	108.18±10.89	68.69±8.19	<0.001*

Table/Fig 1 Clinical characteristics: cases and controls.

BMI – Body Mass Index BP- Blood Pressure

Labor Outcome	Cases	Controls	Significance
Vaginal Delivery	43.3%	74.2%	<0.001*
Cesarean Section	56.7%	25.8%	<0.001*
Birth weight(kg)	2.61 ± 0.53	2.98 ± 0.36	<0.001*

Table/Fig 2 Labor Outcome in cases and controls

Parameters	Cases(n=60)	Controls(n=60)	Significance (P value)
Hemoglobin	10.66±0.17	10.87±0.13	NS
Ferritin(g/l)	29.96±10.63	16.78±7.86	<0.05*
Iron(mg/dl)	79.38±4.37	48.70±2.79	<0.001*

Table/Fig 3 Comparison of iron parameters: cases and controls.

Values are expressed as mean ± SD (Standard Deviation)

* P<0.05 – Statistically Significant NS – Not Significant

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