SERUM IRON AND ITS POSSIBLE LINK TO THE ETIOLOGY OF PREGNANCY INDUCED HYPERTENSION

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ABSTRACT: BACKGROUND: Preeclampsia-eclampsia is an important complication of pregnancy. It is associated with increased maternal morbidity and mortality. It has been well established that endothelial damage due to oxidative stress is involved in the pathogenesis of preeclampsia-eclampsia. Iron may act as catalyst in this oxidative process. So in preeclampsia, pregnant women should be investigated for elevated serum iron and serum ferritin. **OBJECTIVE:** To evaluate serum iron parameters in preeclampsia-eclampsia and whether it has any possible contribution to the etiology. **MATERIALS AND METHODS:** Consecutive 200 women with eclampsia were studied. Controls were 200 normal pregnant women. Blood was collected from all the women. We estimated hemoglobin and hematocrit concentration, MCV, MCH, MCHC, serum iron and ferritin level of all the women. Data were analyzed using SPSS software. **RESULTS:** Mean serum iron concentration in women with eclampsia and controls were 22.93 ± 6.68 and 14.74 ± 2.76 ($p<0.01$) respectively and serum ferritin were 31.23 ± 6.16 and 20.69 ± 6.71 ($p<0.005$) respectively. But there were no significant differences in the hematological parameters among the two groups.
CONCLUSION: Serum iron and ferritin were elevated in eclampsia. Catalytic iron may be involved in the pathogenesis of pregnancy induced hypertension.
KEY WORDS: eclampsia, serum iron, ferritin**.**

INTRODUCTION: Preeclampsia refers to a syndrome, characterized by the new onset of hypertension and proteinuria, after 20 weeks of gestation, in a previously normotensive woman [1]. Eclampsia refers to the development of grand mal seizures in a woman with gestational hypertension or preeclampsia [2].However, the incidence varies with geographic location. Eclampsia is a rare, but serious complication of preeclampsia. It complicates about 1: 2000 deliveries in Europe and developed countries [3] and from 1:100 to 1: 1700 deliveries in developing countries [4]. The higher incidence in developing countries is due to inadequate antenatal care, with late presentation. Preeclampsia has a complex pathophysiology. Increased uterine arterial resistance induces higher sensitivity to vasoconstriction and thus chronic placental ischemia and oxidative stress. In addition, oxidative stress induces release of free radicals, oxidised lipids, cytokines and serum soluble vascular endothelial growth factor 1 into the maternal circulation. These abnormalities are responsible for endothelial dysfunction, with vascular hyperpermeability, thrombophilia (HELLP syndrome) and hypertension, so as to compensate for the decreased flow in the uterine arteries due to peripheral vasoconstriction[5]. The mechanism that is responsible for the development of seizures is unknown, but proposed theories include cerebral vasospasm, edema and possibly that severe hypertension might disturb cerebral auto

regulation and disrupt the blood- brain barrier. Reactive oxygen species, like superoxide and hydrogen peroxide are produced as a result of ischemia, but these are not reactive enough to induce cellular damage directly [6]. But in presence of catalytic iron, which are produced from the ischemic placenta due to hemolysis [7, 8] these reactive species can produce the highly reactive hydroxyl radical [9]. This radical can initiate the process of lipid per oxidation which causes the endothelial-cell damage, as described by Hubel and colleagues [10]. A study of serum iron and ferritin levels in Indian women with pregnancy induced hypertension and eclampsia when compared with controls of similar gestational ages, revealed that mean serum iron was elevated slightly in pregnancy induced hypertension and significantly in eclampsia, but mean ferritin levels were significantly elevated in both pregnancy induced hypertension and eclampsia[11]. This study was carried out to evaluate iron status in severe pregnancy induced hypertension and whether they have any possible contributory role in the etiology of the disease.

MATERIALS AND METHODS: This study was conducted in the Department of Obstetrics & Gynaecology, Burdwan Medical College, Burdwan, West Bengal, for duration of two year from May 2010 to April 2012, after approval from the Ethical Committee of this Institution. We have included consecutive 200 eclamptic women and 200 normal pregnant women who were matched for parity and age. Eclampsia was diagnosed in women with blood pressure of ≥140 mm of mercury systolic and or 90 mm of mercury diastolic, after 20 weeks of pregnancy, along with proteinuria of ≥300 mg/24hr urine or ≥2 dipstick [12] and associated with seizures. Control group were matched with similar gestational age of eclampsia mothers. Singleton pregnancies in the last trimester were included. Women who had anemia in pregnancy (Hb<10gm%), multiple pregnancy, superimposed preeclampsia on chronic hypertension, received blood transfusion, suffering from fever or any infections, were excluded from the study. Enrolled women for this study did not receive any iron supplement. Informed consent was taken from all the mothers. Body mass index of the women were calculated from body weight in kg and height in meters. Blood samples were taken from eclamptic women at the time of their admission to the hospital .About ten ml of venous blood from the antecubital vein was withdrawn, taking all aseptic precautions, five ml in EDTA vial for estimation of hematological parameters, and another five ml in clotted vial for estimation of serum iron parameters (serum iron and ferritin) and liver enzymes (LFT).Estimation of hematological parameters include Hb%, PCV, MCV, MCH and MCHC and these were reported from our hospital laboratory. Enzyme immunoassay kit method was used for estimation of serum iron and ferritin. Data were analyzed by using SPSS Software version 18.

RESULTS AND ANALYSIS: Age of the eclamptic women varied from 17 to 25 years, with a mean of 20.82±2.11. There were no significant differences in the age between the two groups (control group 19.9 ± 1.96, p=0.42). There were also no differences in BMI between the groups (eclampsia 31.2 ± 4.27; normal 30.1 ± 5.20, p=0.38). There were significant differences in both the systolic and diastolic blood pressures of eclampsia mothers, when they were compared to normal women (Systolic BP 171.76 ± 17.18 vs.113.08 ± 6.87 and diastolic BP 110.16 ± 8.79 vs.71.04 ± 5.84 ; $p < 0.001$). (Table-I)

Table-I

	Eclampsia Group n = 200 Mean ± SD	Normal n = 200 Mean ± SD	*P* value
Age (years)	20.82±2.11	19.9±1.96	0.42
BMI(kg/m^2)	31.2 ± 4.27	30.1 ± 5.20	0.38
SBP (mm of Hg)	171.76 ± 17.18	113.08 ± 6.87	0.0001
DBP (mm of Hg)	110.16 ± 8.79	71.04 ± 5.84	0.000

SD standard deviation, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure significant difference at p

It was found that there were no significant differences in the hematological parameters including Hb% (11.26 ± 0.79 vs. 11.29 ± 0.58, p=0.151); PCV (31.99 ± 0.998 vs.31.69 ± 1.08, p=0.264); MCV (82.37 ± 6.39 vs. 78.24 ± 5.49, p=0.343), MCH (28.34 ± 2.26 vs. 29.29 ± 2.55, p=0.113) and MCHC (34.66 ± 6.27 vs. 33.99 ± 7.49, p=0.162) among the two groups. (Table-II)

Table-II

	Eclampsia Group n = 200, Mean ± SD	Normal n = 200 Mean ± SD	*P* value
Hb (gm %)	11.26 ± 0.79	11.29 ± 0.58	0.151
PCV (%)	31.99 ± 0.998	31.69 ± 1.08	0.264
MCV (fl)	82.37 ± 6.39	78.24 ± 5.49	0.343
MCH (pg)	28.34 ± 2.26	29.29 ± 2.55	0.113
MCHC (%)	34.66 ± 6.27	33.99 ± 7.49	0.162

Hb -Hemoglobin concentration, PCV -Packed cell volume, MCV- Mean corpuscular volume, MCH - Mean corpuscular hemoglobin, and MCHC- Mean corpuscular hemoglobin concentration,
SD- Standard deviation. Significant difference at p

Mean serum iron concentration were 22.93 ± 6.68 and 14.74 ± 2.76, p<.01 in the eclamptic group and normal women respectively. Mean serum ferritin level were 31.23 ± 6.16 and 20.69 ± 6.71 p<.005 in both the groups respectively. (Table-III). They were significantly elevated in the hypertensive women when compared to normal controls.

Table-III

	Eclampsia Group n = 200 Mean ± SD	Normal n = 200 Mean ± SD	*p* value
Serum iron (µg/dL)	22.93 ± 6.68	14.74 ± 2.76	0.009
Serum Ferritin (ng/ml)	31.23 ± 6.16	20.69 ± 6.71	0.004

SD- Standard deviation
Significant difference at p

DISCUSSION: In our study we did not find any significant differences in the RBC indices among the two groups. Siddiqui et al also had same observations when they compared 40 pre-eclamptic women with 80 normal pregnant females [13]. In their study, Hershkovitz et al. reported similar observations. They also reported that there was increased serum erythropoietin concentration in hypertensive women and this rise of erythropoietin level was not statistically significant when compared with controls [14]. Makuyana et al. reported similar observations regarding hematological parameters in the pre-eclamptic women as in our study [15]. But there are some studies in which hematological parameters, including total RBC count; PCV, MCV, MCH and MCHC were raised in hypertensive women, when compared with controls [16, 17]. This is due to raised serum erythropoietin concentration, as a consequence of diminished perfusion to the kidneys in eclamptic women [18]. Zafar et al. in their study showed hemoglobin and hematological parameters were significantly higher in pre-eclamptic women, when compared to controls [19].In their study Gupta S et al. also showed raised hematological parameters in hypertensive women when compared with normal controls [20]. In our study we did not find any significant difference among the hematological parameters between eclamptic women and normal controls.

Increased serum iron, promotes lipid peroxidase activity and induces endothelial cell damage. There is evidence that increased serum iron level plays a pathogenic role in the development of preeclampsia [10, 15]. In our study both serum iron and ferritin levels were increased in hypertensive women than the normal women. The study conducted by Entman SS et al. [21] also showed similar findings. Rayman et al. in their study showed that there was significant increase in serum iron, ferritin and transferrin saturation and decreased total iron binding capacity in the pre-eclamptic subjects, than the normal controls, when they compared 40 pre-eclamptic women with equal numbers of controls [22]. The findings in our study also were in agreement with the study conducted by Siddiqui et al [13]. Diminished concentration of serum ferritin indicates iron deficiency anemia, but increased concentration of serum ferritin may not be associated with iron overload. Increased serum ferritin raises blood pressure and aggravates eclampsia [23]. Furthermore, we found that there was no significant correlation between serum iron levels with liver enzyme levels, which reflect that the raised iron levels could not be explained by liver damage. Limitation of our study was that except the measurement of serum iron and ferritin, we did not measure the other iron parameters like total iron binding capacity, unsaturated iron binding

capacity (UIBC) and transferrin saturation. Serum erythropoietin was also not measured in our study.

CONCLUSION: Serum iron and ferritin are significantly increased in pregnant women who develop eclampsia. In presence of catalytic iron, which is produced from the ischemic placenta due to hemolysis of reactive species like superoxide and hydrogen peroxide, produced as a result of ischemic processes, which can produce the highly reactive hydroxyl radical. This radical can initiate the process of lipid per oxidation which causes the endothelial-cell damage. Oxidative stress induces release of free radicals, oxidised lipids, cytokines and serum soluble vascular endothelial growth factor 1 into the maternal circulation. These abnormalities are responsible for endothelial dysfunction, with vascular hyperpermeability, thrombophilia (HELLP syndrome) and hypertension. Further studies are needed to establish any link between serum iron parameters and hypertensive disorders in pregnancy.

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