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Comparative Study of Serum Iron and Ferritin Levels in Pregnancy Induced Hypertensive and Normotensive Primigravida Mother and Correlation with Oxidative Stress.

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ABSTRACT

Background: Ferritin is a major iron storage protein found in reticuloendothelial system, small intestinal mucosa, placenta, kidney, skeletal muscle and circulates in plasma. The study aims to establish that serum iron and ferritin levels have correlation with oxidative stress and can be used for assessment of PIH development. **Methods:** A comparative cross sectional study was conducted over 18 months taking 50 primigravida with PIH as cases and another 50 healthy normal primigravida as controls, both subject groups belonging to 2nd and 3rd trimesters. Serum iron, ferritin, thiobarbituric reactive substance (TBARS) and superoxide dismutase (SOD) levels in both groups were estimated by ELISA and results were statistically analysed by SPSS version 20. **Results:** Mean serum ferritin level was higher in cases (86.899 ± 30.755 ng/mL) and it was statistically significant (p<0.0001). Highly significant correlation was found between ferritin and TBARS, SOD. **Conclusion:** Rising serum ferritin level could be a good early marker for impending preeclampsia.

Keywords: Ferritin, Iron, TBARS, SOD, PIH.

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INTRODUCTION

Pregnancy induced hypertension (PIH) is one of the leading causes of maternal and perinatal mortality and complicates 10% of pregnancies globally.[1] Worldwide, hypertensive disorders of pregnancy accounts for approximately 14% of all maternal deaths. In western world, they are responsible for almost 26% of maternal deaths, while in Asia they contribute to 9% of deaths.[2] Preeclampsia occurs in 4-5% of all pregnancies.

Although the exact pathophysiology of PIH is not known, but serum ferritin and iron levels are introduced as a probable pathogenesis for preeclampsia. Excess iron is postulated as casual factor in the oxidative stress i.e. in its radical form, which may be involved in the pathogenesis of preeclampsia. Iron promotes lipid peroxidation perhaps facilitated by the hyperlipidemia consequent to the tremendous mobilization of lipid that occur in the later half of human gestation.[3] This could further escalate the cycle by increasing circulating peroxide levels.[4] Biological examples of these are Fenton Chemistry leading to the formation of highly reactive oxygen species (ROS), such as the hydroxyl radical (OH) and the Ferryl ion (FeO2+) and lipid peroxidation. Human cells have developed a wide range of antioxidant systems to limit production of ROS, inactivate them and repair cell damage. The generation of ROS is enhanced by increased placental mitochondrial activity and the greatly increased placental production of the radical superoxide.[5-7] This increase in the generation of superoxide is also reported to be associated with decreased levels of superoxide dismutase (SOD),[6] an antioxidant enzyme, in the placental trophoblast. Malondialdehyde (MDA) is an aldehyde considered to be the terminal compound & the most important marker for monitoring lipid peroxidation & oxidative damage induced by ROS which is strongly associated with development of serious disease. It is also considered as a thiobarbituric reactive substance (TBARS).[8] The increased lipid peroxidation leads to the consumption of antioxidants. With this background, we have conducted this study with the following aims and objectives: i) estimation of serum iron and ferritin levels in pregnancy induced

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hypertensive and normotensive primigravida mother, ii) Estimation of markers of oxidative stress i.e. Thiobarbituric acid reactive substances (TBARS), Superoxide dismutase (SOD) in same, iii) Comparison of serum iron, ferritin, TBARS and SOD levels between these two populations, iv) Correlation among serum iron, ferritin and oxidative stress in PIH.

MATERIALS & METHODS

A comparative cross sectional study was conducted over 18 months from January 2018 to June 2019, in Department of Gynaecology and Obstetrics, Department of Biochemistry of Bankura Sammilani Medical College & Hospital, a rural medical college of West Bengal, India. Study population chosen was 50 primigravida with PIH as cases and another 50 healthy normal primigravida as controls, both subject groups belonging to 2nd and 3rd trimesters. Inclusion criteria for cases were preeclampsia and eclampsia who did not get any MgSO4 injection. Exclusion criteria were known cases of diabetes, hypertension, cardiac disease, chronic liver disease, renal insufficiency, HIV, TORCH infection. Serum iron, ferritin, TBARS and SOD levels in both groups were estimated. All parameters were recorded in predesigned and structured proforma. Results were statistically analysed by SPSS version 20.

RESULTS

Mean and median serum ferritin and TBARS levels were found to be more in cases, whereas iron and SOD levels were less in cases when compared to controls. P value was calculated by Mann-Whitney U test and was statistically significant for ferritin, TBARS and SOD. [Table 1]

Table 1: Levels of serum iron, ferritin, TBARS, SOD in PIH and controls.

Parameters	PIH		Controls		P value by Mann-Whitney U test
	Mean ± SD	Median	Mean ± SD	Median	
Iron (µg/dL)	194.70±52.556	190	204.40±55.608	200	0.324
Ferritin (ng/mL)	86.899±30.755	85.875	28.814±11.25	29.1	<0.0001
TBARS (nmol/mL)	5.973±2.073	5.665	2.901±0.832	3.112	<0.0001.
SOD (U/mL)	19.409±6.158	19.965	24.219±6.095	23.38	<0.0001.

Table 2: Pearson correlation test results

Parameter	Pearson correlation coefficient (r)	p value
Iron vs TBARS	0.035	0.728
Ferritin vs TBARS	0.719	<0.0001
Iron vs SOD	0.02	<0.846
Ferritin vs SOD	-0.386	<0.0001

Pearson correlation test and scatter plots were done between iron, ferritin and TBARS, SOD levels. There was weak positive correlation between iron and TBARS but it was statistically not significant. Highly significant positive correlation was found between ferritin and TBARS. There was non-significant positive correlation between iron and SOD. Statistically significant negative correlation was there between ferritin and SOD. [Table 2, Figures 1-4]

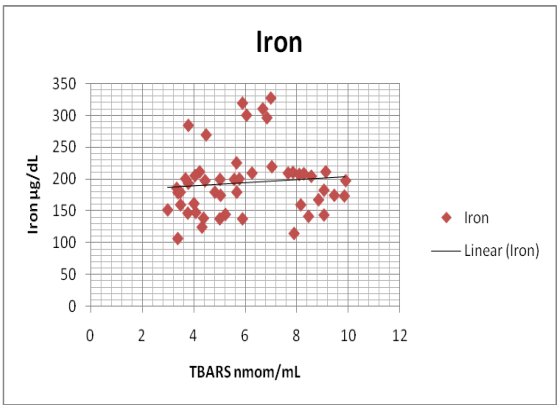

Figure 1: Correlation between serum Iron and TBARS in PIH mothers

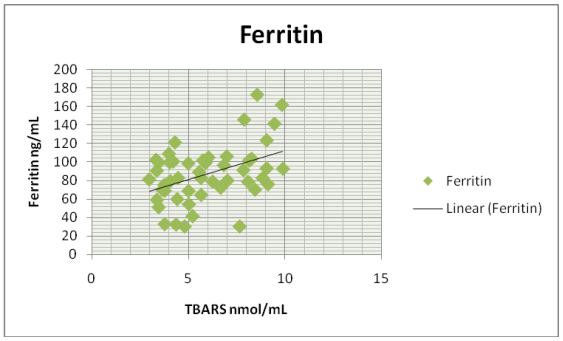

Figure 2: Correlation between serum Ferritin and TBARS in PIH mothers

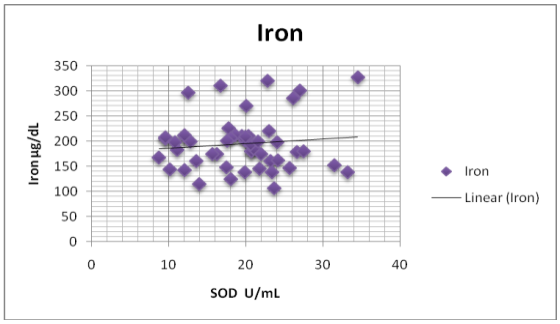

Figure 3: Correlation between serum Iron and SOD in PIH mothers

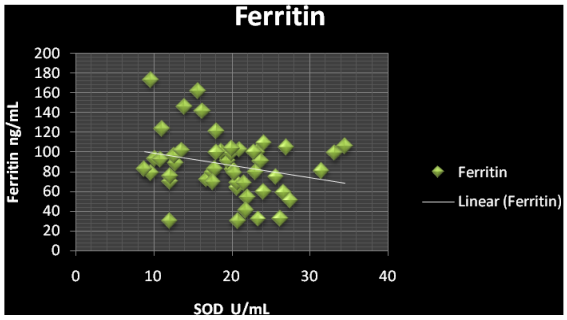

Figure 4: Correlation between serum Ferritin and SOD in PIH mothers

DISCUSSION

Mean iron in cases was 194.70±52.556 µg/dL and insignificantly less compared to controls. Several conflicting results have encountered over decades regarding the status of iron in PIH. Fenzal V et al,[9] and Rathore et al,[10] found significantly lower levels of iron in preeclampsia while Ugwuja et al,[11] found statistically insignificant lower levels of iron in PIH. On the other hand Balla et al,[12] and Hubel et al,[13] identified high level of iron as a contributing factor for the development of preeclampsia. Eaton-Evans et al,[14] in 1996 noted that elevated hemoglobin rather than anaemia in pregnancy was linked to underlying conditions like pregnancy induced hypertension or preeclampsia, which contribute to poor pregnancy outcomes.

In pregnancy, serum ferritin concentration is maximum at 12-16 weeks, then falls to nadir at third trimester.[15] Studies have shown that ferritin increases in PIH as an acute phase reactant and act as a pro-oxidant promoting lipid per oxidase activity and induces endothelial cell damage.[16] There is evidence that increased serum ferritin level plays pathogenic role in development of preeclampsia.[17] Lower ferritin concentrations at 28-30 weeks is associated with decreased risk of preeclampsia.[13,18] In the present study, serum Ferritin was almost three times higher in PIH group than normotensive mothers and it was statistically significant by Mann-Whitney U test (p value <0.0001). Correlation of ferritin with PIH was evaluated by several researchers abroad. In a study done by Taheripanth,[19] Mean serum ferritin level in case and control group was 123.8 ± 46.1 ng/dl and 33.4 ±16.2 ng/dl respectively which is highly significant (< 0.001) similar to our study. Same study also revealed that ferritin level in pre-eclampsia and HELLP syndrome is 3.6 and 10 times to the normal, respectively. Similar results were seen in study conducted by Zafar T and Iqbal Z in 2008.[20] Siddiqui et al,[21] showed in his study that, mean serum ferritin concentration in preeclamptic and normal pregnant women were 32.56 ± 11.72 µgm/L and 19.89 ± 8.86 µgm/L, respectively which was statistically significant (p < 0.05) as in ours.

In our study, there was statistically significant increase of levels of MDA and decrease in levels of SOD in PIH group (p<0.0001 in both). Negi R et al,[22] have shown that SOD was significantly reduced in preeclamptic and eclamptic cases indicating that inappropriate or excessive lipid peroxidation may play an important role in the pathophysiology of preeclampsia. Increase of MDA in preeclampsia has also been shown separately by Fenzal V et al,[9] Ilhan N et al,[23] and Atamer Y.[24] In agreement to our findings, similar results have been published in 2015 by Bakacak M et al.[25] They have compared MDA and SOD among non pregnant, healthy pregnant and preeclampsia. Interpretation was MDA levels in preeclampsia> healthy pregnant> non pregnant and SOD levels in preeclampsia< healthy pregnant< non pregnant.

Ferritin levels were negatively correlated with SOD (r = -0.386, p<0.0001) and positively correlated with MDA (r = 0.719, p<0.0001). This result confirmed ferritin to be a pathogenic mediator in the development of preeclampsia. Though serum iron levels were slightly low in PIH cases and there was positive correlation with SOD and negative correlation with MDA, but none of them were statistically significant. Due to routine iron supplementation to all booked pregnant mothers, there was only slight difference in iron levels of cases and controls. That's why the correlation failed to be significant.

CONCLUSION

Serum ferritin levels can be used as a good cost-effective screening test and early marker for assessment of development of PIH. Serum SOD and MDA levels help us to understand the severity of oxidative stress.

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