www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v6i2.184

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

**Original Article**

# Preeclampsia is Associated with Elevated Iron and Ferritin in Third Trimester of Pregnancy: A Cross Sectional Observational Study from A Tertiary Center At Kolkata

Authors

**Sangeeta Jana (Pramanik)[1], Mousumi Mukhopadhyay[2], Sambhu Nath Bandyopadhyay[3], Tamoghna Jana[4], Subhodip Pramanik[5]**

[1]MBBS, DGO, MD (Biochemistry), Consultant Biochemist

[2]MD (Biochemistry), Professor, Department of Biochemistry, IPGMER, Kolkata, India
Email: *mukhopadhyay90@yahoo.co.in*, Mobile no. 9836010714

[3]MD (G&O), Associate Professor, Dept of G & O, IPGMER, Kolkata, India
Email: *drsnbcal@gmail.com*, Mobile no.- 9830083861

[4]MBBS, DLO, MS (Otorhinolaryngology), Specialist Medical Officer, Udaynarayanpur State General Hospital
Email: *drtamoghna@hotmail.com*, Mobile no- 9903622415

[5]MD (Medicine), DM (Endocrinology), Senior Resident, Dept of Endocrinology, IPGMER, Kolkata, India
Email *subhodip.mck@gmail.com*, Mobile no.- 8820104725

Corresponding Author

**Dr Sangeeta Jana (Pramanik)**

Email: *dr.sangeetapramanik@gmail.com*, Mobile no. - 9748703840

**Abstract**

*Preeclampsia is one of the leading cause of maternal mortality during pregnancy. Generation of reactive oxygen species (ROS) in presence of catalytic amount of iron has been implicated into one of its pathogenesis. The objective of this study was to compare iron status (Iron, Ferritin, Total iron binding capacity [TIBC] and Transferrin saturation) between preeclamptic and normotensive-nonproteinuric pregnant women. In this observational cross sectional study, 80 pregnant women (40 normotensive-nonproteinuric and 40 pre-eclamptic pregnant women of age ranging between 18-35 years and having gestational age between 28 to 36 weeks were recruited. Serum concentrations of iron and TIBC were estimated using Randox Daytona Access Auto analyser. Ferritin was measured by Enzyme Linked Immuno Assay and percentage Transferrin saturation was done by calculation. The Mean± SD of Iron parameters in preeclamptic and non preeclamptic women were as follows: Iron 74.5± 24.8 vs 55.0 ± 13.1 µg/dl, p <0.001; Ferritin 70± 21.9 vs 44.7 ± 16.9 ng/ml, p< 0.001; Transferrin saturation 21.5± 9.1 vs 16.4 ± 9.3%, p<0.001 and TIBC365.5 ± 91.4 vs379.2 ± 111.7 µg/dl, p=0.408. None of the ferrokinetic parameters correlated with blood pressure. There was good correlation between serum iron and ferritin (r = 0.59, p= 0.001) and serum iron and serum percent transferrin saturation (r= 0.68, p= 0.001). To conclude, serum iron, ferritin, and transferrin saturation were significant higher in preeclamptic women as compared with non preeclamptic women in third trimester.*

**Keywords:** *Ferrokinetics in pregnancy, Eclampsia, Oxygen free radicals.*

## Introduction

Preeclampsia is one of the leading causes of maternal & fetal morbidity and mortality. India shared approximately 19% (56,000) of 2, 87,000 maternal deaths occurred globally during pregnancy and childbirth in 2010[(1)]. Currently, the maternal mortality rate (MMR) of India is 178 per one lakh live births whereas the sustainable development goal (SDG) target is to reduce it to 70 per one lakh live births by 2030[(2)]. Hypertensive disorders is the 4th most common cause of MMR after hemorrhage, sepsis and abortion[(3)].The primary defect in preeclampsia, still under debate, is a partial failure of trophoblastic invasion late in the first, or early in the second trimester leads to placental ischemia, followed by widespread endothelial cell damage and generation of the reactive chemical species [(4)], which then leads to the multisystem dysfunction that characterizes preeclampsia. Disturbances in iron homeostasis have already been described in preeclampsia[(5)]. Baser K et al have shown preeclamptic women had higher iron, ferritin and lower total iron binding capacity (TIBC) as compared with non-preeclamptic women. However there is no convincing data showing such relationship from this part of country. In clinical practice, iron supplements in oral/ parenteral form is prescribed to all pregnant women irrespective of their clinical status. So, with the present supplemental scheme, the intestinal mucosal cells are constantly exposed to unabsorbed iron and increases risk of oxidative risk of preeclampsia [(6)].In view of postulated association of high iron with preeclampsia, judicious administration of iron supplements to pregnant women at high risk of preeclampsia may be prudent, especially in absence of evidence in iron deficiency. The present study aims to compare iron status in preeclamptic and non-preeclamptic mothers in a tertiary care center.

## Materials and Methods

This was a cross-sectional observational study, performed in a tertiary care center in Eastern India. Consecutive 40 third trimester pregnant women of age ranging 18-35year having i) BP ≥140/90mm of Hg and ii) Proteinuria >1+ on dipstick or urine total protein >300mg in 24h were selected as case group and 40 normotensive and nonproteinuric pregnant patient in the same age group and trimester were selected as control group from the indoor and outdoor of Dept. of Gynaecology & Obstetrics. All the patients were taking iron supplement as per current government policy. Complicated pregnancy, diabetes, liver dysfunction, heart disease, essential hyper-tension, thalassemia & blood dyscrasias, haemolytic anaemia, urinary tract infection and known parasitic infestations were excluded. Patients were recruited from January 2016-June 2017. The study was approved by the Institutional Ethics Committee.

Detailed history was taken and relevant clinical examination done according to predesigned proforma. Venipuncture was done and 5 ml venous blood collected from cases and controls. Biochemical parameters were analyzed in the Dept. of Biochemistry at our institute. Serum iron &TIBC measured in Randox Daytona Access Autoanalyser, Serum ferritin by Enzyme Linked Immuno Assay and percentage Transferrin saturation was done by calculation. Reference range for serum iron, serum TIBC and serum ferritin in females were 37-145 µg/dl, 250-450 µg/dl and 10-124 ng/ml, respectively. Interassay coefficient of variance (CV) of serum iron, serum TIBC, serum ferritin were 2.82%, 1.83% and 7.2%. Reference range for transferrin saturation was 25-35%.

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) for Windows (version 15.0). Results on continuous measurements were presented on Mean ± SD and results on categorical measurements were presented in number (N) and percentage (%). Mann Whitney U Test was used to comparethe iron status between cases and controls, as study variables did not follow the normal distribution. Relationship between serum iron, TIBC and

ferritin were determined by Spearmann's Correlation Coefficient.

**Results**

Total 80 patients were recruited in this study, 40 being cases and 40 controls. The mean age of cases and controls were 22.9 ± 2.0 and 23.8± 3.9 (p=0.53). However, those suffering from preeclampsia had lesser earlier pregnancies than those who did not (Mean gravida in cases and controls were 1.2 ± 0.4 and 1.7 ± 1.2, respectively p=0.03). (Table I). Mean ± SD of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 152 ± 11.2 vs 107 ±10.7 mm of Hg (p=0.01) and 99 ± 6.7 vs 78 ± 9.3 mm of Hg (p=0.02), respectively. All patients in the case group had proteinuria, whereas none in the control group was suffering from proteinuria. Haemoglobin levels did not differ between the groups (11.2 ± 1.7 vs 10.9 ± 2.1 g/dl, p=0.62).

Results from ferrokinetic study were as follows: The serum level of iron was found to be significantly (p< 0.001) higher in Case group (74.5± 24.8 µg/dl) compared to Control group (55.0 ± 13.1 µg/dl), p <0.001. Mean serum ferritin was around one and half-fold higher in the pre-eclamptic patients than in the matched pregnant controls (70± 21.9 ng/ml vs. 44.7 ± 16.9 ng/ml;p< 0.001). The level of Percent Transferrin Saturationin this study was found to be 1.3 times (p< 0.001) higher in Case group (21.5± 9.1%) compared to Control group (16.4 ± 9.3%). However, although control group had a numerically higher TIBC than case group (control group 379.2 ± 111.7 µg/dl vs case group 365.5 ± 91.4 µg/dl, p=0.408), it did not reach statistical significance. (Table 2)

There was strong correlation between serum Iron and serum Ferritin level in the population studied (r = 0.59, p= 0.001). Similarly, serum iron and serum percent transferrin saturation level were also strongly correlated (r= 0.68, p= 0.001). (Figure 1 and 2 respectively). However none of the ferrokinetic parameters did correlate with either SBP or DBP.

**Table 1:** Baseline characteristics of study population (All variables are presented as mean ± SD)

| Parameters | Case (n=40) | Control (n=40) | P value |
|---|---|---|---|
| Age(year) | 22.9 ± 2.0 | 23.8 ± 3.9 | 0.53 |
| Gravida | 1.2 ± 0.4 | 1.7 ± 1.2 | 0.03 |
| Gestational age (Weeks) | 33.6 ± 0.5 | 34.2 ± 2.3 | 0.41 |
| SBP (mm of Hg) | 152 ± 11.2 | 107 ±10.7 | 0.01 |
| DBP (mm of Hg) | 99 ± 6.7 | 78 ± 9.3 | 0.02 |
| Haemoglobin (g/dl) | 11.2 ± 1.7 | 10.9 ± 2.1 | 0.62 |

**Table 2:** Comparison of Se Iron, Se TIBC, Se Ferritin and Percent Transferrin Saturation between the case and controls (Abbreviations: TIBC= Total iron binding capacity) (All variables are presented as mean ± SD)

| Parameters | Case (n=40) | Control (n=40) | P value |
|---|---|---|---|
| Serum Iron (µg/dl) | 74.5± 24.8 | 55.0 ± 13.1 | <0.001 |
| Serum TIBC (µg/dl) | 365.5 ± 91.4 | 379.2 ± 111.7 | 0.408 |
| Serum Ferritin (ng/ml) | 70± 21.9 | 44.7 ± 16.9 | <0.001 |
| Transferrin saturation (%) | 21.5± 9.1 | 16.4 ± 9.3 | <0.001 |

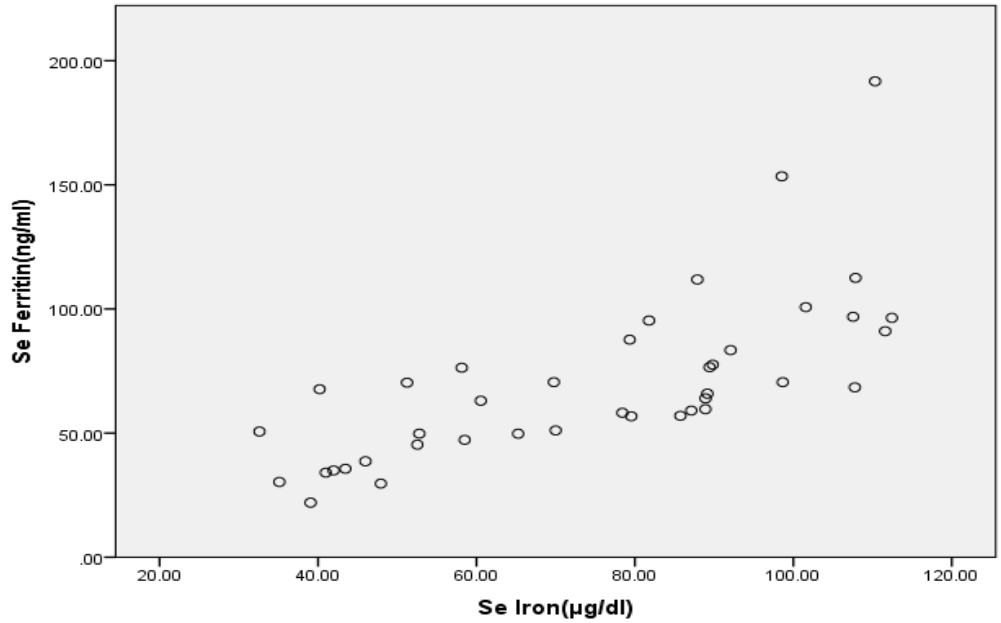


**Figure: 1**.Correlation analysis between serum iron and serum Ferritin level in the study population (r = 0.59, p= 0.001, spearman correlation coefficient)

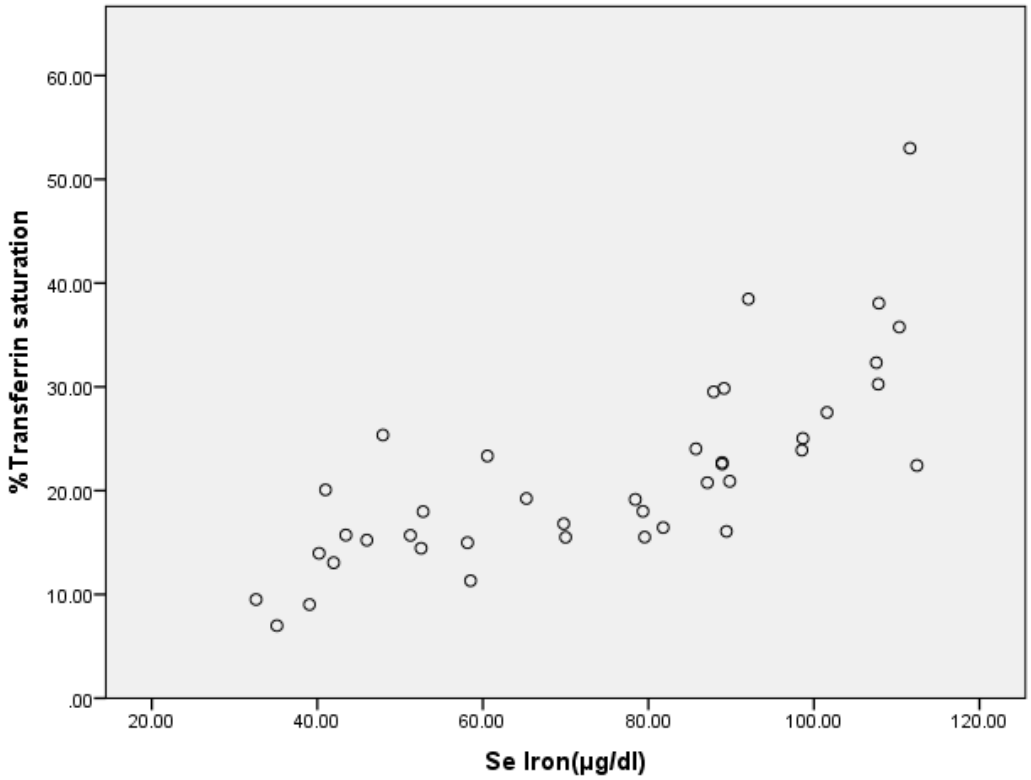


**Figure 2:** Correlation analysis between serum iron and serum percent transferrin saturation level in the study population. (r= 0.68, p= 0.001, spearman correlation coefficient)

**Discussion**

In our study, the serum level of iron was found to be significantly higher in Case group compared to Control group, which correlates with the findings of Margaret P et al.[7] According to our study, the difference of serum TIBC level between case group & control group was not significant . This value also correlates closely to the findings of a study conducted by Zafar and Iqbal.[8] But in another study of Margaret P et al TIBC were

significantly lower in the pre-eclamptic patients. In this study, median serum ferritin was around one and half-fold higher in the pre-eclamptic patients than in the matched pregnant controls .Previously Dr. Zafar T and Dr. Iqbal Z found that the median serum ferritin was around four fold higher in the pre-eclamptic patients than the control group. The level of Percent Transferrin Saturation in this study found to be 1.3 times higher in Case group compared to Control group which closely resembles with the data suggested by Zafar and Iqbal Z.

Preeclampsia is a term which is associated with gestational hypertension and gestational proteinuria with multiorgan effect after 20 weeks of pregnancy. It is one of the major causes of maternal & fetal morbidity and mortality.[9] Anti-hypertensive treatment is often initiated to reduce the risk of maternal complications such as eclampsia and cerebral hemorrhage. However, no treatment has so far proven to have a beneficial effect on the fetus and the only causal treatment for preeclampsia is termination of pregnancy.The etiology of this syndrome still remains elusive. Destruction of RBC takes place in thrombotic and necrotic areas of placenta releasing catalytic amount of transitional metal ions specially iron (Fe).[10] Highly reactive hydroxyl radicals (.OH) are produced by Fenton's reaction and the process of lipid peroxidation continues through the initiation and propagation phase. However, in the presence of iron, these species can generate the highly reactive hydroxyl radical by Haber-Weiss reaction or Fenton reaction.

- Haber-Weiss reaction-
  $H_2O_2 + O_2^{\cdot-} \rightarrow O_2 + OH^{\cdot} + OH^{-}$.
- Fenton reaction-
  $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{-} + OH^{\cdot}$.

Thus alteration of iron status has been claimed as a factor for increased oxidative stress vascular endothelial cell damage of preeclampsia and its consequences.[11] Our study reveals, in an age-matched population, serum ferrokinetic parameters (iron, ferritin, transferrin saturation) were higher in preeclamptic population as compared with non preeclmptic population, despite both groups having similar haemoglobin levels. However it is not known whether this is a risk factor or an effect of preeclampsia, for which further large scale prospective study should be undertaken. There was good correlation between iron, ferritin and transferrin saturation, thus allowing any one of them to be used as ferrokinetic marker during pregnancy. Our study also did not reveal any relationship between serum iron/ferritin levels with level of hypertension, indicating the pathogenesis of preeclampsia is actually multifactorial. The limitations of our study were small sample size; quantitative measurement of urinary protein was not done and patients were not followed up for pregnancy outcomes.

## Conclusion

Serum iron, ferritin and transferrin saturation was significantly higher in preeclamptic women as compared with non-preeclamptic women. Serum TIBC did not differ significantly between these two groups and ferrokinetic parameters did not correlate with level of hypertension.

## Acknowledgement

Prof. Sasanka Chakrabarti, Professor & head, Department of Biochemistry, ICARE Institute Of Medical Sciences & Research.

**Source(s) of support:** Nil
**Presentation at a meeting:** No
**Conflicting Interest (If present, give more details):** Nil

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