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# Comparative study of iron status between toxemia of pregnancy and normal pregnancy

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## ABSTRACT

**Objective:** Comparison of iron parameters in toxemia of pregnancy with controls and their role in etiology, pathogenesis, fetal outcome, and maternal complications. **Materials and Methods:** This study was conducted on hundred pregnant women between 20 and 35 years age group during the third trimester. 60 were identified as toxemia of pregnancy and forty matched healthy pregnant women were taken as controls in the study. Iron parameters were analyzed and evaluated the role of iron in high-risk pregnancies. **Results:** Of the 60 toxemia of pregnancy patients enrolled in the study, 35 (58.3%) were classified as preeclampsia and 25 (41.7%) were classified as eclampsia. There was significantly increased serum iron, ferritin, % saturation of transferrin in toxemia of pregnancy than in controls, but unsaturated iron binding capacity (UIBC) was significantly decreased in toxemia of pregnancy than in controls. Total iron binding capacity and transferrin did not differ much significantly in both the groups. 20% of preeclampsia and all (100%) eclampsia has a higher % saturation of transferrin levels (>60-100%). **Conclusion:** Iron status of all pregnant women should be assessed before giving the iron supplements as they cause more harm than benefit. The estimation of iron parameters particularly ferritin, % saturation of transferrin, and UIBC are useful markers to predict prognosis, severity of liver damage, and emergence of hemolysis, elevated liver enzymes, low platelets syndrome in toxemia of pregnancy especially in eclampsia, as iron species implicated in the etiology of toxemia of pregnancy likely to increase oxidative stress and promote the endothelial cell damage.

**KEY WORDS:** Eclampsia, ferritin, iron, preeclampsia, % saturation of transferrin, total iron binding capacity, toxemia of pregnancy, unsaturated iron binding capacity

## INTRODUCTION

Toxemia of pregnancy is characterized by high blood pressure, proteinuria, and edema [1]. It includes both preeclampsia and eclampsia. The basic pathology is vasospasm, causes resistance to blood flow, destruction of red blood cells from necrotic, and hemorrhagic areas of the ischemic placenta or intravascular hemolysis [2,3]. Heme can bind to iron regulatory protein (IRP) and induce dissociation of IRP from iron response element (IRE) [4-8]; correlates with an increase of apoferritin production and decrease of transferrin receptor synthesis. Eisenstein *et al.* have shown that heme entry appears to upregulate the iron storage and antioxidant capacity [9], by triggering the irreversible degradation of IRP [4,5]. Mutations in the IRP's or IRE sequences may lead to a failure to maintain cellular iron metabolism [10,11].

Release of free iron from damaged tissues during postischemic reperfusion of placenta and intravascular hemolysis, capable of accelerating free radical reactions [2,12,13], cause's lipid peroxidation. Transferrin effectively eliminates iron-catalyzed free radical activity in the circulation under normal circumstances. Iron bound to transferrin is known to be redox inert, it does not induce free radical oxidation, but any free metal ion that escapes during cell death or turnover is rapidly sequestered to prevent redox activity and leads to the formation of hydroxyl radicals.

Fenton reaction [14]:

$$Fe^{+2}+H_2O_2 \rightarrow Fe^{+3}+OH'+OH^-$$

Iron catalyzed Haber-Weiss reaction:

$$O_2+H_2O_2 \rightarrow O_2+OH'+OH^-$$
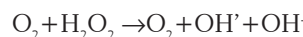
These hydroxyl radicals (OH) implicated in producing damage to polysaccharides, DNA, and enzymes, causing lipid peroxidation. Ferryl ions ($FeO_2$) may play a role in mediating tissue damage [2]. These lipid hydroperoxides interact with hemoglobin results in an increase in transferrin saturation. There is an imbalance between increased oxidant status [12,15] and decreased antioxidant activity, contribute to oxidative stress in preeclampsia. In preeclampsia, there is increased

xanthine oxidase activity generates superoxide's ($O_2^-$) during postischemic reperfusion of placenta, mediates release of iron from ferritin ultimately leads to increased % saturation of transferrin. Increased % saturation of transferrin in toxemia of pregnancy results from the combined effect of increased serum iron and decreased serum total iron binding capacity (TIBC); this explains the deficit in serum anti-oxidant activity [16]. This study compares a number of iron parameters serum iron, ferritin, % saturation of transferrin, TIBC, unsaturated iron binding capacity (UIBC) between toxemia of pregnancy, and matched control groups.

Aim of this study is:
1. To evaluate the importance of iron status as a routine test in women susceptible for high-risk pregnancy and its possible contributory role in the etiology of toxemia of pregnancy.

Whether iron supplementation is required routinely in toxemia of pregnancy as in normal pregnancy.

## MATERIALS AND METHODS

This study was conducted in the department of biochemistry and the department of obstetrics and gynecology, Government Maternity Hospital, Hyderabad, India. The study was approved by the institutional ethical committee of Osmania Medical College, Hyderabad and informed consent was obtained from all pregnant women. Study was performed on 100 pregnant women between 20 and 35 years age group during the third trimester. 60 pregnant women were classified as toxemia of pregnancy according to specific criteria: preeclampsia defined as patients having blood pressure >140/90 mm Hg, proteinuria >2+, pedal edema and eclampsia defined as convulsions in patients with preeclampsia. 40 healthy pregnant women were classified as controls. Out of 60 toxemia of pregnancy cases, 35 were classified as preeclampsia and 25 were classified as eclampsia. Neither toxemia of pregnancy or controls received iron supplements, blood transfusion or any other medication. Subjects having hemolytic anemia, liver disease, chronic renal disease, chronic hypertension, diabetes, thyroid diseases, and hematomas were excluded.

The serum was prepared from 5 ml of collected venous blood from all the selected pregnant women and stored in the refrigerator between 0°C to 4°C and subsequently analyzed. The parameters estimated from serum are: Iron, TIBC, UIBC, ferritin, % saturation of transferrin, transferrin. Serum total iron, total iron binding capacity was measured by transasia chem 5× semi auto analyzer using ERBA kits. Serum ferritin was estimated by solid phase Enzyme-linked immunosorbent assay using ERBA kits. All the kits were supplied by National Scientific, Hyderabad. The recommended quality control procedures of the manufacturer were carefully followed.

% saturation of transferrin was calculated as:

$$\text{\% saturation of transferrin} = \frac{\text{iron} \times 100}{\text{TIBC}}$$

Serum transferrin was calculated as the product of TIBC and 0.007.

UIBC was calculated as: UIBC = TIBC-iron.

### Statistical Analysis

Results were presented as mean, standard deviation (SD) for continuous variables; frequency, and percentage are given for qualitative variables. One-way ANOVA used to calculate $P$ value between three different groups by Statistics calculators version 3. Unpaired $t$-test between two groups used for $P$ values calculation from the mean, SD, number by using the Graph pad software. $P \leq 0.005$ was taken as statistically significant.

## RESULTS

There was significant elevation of serum iron concentration 2.6 fold rise in preeclampsia (mean 163.6 $\mu$g/dl vs. 62.6 $\mu$g/dl) and 3.8 fold rise in eclampsia (mean 239.5 $\mu$g/dl vs. 62.6 $\mu$g/dl) than in controls with $P = 0.000$. The mean of serum TIBC in controls was 331.8 $\mu$g/dl in preeclampsia 314.7 $\mu$g/dl and in eclampsia 295.1 $\mu$g/dl. Thus, the TIBC values did not differ much significantly in preeclampsia and eclampsia than in controls with a $P = 0.019$ (NS). There was significant elevation of serum ferritin concentration around 6.5 fold rise in preeclampsia (mean 104.7 ng/ml vs. 15.9 ng/ml) and 36.5 fold rise in eclampsia than in controls (mean 584.2 ng/ml vs. 15.9 ng/ml) with $P = 0.000$.

The % saturation of transferrin was 2.7 fold higher in preeclampsia (mean 53% vs. 19.6%) and 4.1 fold higher in eclampsia (mean 81.4% vs. 19.6%) than in controls with a $P = 0.000$. Seven of 35 preeclampsia (20%) and all the eclampsia (100%) had % saturation of transferrin in the range associated with the iron overload states (>60-100%). The mean of serum transferrin concentration in controls was 2.3 $\mu$g/dl, in preeclampsia 2.2 $\mu$g/dl, and in eclampsia 2.1 $\mu$g/dl. As the serum transferrin concentration depends on the serum TIBC concentration, thus the serum transferrin did not differ much significantly in toxemia of pregnancy than in controls with $P = 0.075$ (NS). The serum UIBC was significantly decreased 1.78 fold in preeclampsia (mean 157.8 $\mu$g/dl vs. 269.2 $\mu$g/dl) and 4.83 fold decrease in eclampsia (55.7 $\mu$g/dl vs. 269.2 $\mu$g/dl) than in controls with a $P = 0.000$ [Table 1 and Figure 1].

Table 1: Comparison of iron parameters in preeclampsia and eclampsia with controls

| Iron parameters | Mean±SD | | | P value |
|---|---|---|---|---|
| | Controls | Preeclampsia | Eclampsia | |
| Serum iron μg/dl | 62.6±22.6 | 163.6±29.3 | 239.5±38.4 | 0.000* |
| Serum TIBC μg/dl | 331.8±63.6 | 314.7±36.5 | 295.1±42.7 | 0.019† |
| Serum ferritin ng/ml | 15.9±7.2 | 104.7±98.3 | 584.2±203.7 | 0.000* |
| % Saturation of Tf | 19.6±8.3 | 53±12.2 | 81.4±7.1 | 0.000* |
| Serum Tf μg/dl | 2.3±0.4 | 2.2±0.3 | 2.1±0.3 | 0.075† |
| Serum UIBC μg/dl | 269.2±67.9 | 157.8±35.4 | 55.7±24.4 | 0.000* |

TIBC: Total iron binding capacity, Tf: Transferrin, UIBC: Unsaturated iron-binding capacity, *significant, †non-significant, SD: Standard deviation

About 2.8% (one of 35) of preeclampsia and 60% (15 of 25) of eclampsia had increased levels of liver indices (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) suggesting a component of liver damage, excluding these subjects there was 24 fold rise of ferritin, 3.7 fold rise of serum iron, 3.9 fold rise of % saturation of transferrin in toxemia of pregnancy than in controls. There was significant elevation of AST (mean 24.7 U/l vs. 14.4 U/l, $P = 0.0001$, 95% CI 5.64-14.9) and ALT (mean 27.1 U/l vs. 16.5 U/l, $P = 0.0001$, 95% CI 6.2-15) in eclampsia than in preeclampsia. The elevated ALP levels did not differ significantly in eclampsia than in preeclampsia (mean 111.2 U/l vs. 88.3 U/l, $P = 0.353$, 95% CI −26-71.8) [Table 2 and Figure 2].

Table 2: Comparison of liver enzymes between preeclampsia and eclampsia

| Parameter | Mean±SD | | P value |
|---|---|---|---|
| | Preeclampsia | Eclampsia | |
| AST U/l | 14.4±8.1 | 24.7±9.9 | 0.0001* |
| ALT U/l | 16.5±6.1 | 27.1±10.8 | 0.0001* |
| ALP U/l | 88.3±93.2 | 111.2±93.6 | 0.353† |

AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, *significant, †non significant, SD: Standard deviation
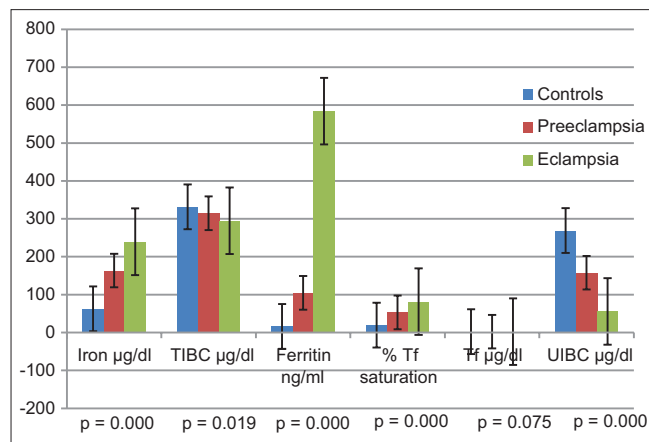


**Figure 1:** Comparison of iron parameters in preeclampsia and eclampsia with controls
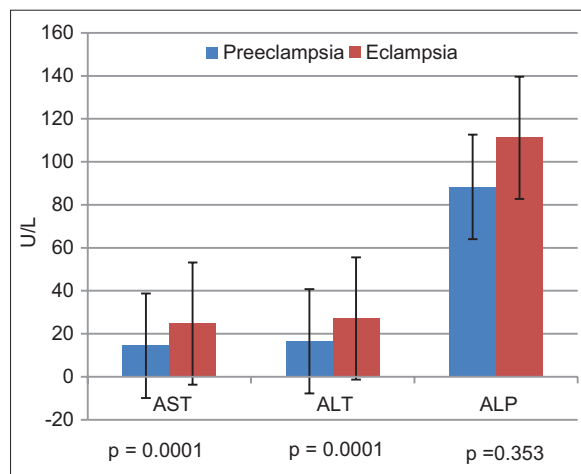


**Figure 2:** Comparison of liver function tests between preeclampsia and eclampsia

In eclampsia, there was significant direct relation between serum ferritin, % transferrin saturation with raised liver indices, but UIBC had a significant inverse relation with raised liver indices. In eclampsia with hepatocellular injury, the mean serum ferritin significantly increased than eclampsia without hepatocellular injury (mean 717.8 ng/ml vs. 383.7 ng/ml, $P = 0.0001$, 95% CI 214.8-453.4). There was significant rise of % transferrin saturation (mean 85.9% vs. 74.6%, $P = 0.0001$, 95% CI 6.96-15.64) and significant decrease of UIBC (mean 40 µg/dl vs. 79.1 µg/dl, $P = 0.0001$, 95% CI −53.6 to −24.6) in eclampsia with hepatic damage than eclampsia without hepatic damage. However, there was no significant relation between iron (245 µg/dl vs. 231 µg/dl, $P = 0.388$, 95% CI −18.8 to 46.6) and TIBC (285 µg/dl vs. 310 µg/dl, $P = 0.158$, 95% CI −60.5 to 10.5) with or without raised liver indices in eclampsia [Table 3 and Figure 3].

## DISCUSSION

Toxemia of pregnancy is one of the leading causes of maternal and fetal morbidity and mortality. The etiology of this disorder remains an enigma, but the condition may be associated with placental ischemia, leads to the release of oxidized products which may induce endothelial dysfunction. Our studies are in agreement with those of previous studies done by Rayman et al. 2002 [2], except TIBC, reported that the TIBC was decreased significantly in preeclampsia. Our study

Table 3: Comparison of mean of iron parameters with liver enzymes in eclampsia

| Iron parameters | Mean±SD | | P value |
|---|---|---|---|
| | With increased liver enzymes | With normal liver enzymes | |
| Iron µg/dl | 245±44.3 | 231±27.8 | 0.3880† |
| TIBC µg/dl | 285±46.3 | 310±34.3 | 0.1585† |
| Ferritin ng/ml | 717.8±177.5 | 383.7±45 | 0.0001* |
| %Tf saturation | 85.9±5.1 | 74.6±5.2 | 0.0001* |
| UIBC µg/dl | 40±14.4 | 79.1±20.7 | 0.0001* |

TIBC: Total iron binding capacity, UIBC: Unsaturated iron-binding capacity, Tf: Transferrin, *Significant, †non-significant, SD: Standard deviation
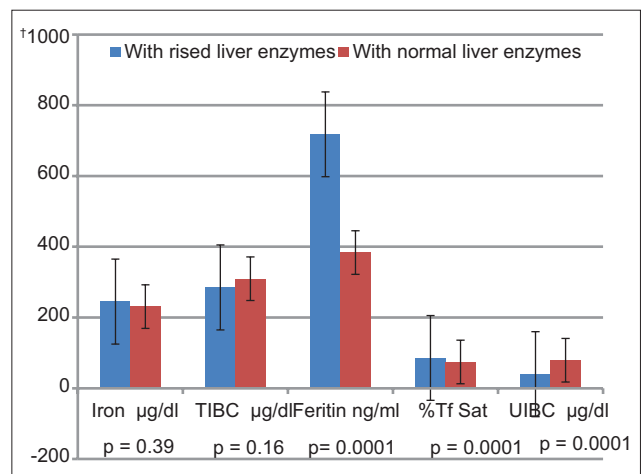


**Figure 3:** Comparison of iron parameters with raised liver enzymes and with normal liver enzymes in eclampsia

is consistent with other studies [17-20] found significantly higher levels of iron in toxemia of pregnancy than in controls ($P = 0.000$), while other studies [21-23] identified lower levels of iron in preeclampsia than in controls.

In our study, there were significantly increased levels of serum iron, serum ferritin, and % saturation of transferrin, but serum TIBC and transferrin did not differ much significantly in toxemia of pregnancy than in controls. UIBC was significantly decreased in toxemia of pregnancy relative to controls. Very early the serum iron and % saturation of transferrin are elevated, as the iron progressively accumulates, the serum ferritin concentration steadily increases. The increase in serum iron and ferritin observed in the present study may be due to the destruction of red blood cells from hemorrhagic areas of the ischemic placenta or intravascular hemolysis [2,3]. The oxidative stress in preeclampsia is indirectly supported by the direct correlation with % saturation of transferrin and inverse correlation with UIBC. This increased iron could be a factor in the generation of the oxidative stress suggesting that the iron might be involved in the etiology of the toxemia of pregnancy.

Our study shows poor correlation between iron parameters and liver indices in preeclampsia suggests that the raised iron parameters cannot be explained by the liver damage, which disagrees with the results of Rayman et al. 2002 [2]. Subclinical hepatic damage is known to occur in pregnancy induced hypertension especially in eclampsia, this is reflected by increased liver indices. In our study, 60% (15 of 25) of eclampsia and 2.8% (1 out of 35) of preeclampsia have increased levels of liver indices suggesting a component of liver damage to develop hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. There was a significant elevation of AST and ALT levels in eclampsia than in preeclampsia with $P = 0.0003$ and $P = 0.0001$, but the elevated ALP levels did not differ significantly in eclampsia than in preeclampsia. Thus, the hepatocellular injury was more common in eclampsia than in preeclampsia. AST and ALT can be useful hepatic markers to predict disease severity therefore they should be measured in all high-risk pregnancy cases. Statistical information indicated that there was a direct relation between ferritin, % saturation of transferrin and emergence of hepatocellular injury, especially in eclampsia than in preeclampsia. UIBC had a significant inverse relation with raised liver indices. However, there was no significant relation between iron and TIBC with raised liver indices in eclampsia. According to Entman et al. 1983, when the hepatocellular injury occurred, mean ferritin increased to 421 ng/ml [24]. In our study, the mean ferritin was increased to 777.5 ng/ml and % saturation of transferrin was 86% with increased liver indices. This suggests that the increased iron parameters can emerge the hepatocellular injury and HELLP syndrome in eclampsia, but the hepatocellular injury cannot be an etiological factor for the rise of iron parameters in toxemia of pregnancy. Thus, the estimation of iron parameters particularly ferritin, % saturation of transferrin, and UIBC are useful markers to predict the prognosis of toxemia of pregnancy and emergence of HELLP syndrome especially in eclampsia.

High ferritin levels are associated with decreased fetal growth, increased preterm deliveries, neonatal asphyxia [25]. It is a better predictor of early preterm birth than of late preterm birth associated with intrauterine infection [26]. There was a direct relation between serum ferritin levels and increased risk of poor pregnancy outcome and the emergence of HELLP syndrome and its severity. Hence, serum ferritin could be done as a routine test, where there is a suspicion of toxemia of pregnancy.

Over supplementation of iron during pregnancy affects the neurological growth of the fetus due to competitive interaction with the zinc, as zinc is essential for proper central nervous system growth of fetus [27]. Iron supplements and increased iron stores have recently been linked to maternal complications like gestational diabetes and increased oxidative stress during pregnancy [28,29]. The striking increase in serum iron, toxemia of pregnancy is independent of chronic oral iron supplements [20]. Indicating that the transfer of dietary iron to the fetus is regulated by maternal and neonatal iron status at the level of the gut, whereas transfer of intravenous (IV) administered iron was not regulated. Thus avoiding the IV iron supplementation and adding antioxidant therapy can lead to the reduction of endothelial cell damage that is related to toxemia of pregnancy.

## CONCLUSION

Iron status of pregnant women should be assessed before giving the iron supplements as they cause more harm than benefit. This work highlighted a significant rise in serum iron, ferritin, % saturation of transferrin and decreased UIBC leads to the deficit in the antioxidant capacity of serum by decreased serum iron buffering in toxemia of pregnancy. Hence, these are bad prognostic indicators in eclampsia than in preeclampsia. The damaged placenta is a likely site for the production of free radicals by releasing iron species may be implicated in the etiology of toxemia of pregnancy, likely to increase oxidative stress and promote endothelial cell damage. Thus, it was observed that evaluation of iron parameters can be helpful in the identification of high-risk subjects and diagnosis of toxemia of pregnancy before obvious clinical findings will be presented, particularly ferritin, % saturation of transferrin, and UIBC are useful markers to predict prognosis, severity of liver damage, and emergence of HELLP syndrome in toxemia of pregnancy especially in eclampsia. Given the prevalence of heterozygosity for hemochromatosis and maternofetal complications, it would seem advisable to assess the iron status before giving iron supplements to women at high-risk pregnancy. Thus, estimation of iron parameters, at least serum ferritin should be included as a routine test for all pregnant cases rather than only hemoglobin.

## ACKNOWLEDGMENT

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