IRON STATUS IN PREECLAMPSIA

ABSTRACT... Objective: To evaluate iron status in pregnancy induced hypertension and role of iron in the etiology and pathogenesis of pre-eclampsia. Design: Coefficient correlation study. Place and Duration. At Department of Biochemistry, Frontier Medical College, Abbottabad with collaboration of Department of Obstetrics and Gynecology, Ayub Medical Complex, Abbottabad from March 2006-March 2007. Material and Methods: Study was performed on hundred pregnant women of age ranging between 15-35 years and having gestational age between 28 to 34 weeks. Fifty obstetric patients were identified as having pre-eclampsia. Fifty healthy pregnant subjects were taken as controls, having uncomplicated pregnancies and were normotensive throughout gestation and without proteinuria. Results: Results depicts that mean age of pre-eclamptic group was significantly low (P<0.001) as compared to control. Both parameters, Hemoglobin and Haematocrit were significantly higher (P<0.05) in pre-eclamptic as compared to controls. Serum iron, serum ferritin and transferrin saturation were significantly higher (P<0.001) in pre-eclamptic in comparison with control group. Total iron binding capacity and unsaturated iron binding capacity were significantly lower (P<0.001) in pre-eclamptic group when compared to control group. Correlation coefficient between serum iron, total iron binding capacity (TIBC), serum ferritin, unsaturated iron binding capacity (UIBC) and systolic and diastolic blood pressure in pre-eclamptic group showed no significant positive correlation in any parameter. Conclusion: It is concluded that hemoglobin, haematocrit, serum iron, serum ferritin and transferrin saturation are significantly increased in pregnant women that later develops pre-eclampsia. Excess iron is postulated as casual factor in the oxidative stress ie; in its radical form, which may be involved in the pathogenesis of pre-eclampsia. Therefore, iron status of pregnant women should be assessed before giving iron supplements as these may cause more harm than benefit.

INTRODUCTION
Pre-eclampsia is a multisystem disorder of unknown etiology and is unique to pregnant women after twenty weeks of gestation. It is progressive disease with a variable mode of presentation and rate of progression1. Hypertension, proteinuria, excessive weight gain and edema are the classic clinical manifestation2. Other features include thrombocytopenia, hyperuricemia, abnormal liver function tests, and hemoconcentration3,4. Preeclampsia occurs in about 6% of the general population5. The incidence varies with geographic location. Predisposing factors are nulliparity black race, maternal age below 20 or over 35 years, low socio-economic status, multiple gestation, hydatidiform mole,
polyhydramnios, twins, obesity and underlying renal
disease. 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 and hematin proteins, play
important roles as catalysts of lipid peroxidation in
tissues. 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.

This could further escalate the cycle by increasing
circulating peroxide levels. Iron ions not safely
sequestered in storage or transport proteins are
hazardous because they can stimulate free radical
reactions. Biological examples of these are Fenton
Chemistry leading to the formation of highly reactive
species, such as the hydroxyl radical (OH) and the Ferryl
ion (FeO$_2^+$) and lipid peroxidation. There is
evidence that oxidative stress also occurs in pre-
eclampsia.

Transitional metals, especially iron, which are abundant
in the placenta, are important in the production of free
radicals. In the presence of Fe$^{2+}$ and lipid peroxides,
lipid peroxidation of membrane phospholipids is
stimulated by alkoxyl radicals generated by the Fenton
reaction. Oxidative stress, hyperlipidemia and increase
iron levels in the maternal compartment in pre-eclampsia
could be responsible for causing oxidative stress in
placenta.

Increased transferrin saturation and decreased
unsaturated iron binding capacity in preeclampsia may
occur consequent to oxidative stress and then further
promote oxidative stress by decreasing serum
antioxidant buffering against redox-active iron. The
approximate doubling of transferrin saturation in
predelivery sera of women with preeclampsia relative to
controls result from combined effect of increased serum
iron and decreased total transferrin concentration.

A study of serum iron and ferritin levels in Indian women
with pregnancy induced hypertension and eclampsia
composed with controls of similar gestational ages,
revealed that mean serum iron was elevated slightly in
pregnancy induced hypertension and significantly in
eclampsia as compared to controls. Mean ferritin levels
were significantly elevated in both pregnancy induced
hypertension and eclampsia as compared to controls. Maternal ferritin concentration is primarily a reflection
of maternal, iron status, and a high level is associated with
unfavorable outcome.

Estimates of gestational iron requirements and of the
proportion of iron absorbed from different iron
supplemental doses suggest that with present
supplementation schemes the intestinal mucosal cells
are constantly exposed to unabsorbed with an increased
risk of fetal growth restriction, preterm delivery and
preeclampsia. Mean value of serum iron is significantly
increased in the preclamptic women in comparison to
controls whereas mean values of both total iron binding
capacity and unsaturated iron binding capacity are
significantly decreased in pre eclamptic women in
contrast to controls. Study was carried out to evaluate
iron status in pregnancy induced hypertension and to
explore the possible contributory role of iron to the
etiology and pathogenesis of pre eclampsia.

**MATERIAL AND METHODS**

Study was carried out in the department of biochemistry,
Frontier Medical College Abbottabad with collaboration
of department of obstetrics and gynaecology, Ayub
Medical Complex Abbottabad. Study was performed on
100 pregnant women of age ranging between 15-35
years and having gestational age between 28 to 34
weeks. Fifty obstetric patients were identified as having
pre eclampsia according to specific criteria. Gestational
hypertension was defined as an increase of 30 mm Hg
systolic or 15 mm Hg diastolic blood pressure compared
with values obtained before 20 week’s gestation or an
absolute blood pressure >140/90 mm Hg after 20 weeks
gestation if earlier blood pressure were not known.
Proteinuria was defined as >500 per 24 hr urine
collection or >2+ on a voided or >1+ on a catheterized
random urine specimen. Fifty healthy pregnant subjects
were taken as controls, having uncomplicated pregnancies and were normotensive throughout gestation and without proteinuria. Neither pre eclamptic nor control women received iron supplements. Subjects having hemolytic anemia, liver disease, chronic renal disease, chronic hypertension, history of repeated blood transfusion, hematomas and those having chronic disease such as tuberculosis and rheumatoid arthritis were excluded.

The subjects were classified into two groups. Group X: Normal, healthy pregnant women as controls. Group Y: women with pregnancy induced hypertension. The clinical characteristics recorded were maternal age, gestational age at the time of blood sampling, systolic and diastolic blood pressure degree of proteinuria and presence and distribution of edema. Weight in kilograms (Kg) and height in centimeters(cm) were determined by standard methods. The blood pressure was measured and pulse rate was recorded. Ten ml of blood was collected from all the selected subjects of which two ml of blood was transferred to a bottle, containing EDTA and was used for hemoglobin and haematocrit estimation. From the remaining blood, serum was obtained and stored frozen at 20C in iron free microtubes until assayed number.

Hemoglobin was estimated by Cyanmet Hemoglobin Method and Haematocrit values were estimated by microhaematocrit method on Microhaematocrit Machine. Serum iron and iron binding capacity was estimated by using kit method. Transferrin saturation was calculated by the following formula.

\[
\text{Transferrin Saturation (\%)} = \frac{100 \times \text{Serum Iron}}{\text{TIBC}}
\]

Ultrasound iron binding capacity (UIBC) denotes the amount of transferrin unsaturated (unbound to) iron. It is about two third of the total iron binding capacity, as normally about one-third is saturated. The UIBC is calculated by the following formula.

\[
\text{UIBC (mg \%)} = \text{TIBC} - \text{Serum Iron Concentration}
\]

ferritin was estimated by Enzyme-immunoassay Kit method.

RESULTS

Hundred pregnant women of age ranging between 15-35 years and having gestational age between 28-34 weeks were enrolled. Fifty were uncomplicated normal pregnant subjects and fifty were pre eclamptic women. Table I shows the comparison of age, weight and height between control and pre eclamptic subjects. It shows that mean age of pre eclamptic group (Y) was significantly low (p<0.001) as compared to control group (X).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group (X) (n=50)</th>
<th>Group (Y) (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age year</td>
<td>24.88±0.60</td>
<td>19.98±0.43*</td>
</tr>
<tr>
<td>Weight Kg</td>
<td>58.60±0.65</td>
<td>57.40±0.87</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.54±0.01</td>
<td>1.53±0.87</td>
</tr>
</tbody>
</table>

*p<0.001 when compared to control, Group X= Control, Group Y=Pre eclamptic

The comparison of haemoglobin and haematocrit between control and pre eclamptic was shown in table II. Both parameters were significantly higher (p<0.05) in pre eclamptic group as compared to control group.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group (X) (n=50)</th>
<th>Group (Y) (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>10.33±0.15</td>
<td>10.84±0.18</td>
</tr>
<tr>
<td>Haematocrit(%)</td>
<td>31.30±0.46</td>
<td>32.80±0.53</td>
</tr>
</tbody>
</table>

The mean values of serum iron, total iron binding, serum ferritin unsaturated iron binding capacity and percent saturation of transferring are shwon in table III. Serum iron, ferritin and transferring saturation were significantly higher (P<0.001) in pre eclamptic (Group Y) when compared to control (group X).
Table-III. Comparison of serum iron, ferritin, total iron binding capacity which unsaturated iron binding capacity and % saturation of transferrin in normal and pre eclamptic patients.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group (X) (n=50)</th>
<th>Group (Y) (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron (mg/dl)</td>
<td>53.70±2.99</td>
<td>86.38±4.57*</td>
</tr>
<tr>
<td>Total iron binding capacity (mg/dl)</td>
<td>443.98±5.83</td>
<td>403.78±5.57*</td>
</tr>
<tr>
<td>Serum ferritin (ng/dl)</td>
<td>12.88±0.88</td>
<td>48.33±3.41*</td>
</tr>
<tr>
<td>Unsaturated iron binding capacity (mg/%)</td>
<td>390.28±8.20</td>
<td>317.35±9.61</td>
</tr>
<tr>
<td>Transferring saturation (%)</td>
<td>12.05±0.81</td>
<td>21.68±1.38</td>
</tr>
</tbody>
</table>

*=P<0.001 when compared to control

Table IV shows correlation coefficient between serum iron, total iron binding capacity (TIBC), serum ferritin, unsaturated iron binding capacity (UIBC) between systolic and diastolic blood pressure in pre eclamptic group. No significant positive correlation was observed in any parameter.

Table-IV. Correlation coefficient of serum iron, ferritin, total iron binding capacity and unsaturated binding capacity b/w systolic and diastolic blood pressure in pre eclamptic patients.

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron (mg/dl)</td>
<td>r=0.04</td>
<td>r=0.16</td>
</tr>
<tr>
<td>Total iron binding capacity (mg/dl)</td>
<td>r=0.08</td>
<td>r=0.12</td>
</tr>
<tr>
<td>Serum ferritin (ng/dl)</td>
<td>r=0.05</td>
<td>r=0.16</td>
</tr>
<tr>
<td>Unsaturated iron binding capacity (mg/dl)</td>
<td>r=0.07</td>
<td>r=0.4</td>
</tr>
</tbody>
</table>

r=coefficient of correlation, statically non significant.

DISCUSSION
Pre eclampsia is still one of the leading cause of maternal and fetal morbidity and mortality. Despite active research for many decades, the etiology of this disorder remains exclusive to human pregnancy is an enigma. Recent evidence suggests there may be several underlying causes or predispositions leading to endothelial dysfunction and causing the signs of hypertension, proteinuria and edema-findings that allow to make the diagnosis of the syndrome of Pre eclampsia. Many hypotheses have been offered and include prostacyclin thromboxane imbalance, endothelial dysfunction and immunogenetic and absolute or relative placental ischemia. The current study is undertaken to evaluate iron status and its possible contributory role in oxidative stress in pre eclampsia. There is a significant difference in maternal age between normal pregnant and pre eclamptic women. This was in disagreement to study conducted by, but no difference between weight and height was found in both groups. No significant difference was observed in hemoglobin concentration and hematocrit in pre eclamptic group. While in present study, it was observed that hemoconcentration occurs in pre eclampsia and altered hemodynamic may play a partial role in causing hyperferritinemia. Normal women has 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. However, elevated level of serum iron is observed in pre eclamptic as compared to normal pregnant women, a study supported by. Local iron excess and iron mediated oxidative stress have been demonstrated in the intestinal mucosa, liver spleen, bone marrow and placenta and the production of hydroxyl and methoxyl radicals in both the luminal and mucosal contents of the gastrointestinal tract verify the role of iron in free radical damage. Total iron binding capacity (TIBC) is low in pre eclamptic group as compared to control. Similarly, unsaturated iron binding capacity, a measure of the iron binding reserve of serum is also significantly lower in women with pre eclampsia relative to normal pregnancy. Similar findings regarding the TIBC and UIBC were observed. The results allude to the possible contribution of released iron free radicals from ischemic placenta in pre eclampsia to its etiology. Serum ferritin is found elevated in pre eclamptic group, which is in agreement with study conducted by. Serum
ferritin is a reliable indicator of total body iron status in non diseased individuals, with low concentration diagnostic of iron deficiency. However a high ferritin does not always signify iron excess17.

Elevated serum ferritin occurs in a variety of clinical conditions with non utilization of iron and destruction of tissues such as in hemolytic anemia, hepatic damage or suppression of erythropoiesis leading to accumulation of storage iron39. A prospective observational study was performed on 450 women by12. He observed that high ferritin was associated with increased risk for preterm delivery and neonatal asphyxia, while the lower ferritin level was associated with decreased risk of pre eclampsia, pre labour rupture of membranes40. Increased concentration of serum ferritin during third trimester may be part of an acute phase response, which suggests maternal infection and increased risk of poor pregnancy outcome33. Increased percent saturation of transferrin in pre eclamptic group is observed, which is in agreement with data collected by17,37.

Serum transferrin concentration increases during the course of normal gestation, whereas serum iron concentration falls, resulting in a marked decrease in transferrin percent saturation. Iron bound to transferrin is known to be redox inert; it does not induce free radical oxidations16. On the other hand iron supplements and increased iron stores have recently been linked to maternal complications e.g. gestational diabetes and increased oxidative stress during pregnancy5,27.

Consequently while iron supplementation may improve pregnancy outcome when the mother is iron deficient. It is also possible that prophylactic supplementation may increase risk when the mother does not have iron deficiency. Estimates of gestational iron requirements and of the proportion of iron absorbed from different iron supplemental doses suggest that with present supplementation schemes the intestinal mucosal cells are constantly exposed to unabsorbed iron excess and oxidative stress23,41,42,43.

CONCLUSION

It is concluded that haemoglobin, haematocrit, serum iron, serum ferritin and transferrin saturation are significantly increased in pregnant women that later develops pre eclampsia. Excess iron is postulated as casual factor in the oxidative stress i.e in its radical form, which might be involved in pathogenesis of pre eclampsia. Therefore, iron status of pregnant women should be assessed before giving iron supplements as these may cause more harm than benefit.

REFERENCES


34. Kaneshige E. Serum ferritin as an assessment of iron


