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Pre Eclampsia and Iron Status: A Review

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Abstract Preeclampsia is an idiopathic multisystem disorder specific to pregnancy and development of hypertension and proteinuria, increased vascular resistance and endothelial dysfunction in the mother , altered placental perfusion and restricted fetal growth. The vasospasm leads to destruction of RBCs release iron thus, there is elevated serum iron levels in preeclamptic women. The excess iron released from destruction of RBCs can react with free radicals produced from cell membrane (as it is rich in polyunsaturated fatty acids) and circulating lipoproteins initiates lipid peroxidation both in placenta and vasculature. This is one of the significant etiologic factors in the endothelial cell damage of preeclampsia. the raised serum iron levels in turn alters the iron related parameters like total iron binding capacity(TIBC), serum ferritin, transferrin, percent saturation.

Keywords: *preeclampsia, serum iron levels, TIBC, transferrin*

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1. Introduction

When tissues become ischemic, reactive oxygen species (ROS) such as superoxide and hydrogen peroxide are produced, but these ROS may not be able to initiate any cellular damage directly. The transition metal ions such as iron, arising from ischemic placenta by destruction of red blood cells from thrombotic, necrotic and hemorrhagic areas can generate highly reactive hydroxyl radical by Fenton reaction. This radical can initiate lipid peroxidation which if uncontrolled results in endothelial cell damage [1,2].

$Fe^{+2} + H_2O_2 \rightarrow Fe^{+3} + OH + OH^-$ (Fenton reaction)

$Fe^{+3} + O_2^{\cdot -} \rightarrow Fe^{+2} + O_2$

$O_2^{\cdot -} + H_2O_2 \rightarrow O_2 + OH^{\cdot} + OH^-$ (HABER– WEISS REACTION)

2. Iron Metabolism

A very small quantity of iron is present in most of the cells of the body, in plasma and in other extra cellular fluids. The body conserves iron supply, so that less than 0.1% of the body iron is lost daily, mostly in desquamated cells [3,4]. The iron exist in two oxidised states ferric (Fe+3) and ferrous(Fe+2) ionic forms. The mucosal cells take up ferric form of iron during its absorption. The iron (Fe+3 / Fe+2) act as cofactor for many biochemical activities of the cell.

Ferritin is the storage form of iron. Free iron acts as prooxidant agent and it is released from ferritin by the reducing agents that convert Fe+3 into Fe+2. Under stress or pathological conditions, it undergoes Fenton reaction and Haber – Weiss reaction to generate ROS, which in turn damage the biological macro molecules. Transferrin, the iron transfer protein may also undergo glycation due to stress or pathological conditions causing increased free iron levels. Glycated transferrin also enhances the production of free oxygen radicals such as hydroxide which amplify the oxidative effects of iron [5]. The iron levels of blood can be measured as serum Iron, Serum Total Iron Binding Capacity(TIBC), % Transferrin saturation, UIBC, Serum Ceruloplasmin, Serum Ferritin.

2.1. Total Iron Binding Capacity (TIBC)

It measures the maximum amount of iron that serum proteins can bind and therefore is an indirect way of assessing transferrin levels.

Increased TIBC levels are seen in

- Iron deficiency anaemia
- Acute viral hepatitis

Decreased TIBC levels are seen in

- Liver elated inflammation, neoplasia and chronic diseases
- Severe malnutrition
- Renal & Gastrointestinal diseases [6,7].

2.2. Unsaturated Iron Binding Capacity (UIBC)

It denotes the amount of transferrin unbound to iron. It is 2/3rd of TIBC [7].

$$\text{TIBC} = \text{UIBC} + \text{S. IRON}$$

2.3. Transferrin Saturation

The percent of saturation of transferrin is calculated by S. Iron and S. TIBC by the formula [7].

$$\% \textbf{ Saturation of Transferrin } = \textbf{S.Iron / TIBC X 100}$$

- The percent saturation of transferrin levels helps to differentiate iron deficiency anaemia from iron overload.

The percentsaturation of transferrin

< 20% – Iron deficiency anaemia

The percentsaturation oftransferrin

> 50% – Iron overloadstatus

2.4. Serum Ferritin

It is iron storage protein containing 24 subunits and each ferritin can store about 4,500 iron(Fe+3) atoms. Ferritin participates in ferroxidase activity, iron binding, oxido reductase activity, metal ion binding [8,9].

- Decreased Ferritin - Anaemia
- Increased Ferritin - Severe malnutrition, iron overload disorders.

2.5. Ceruloplasmin Having Ferroxidase Activity

Ceruloplasmin (CP) is a copper containing protein seen in serum. The primary physiological role of CP is its action in plasma redox reactions. It can act as oxidant or antioxidant depending on factors such as free ferric ions and ferritin binding sites. It plays an important role in oxidation of Fe+3 to Fe+2 and vice versa. It thus permits incorporation of iron into transferrin without forming toxic iron products.

CP under physiological conditions controls lipid peroxidation (by direct oxidation of cations). But in the presence of superoxide, CP is a major contributor to Low Density Lipoprotein (LDL) oxidation [10,11].

CP levels are increased in

*Menke's disease

- Wilsons disease
- Copper deficiency

CP levels are seen in

- Pregnancy
- Acute & Chronic inflammation
- Lymphoma

3. Preeclampsia and Iron Levels

An imbalance between pro -oxidants and anti -oxidants results in oxidative stress which increases the potential for the development of pre eclampsia [12]. There is raised serum iron, percent transferrin saturation, serum ferritin and decreased TIBC, UIBC and serum transferrin and ceruloplasmin levels in preeclamptic women compared to the normal healthy pregnant controls.

The elevated serum iron levels are due to hemolysis caused by physical destruction of RBC as a result of vasospam or abnormal endothelial cell erythrocyte interactions. Excess iron is a causative factor of oxidative stress (i.e., in its radical form) involved in the pathogenesis of pre eclampsia [13,14]. The excess iron released from destruction of RBCs can react with free radicals produced from cell membrane (as it is rich in polyunsaturated fattyacids) and circulating lipoproteins initiates lipid peroxidation [15]. In addition to this the damaged placenta is a site for release of free radicals(FR) in pre eclampsia. The elevation or excess iron can also react with these released FR of placenta and can initiate and propagate lipid peroxidation both in placenta and vasculature. This is one of the significant etiologic factor in the endothelial cell damage of pre eclampsia [16]. The doubling of percent transferrin saturation is due to raised serum iron and decreased serum transferrin levels. Even at low concentrations iron components such as hemoglobin and heme can increase LDL oxidation, suggesting a role of iron in LDL oxidation of preeclampsia [17].

The decreased TIBC correlates well with decreased s. Transferrin levels. This effect can cause increased proliferation of bacteria in blood due to excessive availability of free iron, and it also causes increased production of hydroxyl radicals in the tissues. The reduced transferrin levels also leads to proteinuria in pre eclampsia [18]. The decreased UIBC contributes to release of iron free radicals from ischemic placenta in pre eclampsia. The decreased UIBC, S. Transferrin levels suggests a role of iron in the development of endothelial dysfunction seen in pre eclampsia [19].

The increased ferritin levels of serum in pre eclampsia women are thought to be due to hepatic damage, resulting in leakage of ferritin into circulation [20]. James M Roberta et al. quoted that serum ferritin increase in pre eclampsia as a marker of acute phase reaction. Because inflammatory responses are increased in preeclampsia, these results in alterations in iron homeostasis [21]. The hyper ferritinemia seen in pre eclampsia is due to hepatic cell damage and increased ferritin synthesis by placenta. Thus, hepatocellular damage is the likely reason for the increase in ferritin levels of women with pre eclampsia [22].

The decreased ceruloplasmin levels seen in pre eclampsia indicate reduced ferroxidase activity. The raised serum ferritin and reduced ceruloplasmin levels suggest the intensification of free radical oxidation, results in disturbance of anti oxidant defense. The enzymatic function of Ceruloplasmin and transferrin contributes to an increase in vascular resistance and development of endothelial dysfunction [23,24,25].

4. Conclusion

The existing literature indicates that in preeclampsia, there is a possibility of vasospasm which may result in the destruction of RBC's leading to anemia and raised serum iron levels. Excess iron reacts with free radicals of cell membrane and lipoproteins initiating lipid peroxidation. This causes a change in the serum activities of ferretin, transferrin, ceruloplasmin and TIBC which may be responsible for hepatic dysfunction, increased vascular resistance and endothelial dysfunction. Therefore early identification of preeclampsia associated with genetic predisposition, physiological and other associated contributing factors will help in better management and reduction in the morbidity and mortality to mother and fetus.

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