

Relation between Serum Ferritin and Iron Parameters with Preeclampsia

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Abstract

Objective: Preeclampsia is one of the most important complications of pregnancy that is associated with increased morbidity and mortality. The aim of this study was to investigate the relation between serum iron status and ferritin with pre-eclampsia.

Materials and Methods: This case control study evaluated 33 preeclamptic patients and 33 normal pregnant women before parturition in Imam Hossein hospital, from March 2003 till March 2004. Anemia, diabetes and multiple pregnancies were excluded from the study. Blood samples were taken before delivery and patients with HELLP syndrome were considered separately. Data were analyzed using the SPSS software and P value <0.05 was considered statistically significant. T-test, chi-square and Fisher exact test were used.

Results: The mean of serum iron level in case and control group was $79.9 \pm 32.4 \mu\text{g/dl}$ and $88.6 \pm 40.8 \mu\text{g/dl}$, respectively (NS). TIBC was $443.4 \pm 55.0 \mu\text{mol/l}$ and $383.7 \pm 63.6 \mu\text{mol/l}$ in normal patients and preeclamptics respectively ($P = 0.002$). Mean serum ferritin was $32.1 \pm 16.2 \text{ ng/dl}$ in control group and $123.8 \pm 46.1 \text{ ng/dl}$ in preeclamptics ($P < 0.001$). No meaningful relation was observed between hematocrit, ferritin and iron.

Conclusions: Ferritin increases and TIBC decreases in preeclampsia regardless of hepatic function. It seems that elevated serum ferritin (as an oxidative stress) can accelerate vascular damage. So, routine iron supplementation in preeclamptic women is questionable.

Key words: Preeclampsia, Iron, Ferritin, TIBC, Hematocrit, HELLP syndrome

Introduction

Pre-eclampsia is one of the worrisome concerns for pregnant women and physicians (1). Generally 3%-5% of pregnancies are complicated with pre-eclampsia (2, 3) a multi-systemic disorder characterized by hypertension and proteinuria that occurs after 20 weeks of gestation. Pre-eclampsia is one of the

most important complications of pregnancy that is associated with increased maternal and fetal mortality and 18% of pregnant women die because of this problem (4). Other major complications of pre-eclampsia are premature delivery and need for NICU utilization with its inherent problems. About 10 percent of women with preeclampsia/eclampsia will develop HELLP Syndrome (H: hemolysis, EL: elevated liver enzymes, LP: low platelet count) (2).

Although inflammation and extensive endothelial dysfunction of vessels are the main possible mechanisms of pre-eclampsia (5), but the pathogenesis of this syndrome has not been well-understood (2).

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In fact, this pathophysiologic phenomenon is silently started from a long time (2-3 months before the emergence of hypertension), and will be clinically demonstrated as preeclampsia. Different studies have been performed about the etiology of preeclampsia, but there is not any reliable and cost-effective screening test (5, 6). Ferritin level and iron parameters are introduced as a probable pathogenesis for preeclampsia. Recent studies in pregnant women have shown that an elevated maternal serum ferritin, iron concentration and abnormal transferrin metabolism can occur in association with pregnancy induced hypertension and eclampsia (7-10). One additional complication is the role of ferritin as an acute phase reactant which has been shown in pre-eclampsia. Increasing level of lipid peroxides and different kinds of pro-oxidants such as iron are considered as parameters in the diagnosis and prevention of preeclampsia (11, 12). Indeed, in some other studies different results have been observed (9, 13, 14, 15). There are three main reasons for performing this study: pre-eclampsia's unknown points, absence of similar study in Iran and the importance of its etiology.

Materials and methods

This analytic case-control study included sixty six pregnant women whom were admitted for termination of their pregnancy from March 2003 till March 2004 in Imam Hossein hospital, Tehran. Informations were gathered and recorded in questionnaires by a physician. The case group (33 pre-eclamptic women) and the control group (33 healthy parturients) were admitted for termination of pregnancy due to medical or obstetrical indications. The diagnostic criteria of preeclampsia consisted of blood pressure of 140/90 mmHg or more (using fifth phase sound of Korotkoff) and proteinuria on two accidental urine samples (with at least +1 with dipstick) or urine total protein >300 mg in 24 hours. In order to eliminate the confounding effect of anemia on increasing the ferritin and TIBC level, patients with history of anemia and

hemoglobin <11mg/dl were excluded. Moreover, diabetics and women with multiple pregnancies were not included in this study. Both groups were matched by gestational age, social and economical situation. In order to determine serum iron, ferritin and TIBC level, blood samples of case and control groups were taken before delivery and analyzed. Ferritin was measured by IRMA and TIBC and iron were measured with calorimetric method. For analyzing data SPSS software was used and t-test, chi-square, Fisher exact test and odds ratio for abnormal ferritin and TIBC in pre-eclamptic patients were calculated. For statistical significance 95% confidence interval, and P-value <0.05 were considered.

Results

In case group 28 patients had normal liver enzymes and platelet count and 5 cases had HELLP syndrome. The mean age of control and preeclampsia groups were 24±5.5 and 27±6.3 years respectively (NS). Serum iron, ferritin, TIBC and hemoglobin level were measured and are shown in table 1. There were no significant differences in serum iron, hemoglobin and hematocrit level between two groups. Total iron-binding capacity (TIBC) level in control and preeclampsia groups were 443.4±55.0 µmol/l and 383.7±63.6 µmol/l respectively. In preeclampsia TIBC level was about 13% lower than the control group (P = 0.002). Serum ferritin level in preeclampsia and control group were 123.8±146.0 ng/dl and 33.4±16.2 ng/dl, respectively (OR=3.7, P <0.001). It is worth to mention that we didn't find any meaningful relation among hemoconcentration and ferritin with preeclampsia. Hemoglobin in control group was 14.2±1.3 mg/dl versus 13.5±2.9 mg/dl in case group and hematocrit (41.8±4.3 mg/dl versus 39.8±2.8 mg/dl, respectively) level was similar in both groups (NS).

We divided the patients in two groups of normal and high ferritin (abnormal group). Distribution of preeclampsia according to the ferritin level showed that there wasn't any abnormal ferritin in normal wo-

Table 1: Ferritin & iron parameters of study groups

	Preeclampsia	Control	P-value
Iron (µm/dl)	79.9±32.4	88.6±40.8	NS
TIBC (µmol/l)	383.7±63.66	443.1±55.0	0.002
Ferritin (ng/dl)	123.8±146.0	33.4±16.2	<0.001
Hemoglobin (mg/dl)	14.2±1.3	13.5±2.9	NS
Hematocrit (mg/dl)	39.8±2.8	41.8±4.3	NS

Table 2: Preeclampsia and normal distribution according to the ferritin and TIBC levels

	Preeclampsia / n (%)	Control / n (%)
Ferritin:		
Normal	18 (54.5)	33 (100)
Abnormal	15 (45.5)	0 (0)
TIBC:		
Normal	13 (39.4)	28 (84.4)
Abnormal	20 (60.6)	5 (15.2)

men and 45.5% of pre-eclamptic patients had abnormal ferritin. Fisher test analysis indicated significant differences (OR= 10, $P<0.0001$) Distribution of preeclampsia according to the TIBC level shows the abnormal TIBC in normal and pre-eclamptic pregnant women was 84.8% and 39.4%, respectively. So, there was more frequent normal TIBC in pre-eclampsia (OR=8.6, 95% CI: 2.6-28, $P<0.0005$) (Table 2).

Regarding to the increased level of liver enzymes and decreased level of platelets, we had 28 preeclampsia and 5 HELLP syndrome cases. Ferritin level of preeclamptic patients was compared to the ferritin level of control group.

Statistical information indicated that there was a direct relation between ferritin level and emergence of HELLP syndrome and its severity. As it is shown in table 3, there was no meaningful relation between serum iron and TIBC in preeclampsia and HELLP syndrome subjects but ferritin level in HELLP syndrome cases with platelet disorders and/or elevated liver enzymes was 3.6 times to the preeclamptic patients and 10 times to normal pregnant women who had not thrombocytopenia and enzymes disorders ($P<0.001$).

There was no significant difference regarding SI, TIBC and Hematocrit between two groups of preeclamptics (NS) (Table 3).

Discussion

Some evidences suggest that, serum iron level in

preeclampsia is more than normal. Increased serum iron promotes lipid peroxidase activity and induces endothelial cell damage. There is evidence that increased serum iron level plays a pathogenic role in the development of pre-eclampsia (11, 12). Iron status markers such as serum iron and ferritin perform as an acute phase reactant (16, 17, 18). Whether serum ferritin in chronic inflammatory diseases acts as an acute phase reactant or not, is a controversial issue yet (3, 16, 19) but its level is increased in chronic diseases secondary to elevated iron storage in reticuloendothelial cells (20). The intra-cellular iron storage ferritin protein can hold up to 4000 iron atoms. In normal pregnancy, serum ferritin concentration depicts replaceable iron storage that is in the liver, spleen and bone marrow (21-24). Ferritin can be found in low concentrations in normal women because of active secretion from reticuloendothelial or parenchymal cells (25, 26).

Serum ferritin level changes during the pregnancy with advancing gestation and reaches the minimum at the third trimester to 20 ng/dl (19, 27). Although, serum ferritin depicts iron level and its low level indicates iron deficiency anemia, but increased serum ferritin doesn't suggest that the iron level is more than normal. It seems that in pregnancy, increased serum ferritin exacerbates hypertension and eclampsia. Correlation of iron and ferritin with preeclampsia was evaluated in some researches. These studies suggest serum iron, ferritin and transferrin saturation rate are remarkably higher in preeclampsia and TIBC level is

Table 3: Iron parameters in both groups and its relation with liver enzymes & platelets count

	Pre-eclampsia		Pre-eclampsia		P-value
	High LFT*	Normal LFT	Plt<10 ⁵	Plt>10 ⁵	
Iron (µg/dl)	80.3±41	79.6±41	78.8±27	80±43	NS
Ferritin (ng/dl)	209.4±194	60.9±28	323.4±204	88.2±101	0.001
TIBC (µmol/l)	365.5±67	397.1±58	359.0±76	388.1±61	NS
Hematocrit (mg/dl)	43.4±3	40.7±2	41.8±3	41.7±4	NS

* LFT: Liver Function Test

lower than normal subjects (13, 15, 28). In another study in preeclamptic cases, serum iron and TIBC level were 46% higher and 14% lower than normal subjects respectively (9,15). This study revealed that ferritin level in preeclampsia and HELLP syndrome was 3.6 and 10 times to the normal, respectively. Also, a direct relation between ferritin level and severity of preeclampsia may be observed. Lower ferritin level during 28-30 weeks of pregnancy would be associated with lower incidence of preeclampsia (29).

It seems that in preeclampsia, antioxidant activity is decreased remarkably. Oxidative stress (imbalance of oxidant forces & anti oxidant in favor of oxidants) with enhanced lipid peroxide formation could lead to endothelial dysfunction in preeclampsia. Other conditions, such as increased transferrin saturation and decreased iron-binding capacity, directly and indirectly promote the process of oxidative stress and subsequent endothelial dysfunction. It seems that the reaction of maternal components - especially neutrophils & oxidative lipids - with placental factors & cells are conducted to oxidative stress activity (13). Antioxidant treatment can lead to the reduction of endothelial cell damage that is related to preeclampsia.

Human serum has antioxidant activity and is an effective inhibitor of lipid peroxidase and its clinical importance should be considered (22, 27, 30). Inhibition of iron ions transport and prevention of acute radical reaction are the most important antioxidative impacts of the human serum (22, 30, 31). It seems free iron of serum in mild preeclampsia is more than normal pregnancy due to destruction of red blood cells and this increased level exacerbates lipid peroxidation and endothelial cell damage (8).

Unlike other reports (9, 13, 14, 15), our finding specified that serum iron measurement has not any valuable role in the prediction of preeclampsia (28). Lack of obvious change in liver enzymes and hemoglobin concentration in eclampsia and preeclampsia confirms that liver damage and hemodynamic changes have a relative and negligible role in hyperferritinemia (15). Furthermore; we found out that serum ferritin level is several times more than normal in preeclampsia, even without elevated liver enzymes or decreased platelet. Also, there was no relation between Ferritin and hemoglobin concentration in PIH. Elevation of serum ferritin level in preeclamptic patients is an unknown issue. Confirmation of the probable role of plasma ferritin that is released following the placental damage, needs more diagnostic measures.

Contrary to intracellular ferritin, which is non gly-

cosylated and high in iron, 60%-80% of serum ferritin is glycosylated and very low in iron. non glycosidic ferritin concentration was 2 and 5 times more than normal suggesting that tissue damage contributes up to 5 times increase in serum ferritin in preeclampsia (32). In our study, serum ferritin level in preeclamptic and HELLP syndrome were nearly 3.6 and 10 times to the normal respectively.

Although; in normal group there is not any relation between TIBC and ferritin level but, in preeclampsia a significant negative relation was observed. 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. On the other hand, there is not any meaningful difference between serum iron level of preeclamptic and HELLP syndrome patients and normal pregnancy.

So we concluded the serum ferritin concentration is a marker of maternal iron status, and its high level is associated with preeclampsia but we found no relation between serum ferritin level changes and anemia in pregnancy. However, there is a strong relation between ferritin and preeclampsia. At the end, it was observed that evaluation of ferritin and TIBC can be helpful in the identification of high risk subjects and diagnosis of preeclampsia before obvious clinical finding will be presented (11). So, the rationale of routine iron supplementation in non-anaemic women is questionable and needs further investigations (29).

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