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A Prospective Study of Evaluation of Changes in Biochemical and Urine Parameters in Pre-eclampsia

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ABSTRACT

The purpose of this study was investigated that whether the measure of the biochemical and urine parameters in pregnant women has correlation relationship with preeclampsia. This study was targeted singleton pregnant women as the case group (50 patients of preeclampsia) or the control group (50 healthy parturients) who were admitted for termination of pregnancy due to medical or obstetrical indications. In order to survey of serum iron, ferritin, creatinine, platelet and liver enzymes, blood samples of case and control groups were taken before delivery and analyzed. There was significant difference in the mean serum iron and ferritin levels between two groups. Also, it was found significant differences in the mean level of serum ferritin of the preeclamptic patients who have ELLP syndrome (EL: Elevated liver enzyme, LP: Low platelet count) in comparison with preeclampsia women with high level of liver enzymes. However, this relation meaningful was not shown among mean serum iron and EELP syndrome with preeclampsia. The correlation coefficients between iron and creatinine/proteinuria/albuminuria as well as ferritin and creatinine/proteinuria/albuminuria concentrations in group of preeclampsia were not significantly different. Present results revealed that a correlation relationship between the concentration of serum ferritin and iron and ELLP syndrome and preeclampsia may in fact exist.

Key words: Iron, ferritin, creatinine, albuminuria, proteinuria, preeclampsia

INTRODUCTION

In relation to the pregnancy, one of the most important trouble that will increase the mortality rate among mothers is preeclampsia, so that, nearly 4% of pregnant women have experienced preeclampsia and also 16% of deaths that occur during pregnancy is due to complications of this disease (Sibai *et al*., 2003). In spite of several decades of extensive investigations, the mechanism responsible for the beginning of preeclampsia in the pregnant mothers is still remain unknown (Fabry *et al*., 2010).

Characteristic symptoms of preeclampsia are high blood pressure (Hypertension), presence of excess protein in the urine (proteinuria), edema and also in severe cases with blurred vision, headache, epigastric pain or even oliguria (Palmsten *et al*., 2010). These signs usually disappear inside a few days after the delivery is done. However, in preterm labour, the risk of complications in case of the neonate increases significantly (Madan *et al*., 2010). Some of these critical

complications could possibly be diminished if it's making a good decision to manage well these patients. The most important symptoms of preeclampsia are proteinuria and also glomerular histologic changes. This is due to the vessel spasm and also activation and injury of the vascular wall (Hladunewich *et al*., 2007).

Properly, the clinical symptoms mentioned above appear at the later stage of the pathologic process that may begin at the time of formation of placenta in the uterine (Kajantie *et al*., 2010).

Thus, it seems that attempting to recognize the early indicators of decrease of placental blood flow, endothelial cells dysfunctions and coagulation disorders is crucial to diminish adverse neonatal effects and to get better survival and quality of life. Such an approach will have an immense influence on societal and public health-care costs.

The cause can be free toxic radicals by creating oxidative stress, activation of coagulation and increase of permeability of vessels that eventually cause proteinuria, thrombocytopenia, edema and the other preeclampsia symptoms (Ramanathan and Bennett, 2003).

It was shown that antioxidants such as vitamin E, C and beta-carotene could prevalence of clinical symptoms of preeclampsia by decreasing toxic effects of free radicals (Gilbert *et al*., 2008). Iron and ferritin are considered as free radicals (Gonul *et al*., 2010). Also it was reported that increase level of iron and subsequent radicals such as ferritin which have been produced from destruction of red blood cells due to placental ischemic, hemorrhagic areas, intravascular hemolysis or hepatocellular injury can make endothelial cells injury and eventually increase the vessel permeability (Kaim *et al*., 2002). Since the data in support of measuring the level serum of iron and ferritin as an important indicator in preventing of preeclampsia and also in preventing of consuming complementary iron for pregnant women at risk is limited. Therefore, this study was carried out to investigate whether the measure of the level serum of iron, ferritin, enzyme liver, creatinine, protein urea and also albumin urea in pregnant women has correlation relationship with preeclampsia.

MATERIALS AND METHODS

This analytic case control study was carried out in the obstetrics and gynecology ward of Imam Khomeini teaching hospitals in Ahvaz. This study was performed between April 2008-2009 and targeted singleton pregnant women as the case group (50 patients of preeclampsia) or the control group (50 healthy parturients) who were admitted for termination of pregnancy due to medical or obstetrical indications. The diagnostic criteria consisted of blood pressure of 140/90 mmHg or more (using fifth phase sound of korotkoff) and proteinuria on two accidental urine total protein >300 mg in 24 h. Exclusion criteria included patients with history of anemia and hemoglobin <11 mg dL^{-1}, obesity, kidney and liver failures, diabetes and women with multiple pregnancies and. Both groups were matched by age (20-35 years), gestational age (the first 3 months of pregnancy), the number of deliveries, social and economical situation (Income and services such as education and health care). In order to survey of serum iron, ferritin, creatinine, platelet and liver enzymes, blood samples of case and control groups were taken before delivery and analyzed. Ferritin was measured by IRMA method (Flowers *et al*., 1986) and creatinine, platelet, liver enzymes and iron were measured with colorimetric assay (Rayman *et al*., 2002).

Statistical analysis: For analyzing of the data, SPSS software was used and was examined accurately by t-test, chi-square, Fisher exact test and odds ratio for abnormal ferritin, creatinine, platelet, liver enzymes and iron in the patients of preeclampsia. For all other outcomes, a nominal p-value of $p<0.05$ was considered significant.

RESULTS

Outcome data were available for 100% of the randomized women. One hundred women were admitted for termination of their pregnancy due to medical or obstetrical indications. Fifty of whom were admitted for preeclampsia and fifty of whom were admitted for healthy parturient. None of the patients was lost to follow up (Fig. 1).

The two groups were similar in the maternal age (20-35 years), gestational age (the third 3 months of pregnancy) at admission, the number of deliveries, social and economical situation. From fifty cases of preeclampsia, 41 ones had normal liver enzyme and platelet count and others had ELLP syndrome. Serum iron, ferritin, hemoglobin and creatinine are shown in Table 1. With respect of maternal age (29.4 vs. 31.6 years, p = 0.84), there was significant differences in biochemical and urine parameters such as the mean serum iron (144.4±42.2 vs. 118.1±37.5 μg dL^{-1}, p = 0.03), ferritin (58.1±19.6 vs. 31.1±21.3 ng mL^{-1}, p = 0.001), hemoglobin (11.1±1.4 vs. 13.2±2.6 mg dL^{-1}, p = 0.04) and creatinine (2.7±1.1 vs. 1.2±0.9 mg dL^{-1}, p = 0.05) between preeclamptic patients and healthy women, respectively.

Also, it was found significant differences in the level of mean ferritin of the preeclamptic patients who have normal level of liver enzymes (n = 41) in comparison with preeclamptic women with high level of liver enzymes (n = 9) (52.4±38.7 vs. 59.4±40.6 ng dL^{-1}, respectively, p = 0.04) (Table 2). However, this relation meaningful was not shown among mean serum iron of the preeclamptic patients who have normal level of liver enzymes (n = 41) in comparison with preeclampsia women with high level of liver enzymes, respectively (n = 9) (144.6±55.7 vs. 150.9±70.4 μ dL^{-1}, respectively, p = 0.12) (Table 2).

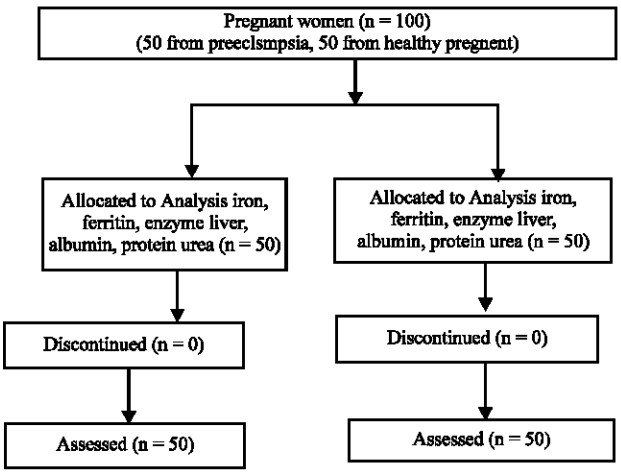

Fig. 1: Flow chart of participants during the clinical trial

Table 1: Maternal demographic and clinical characteristics (Mean±MSE) in preeclamptic women and matched pregnant control subjects

Characteristics	Preeclampsia (N = 34)	Control (N = 34)	p-value
Maternal age (years)	29.4	31.6	0.840
Iron (μg dL^{-1})	144.4±42.2	118.1±37.5	0.030
Ferritin (ng mL^{-1})	58.1±19.6	31.1±11.3	0.001
Hemoglobin (mg dL^{-1})	11.1±1.4	13.2±2.6	0.040
Creatinine (mg dL^{-1})	2.7±1.1	1.2±0.9	0.050

Table 2: Correlation coefficients of serum ferritin and iron (Mean±MSE) between preeclamptic women who have normal and high liver enzyme, platelet, creatinine protein urine and albumin urine levels

Preeclamptic women	Number	Iron (μ dL^{-1})	Ferritin (ng mL^{-1})
Normal liver enzyme	41	144.60±55.7	52.4±38.7*
High liver enzyme	9	150.90±70.4	59.4±40.6
Platelet <100000	44	140.41±62.9	57.2±36.9*
Platelet >100000	6	138.10±49.6	51.1±35.1
Creatinine >1.2 mg dL^{-1}	48	142.20±64.8	57.6±37.4
Creatinine <1.2 mg dL^{-1}	2	140.10±49.9	56.7±36.8
Protein urine level >2 g/24 h	38	138.90±68.0	58.0±37.9
Protein urine level <2 g/24 h	3	133.10±62.4	57.6±38.2
Albumin urine level >2 plus	33	141.20±67.3	59.1±39.2
Albumin urine level <2 plus	17	138.20±66.1	57.3±38.4

*p<0.05, for comparison to preeclampsia women who have abnormal liver enzyme, platelet, creatinine, protein urine level and albumin urine level

Moreover, the mean serum ferritin level in preeclampsia women who have higher than 100000 platelets (n = 6) was lower than preeclamptic patients who have lower than 100000 platelets (n = 44) (51.1±35.1 vs. 57.2±36.9 ng mL^{-1}, respectively, p = 0.01) (Table 2). But, there was no meaningful relation between serum iron and platelets in preeclampsia women who have higher than 100000 platelets (n = 6) in comparison with those have lower than 100000 platelets (n = 44) (138.1±49.6 vs. 140.41±62.9 ng mL^{-1}, respectively, p = 0.66) (Table 2).

Regarding to the increased level of liver enzymes and decreased level of platelets, we had 41 preeclampsia subject and 9 ELLP syndrome cases.

However, In case of urine parameters, there was no significant relation for both the serum ferritin (57.6±37.4 vs. 56.7±36.8 ng mL^{-1}, p = 0.51) and iron (142.2±64.8 vs. 140.1±49.9, p = 0.09) of the preeclamptic patients who have higher than 1.2 mg dL^{-1} level of creatinine (n = 2) in comparison with preeclampsia women with lower than 1.2 mg dL^{-1} level of creatinine respectively (n = 48) (Table 2).

Also, the relevance coefficients of serum iron (138.9±68 vs. 133.1±62.4 μ dL^{-1}) and ferritin (58±37.9 vs. 57.6±38.2 ng mL^{-1}) in preeclamptic women who have higher than normal urine protein levels (n = 3) compared to normal urine protein level (38) were not significantly different, respectively (Table 2).

Moreover, the relevance coefficients of serum iron (141.2±67.3 vs. 138.2±66.1) and ferritin (59.1±39.2 vs. 57.3±38.4 ng mL^{-1}) in case patients who have higher than normal urine albumin levels (N = 17) versus to normal urine albumin levels (n = 33) were not significantly different, respectively (Table 2).

Its worthing to mention that 9 of 50 preeclampsia patients who have abnormal liver enzymes, because of necessity in end of pregnancy, gathering of 24 h urine was not done. But, 24 h urine of all the rest of 41 people was gathered.

DISCUSSION

The present study showed that the level of iron and ferritin in the preeclampsia patients were tended to increase. These findings, with respect of studies of Adam *et al.* (2001) and Siddiqui *et al.* (2010), are in accordance with other studies done by Basher and Deb (2006) and Entman *et al.* (1983). Rayman *et al.* (2002) and Hubel *et al.* (1989) reported that the increasing serum iron level, plays a critical role in the development of preeclampsia disease.

Properly, the level of serum iron acts as an acute phase reactant in chronic inflammatory diseases (Yildirim *et al*., 2004). However, there was a controversy about the action of acute phase reactants of ferritin in chronic inflammatory diseases (Choi, 2005; Braun *et al*., 2004). Entman *et al*. (1983) reported that ferritin can be found in low level in healthy women because of release from reticuloendothelial cells. But its level was increased in chronic diseases, resulting to elevated serum iron in reticuloendothelial cells. It worthing to mention that ferritin protein can storage more than 4000 iron atoms in the cytoplasm (Wagner *et al*., 2003). In fact, in healthy pregnant women, the mean serum level of ferritin represents the mean storage level of iron that is saved in the liver, spleen and bone marrow (Wagner *et al*., 2003; Hubel *et al*., 1989). This study also revealed that the level of serum ferritin was increased secondary to increased iron level.

Although, low level of serum ferritin directly represents iron concentration and so that its low level indicates iron deficiency anemia, but the increased serum ferritin does not indicate abnormally high iron level. Therefore, it seems that in pregnancy, elevated serum ferritin make high blood pressure and eclampsia worse.

It seems that antioxidant activity can suppress the dynamics of preeclampsia. So, if the antioxidant activity decreases remarkably in the pregnant women, the oxidative stress as well as lipid peroxide level will increase. Thus, disorders in the activity antioxidant enzymes could lead to endothelial dysfunction in preeclampsia. Hubel *et al*. (1996) showed that the elevated transferrin saturation and the reduced iron-binding capacity could augment the procedure of oxidative stress action as well. So, the free radical scavenging activity of an antioxidant by metabolizing free radicals or inhibiting prooxidative enzymes can be reduced the endothelial cell damage that is related to preeclampsia.

In overall, there are antioxidant activity and an effective inhibitor of lipid peroxidase in the serum. Therefore, the clinical importance of this activates should be considered (Pepper *et al*., 1994; Finch *et al*., 1986; Shakour-Shahabi *et al*., 2010; Howlader *et al*., 2007). In agreement with the present study, Yip (2000) showed that due to destruction of red blood cells, the serum iron level in moderate preeclampsia lead to increase in comparison to healthy pregnancy. In turn, the elevated serum iron causes increasing level of lipid peroxidation and endothelial cell damage.

The present study showed that the meaningful relation among serum ferritin concentration and appearance of ELLP (elevated liver enzymes, low platelets) syndrome is confirming the existence of hemodynamic changes due to liver injury.

Prior researches have come to different results about whether ferritin concentration is raised in result to increased liver enzymes secretion (Rayman *et al*., 2002; Vitoratos *et al*., 1999).

This study as well as shown that even without increased liver enzymes or decreased platelet, serum ferritin level is higher in preeclamptic patients than normal pregnant women. Therefore, it seems that liver damage is not the only cause of the raised ferritin concentration in preeclampsia.

Taken together, how to elevate of serum ferritin level in preeclamptic patients needs to more researches. For instance, since the human placenta is a source for ferritin, therefore, further experiments are necessary to confirmation the mechanisms of the effects of the placental damage on serum ferritin level in pregnant women and we suggest that other researchers identify the precise relation between placental damage and plasma concentration of ferritin in the preeclamptic women.

On the other hand, there is not any meaningful difference between serum iron level of preeclamptic and ELLP syndrome patients and normal pregnancy. Decreased unsaturated iron (binding capacity) in preeclampsia may take place consequent to oxidative stress by decreasing serum antioxidant buffering against redox-active iron.

Correlation of iron and ferritin levels with preeclampsia and also ELLP syndrome cases was reported in a number of studies. These studies indicated that serum ferritin is higher in preeclampsia, while liver enzymes concentration is lower than healthy cases (Amburgey *et al.*, 2009). Rayman *et al.* (2002) and also Hubel *et al.* (2004) reported that in preeclamptic women, serum iron level and liver enzymes secretion were, respectively remarkably higher and lower than healthy pregnant women.

The present result showed that the average of serum iron and ferritin levels in comparison with levels of serum creatinine, albumin of urine and 24 h proteinuria in patients of preeclampsia statistically was not meaningful.

Rayman *et al.* (2002) reported that there was no correlation between concentrations of the ferritin and albumin. They suggested that an acute phase response is not the cause of the raised levels of serum ferritin. In contrast, Branten *et al.* (2004) showed that there was a relation between serum iron level and excretion of urine (i.e., proteinuria, creatinine and albumin).

CONCLUSION

Although, the present study had a number of restrictions to detect clinically essential outcomes such as levels of some antioxidant enzymes (like catalase and SOD) and so further research is necessary to identify the precise etiopathogenesis of preeclampsia, Nevertheless, It can assert that survey of serum iron and ferritin concentrations in pregnant women, as an essential part of routine pregnancy health care, can make a valuable method to diagnosis preeclampsia instead of urine metabolite analysis before clinical signs appear.

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REFERENCES

Adam, B., E. Malatyalioglu, M. Alvur and C. Talu, 2001. Magnesium, zinc and iron levels in pre-eclampsia. J. Matern Fetal Med., 10: 246-250.

Amburgey, O.A., E. Ing, G.J. Badger and I.M. Bernstein, 2009. Maternal hemoglobin concentration and its association with birth weight in newborns of mothers with preeclampsia. J. Maternal-Fetal Neonatal Med., 22: 740-744.

Basher, K. and K. Deb, 2006. Alteration in iron status in preeclampsia. Mymensingh Med. J., 15: 22-24.

Branten, A.J., D.W. Swinkels, I.S. Klasen and J.F. Wetzels, 2004. Serum ferritin levels are increased in patients with glomerular diseases and proteinuria. Nephrol. Dial. Transplant., 19: 2754-2760.

Braun, S., G. Ndrepepa, N. Von Beckerath, W. Vogt, A. Schomig and A. Kastrati, 2004. Value of serum ferritin and soluble transferrin receptor for prediction of coronary artery disease and its clinical presentations. Atherosclerosis, 174: 105-110.

Choi, J.W., 2005. Sensitivity, specificity and predictive value of serum soluble transferrin receptor at different stages of iron deficiency. Ann. Clin. Lab. Sci., 35: 435-439.

Entman, S.S., L.D. Richardson and P.P. Killam, 1983. Altered ferrokinetics in toxemia of pregnancy: A possible indicator of decreased red cell survival. Clin. Exp. Nyertens., 2: 171-178.

Fabry, I.G., T. Richart, X. Chengz, L.M. Van Bortel and J.A. Staessen, 2010. Diagnosis and treatment of hypertensive disorders during pregnancy. Acta Clin. Belg., 65: 229-236.

Finch, C.A., V. Bellotti, S. Stray, D.A. Lipschitz, J.D. Cook, M.J. Pippard and H.A. Huebers, 1986. Plasma ferritin determination as a diagnostic tool. West J. Med., 145: 657-663.

Flowers, C.A., M. Kuizon, J.L. Beard, B.S. Skikne, M. Covell and J.D. Cook, 1986. A serum ferritin assay for prevalence studies of iron deficiency. American J. Haematol., 23: 141-151.

Gilbert, J.P., M.J. Ryan, B.B. LaMarca, M. Sedeek, S.R. Murphy and J.P. Granger, 2008. Pathophysiology of hypertension during preeclampsia: Linking placental ischemia Am. J. Physiol. Heart Circ. Physiol., 294: 541-550.

Gonul, M., S.K. Cakmak, S. Soylu, A. Kilic and U. Gul, 2010. Serum vitamin B12, folate, ferritin and iron levels in Turkish patients with vitiligo. Indian J. Dermatol. Venereol. Leprol., 76: 448-448.

Hladunewich, M., S.A. Karumanchi and R. Lafayette, 2007. Pathophysiology of the clinical manifestations of preeclampsia. Clin. J. Am. Soc. Nephrol., 2: 543-549.

Howlader, M.Z.H., Y. Kabir, T.A. Khan, M.R. Islam, F. Begum and F.G. Huffman, 2007. Plasma lipid profile, lipid peroxidation and antioxidant status in preeclamptic and uncomplicated pregnancies in Bangladesh. J. Med. Sci., 7: 1276-1282.

Hubel, C.A., A.V. Kozlov, V.E. Kagan, R.W. Evans, S.T. Davidge, M.K. McLaughlin and J.M. Roberts, 1996. Decreased transferrin and increased transferrin saturation in sera of women with preeclampsia: Implications for oxidative stress. Am. J. Obstet. Gynecol., 175: 692-700.

Hubel, C.A., J.M. Roberts, R.N. Taylor, T.J. Musci, G.M. Rodgers and M.K. McLaughlin, 1989. Lipid preoxidation in pregnancy: New perspectives on preeclampsia. Am. J. Obset. Gynecol., 161: 1025-1034.

Hubel, C.A., L.M. Bodnar, A. Many, G. Harger, R.B. Ness and J.M. Roberts, 2004. Nonglycosylated ferritin predominates in the circulation of women with preeclampsia but not intrauterine growth restriction. Clin. Chem., 50: 948-951.

Kaim, A.H., T. Wischer, T. O`Reilly, G. Jundt, J. Frohlich, G.K. von Schulthess and P.R. Allegrini, 2002. MR imaging with ultrasmall superparamagnetic iron oxide particles in experimental soft-tissue infections in rats. Radiol., 225: 808-814.

Kajantie, E., K.L. Thornburg, J.G. Eriksson, C. Osmond and D.J. Barker, 2010. In preeclampsia, the placenta grows slowly along its minor axis. Int. J. Dev. Biol., 54: 469-473.

Madan, J., M. Chen, E. Goodman, J. Davis, W. Allan and O. Dammann, 2010. Maternal obesity, gestational hypertension and preterm delivery. J. Matern. Fetal. Neonatal. Med., 23: 82-88.

Palmsten, K., S.L. Buka and K.B. Michels, 2010. Maternal pregnancy-related hypertension and risk for hypertension in offspring later in life. Obstet. Gynecol., 116: 858-864.

Pepper, J.R., S. Mumby and J.M. Gutteridge, 1994. Sequential oxidative damage and changes in iron-binding and iron-oxidising plasma antioxidants during cardiopulmonary bypass surgery. Free Radic. Res., 21: 377-385.

Ramanathan, J. and K. Bennett, 2003. Pre-eclampsia: Fluids, drugs and anesthetic management. Anesthesiol. Clin. North America, 21: 145-163.

Rayman, M.P., J. Barlis, R.W. Evans, C.W. Redman and L.J. King, 2002. Abnormal iron parameters in the pregnancy syndrome preeclampsia. Am. J. Obstet. Gynecol., 187: 412-418.

Shakour-Shahabi, L., S. Abbasali-Zadeh and N. Rashtchi-Zadeh, 2010. Serum level and antioxidant activity of ceruloplasmin in preeclampsia. Pak. J. Biol. Sci., 13: 621-627.

Sibai, B.M., S. Caritis and J. Hauth, 2003. What we have learned about preeclampsia. Semin. Perinatol., 27: 239-246.

Siddiqui, I.A., A. Jaleel, H.M. Kadri, W.A. Saeed and W. Tamimi, 2010. Iron status parameters in preeclamptic women. Arch. Gynecol. Obstet.,

Vitoratos, N., E. Salamalekis, N. Dalamaga, D. Kassanos and G. Creatsas, 1999. Defective antioxidant mechanisms via changes in serum ceruloplasmin and total iron binding capacity of serum in women with pre-eclampsia. Eur. J. Obstet. Gynecol. Reprod. Biol., 84: 63-67.

Wagner, K.R., F.R. Sharp, T.D. Ardizzone, A. Lu and J.F. Clark, 2003. Heme and iron metabolism: Role in cerebral hemorrhage. J. Cereb. Blood Flow Metab., 23: 629-652.

Yildirim, K., S. Karatay, M.A. Melikoglu, G. Gureser, M. Ugur and K. Senel, 2004. Associations between acute phase reactant levels and disease activity score (DAS28) in patients with rheumatoid arthritis. Ann. Clin. Lab. Sci., 34: 423-426.

Yip, R., 2000. Significance of an abnormally low or high hemoglobin concentration during pregnancy: Special consideration of iron nutrition. Am. J. Clin. Nutr., 72: 272S-279S.