The Relationship Between Maternal Serum Highly Sensitive C-Reactive Protein, Leptin And Hypertensive Disorders Of Pregnancy

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Citation

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Abstract

The relationship between maternal serum highly sensitive C-Reactive protein, leptin and hypertensive disorder of pregnancyBackground: Hypertensive disorders of pregnancy are amongst the most common conditions adversely affecting maternal and fetal prognosis, leading to a noticeably increased morbidity and mortality in the prenatal period. Pre-eclampsia is considered as a multi-system mainly cardiovascular complication during pregnancy, having risk factors in common with metabolic syndrome of which insulin resistance and obesity are a part. C-Reactive protein as a marker of systemic inflammation is shown to be elevated in women with pre-eclampsia; however, whether highly sensitive C-Reactive protein level is correlated with biochemical and clinical parameters in pre-eclampsia remains unknown. Leptin is an adipokine the serum level of which is known to contribute to pre-eclampsia. The current study aims to compare maternal serum leptin and highly sensitive C-Reactive protein in normal and pre-eclamptic pregnant women in their third trimester of pregnancy to elaborate on the contributive role of these proinflammatory factors in the life-threatening pregnancy disorder, pre-eclampsia. Materials and methods: This cross-sectional study which recruited cases of mild pre-eclampsia (N=40), severe pre-eclampsia (N=40) and chronic hypertension (N=40), also included normal pregnant subjects as control (N=60). These cases were the hospitalized patients during their 28th and 42nd weeks of pregnancy at Shiraz medical university affiliated hospitals. The controls consisted of referrals to the out-patient departments. The standard biochemical and hematological parameters were measured. Fasting Venous blood samples were drawn and kept at -20°C. The double sandwich Enzyme Linked Immunosorbent Assay (ELISA) method was applied to measure highly sensitive C-Reactive protein and leptin. ANOVA was used to analyze the data. Results: Leptin levels were significantly increased in severe pre-eclamptic patients compared to controls (p<.001). Alteration in leptin levels in mild pre-eclamptic and chronically hypertensive cases compared to controls was insignificant. Serum concentration of highly sensitive C-Reactive protein did not show an statistically significant change in the four groups.
Conclusion: Determination of serum leptin can be considered as a non-invasive and practical measure in risk prediction of severe pre-edampsia; however, highly sensitive C- Reactive protein assessment for this purpose is not advised. Meanwhile, further well-designed prospective longitudinal studies are needed to carefully assess the contribution of this important factor to pathogenesis of hypertensive disorders of pregnancy. .

INTRODUCTION

Common pregnancy disorders include hypertensive disorders of pregnancy, gestational diabetes and premature birth (1). Maternal health and pregnancy outcome are noticeably affected when pre-eclampsia (PE) or more complicated conditions such as eclampsia or HELLP develop. These syndromes substantially contribute to maternal morbidity and mortality (1).

PE develops in 4-5% of human pregnancies. It is characterized by an increased BP equal to or above 140/90 mmHg in the presence of proteinuria developed after 20 weeks of gestational age. PE can result in eclampsia when convulsion develops or manifests as hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome. Eclampsia and HELLP syndrome are known to be associated with severe complication such as cerebral hemorrhage, renal insufficiency, lung edema and liver hemorrhage (2). The current hypothesis regarding the etiology of PE focuses on mal-adaptation of the immune responses and defective trophoblast invasion. Thus, an excessive maternal inflammatory response, perhaps directed against foreign fetal antigens, results in a chain of events including shallow trophoblast invasion, defective spiral artery remodeling, placental infarction and release of pro-inflammatory

cytokines in the systemic circulation (3,4).

Over recent years, there has been an increasing interest for the detection of pregnancy disorders before the symptoms actually occur. Endothelial dysfunction is accompanied by elevated levels of inflammatory markers. Indeed, such marker levels have been shown to be much higher in women with PE compared to normal pregnant ladies. C-Reactive protein (CRP) is a marker for systemic inflammation (2). This marker is an acute phase reactant which is produced in response to stress, tissue injury and other inflammatory stimuli (5). CRP is mainly synthesized by hepatocytes when the body is confronted with severe tissue injury, microbial infections, systemic autoimmune disease and malignant tumors. The CRP production is regulated by the correspondent gene located on the long arm of chromosome 1, induced at the transcriptional level by interleukin-6 (6). In pregnant patients, there has been an interest in identification of low-grade systemic inflammation to predict or explain pregnancy specific conditions (such as PE and preterm labor). The significance of maternal inflammation in both healthy and diseased pregnancies is yet to be fully explored (5).

Highly sensitive CRP (hsCRP) is a protein measured by an antibody labeled with ELISA and either a fluorescent compound or polystyrene antibodies. Determination of hsCRP has been suggested to be more sensitive than conventional measurement of CRP and provides a better sensitivity in establishing inflammation. Recently, few studies have been conducted to unveil whether there is a correlation between PE and serum hsCRP. The hcCRP has been used to predict the development of coronary artery disease and several attempts have been made based on its implication in inflammatory conditions to determine its predictive value in pathogenesis of PE (2-5). Leptin is also a novel proinflammatory adipocyte-derived factor, operating in the cytokine network by linking the immune and inflammatory processes to the neuroendocine system (1). Leptin is mainly secreted by the white adipose tissue and synthesized in several non-adipose tissue organs including the placenta (7). Leptin plays important roles not only in modulating satiety and energy homeostasis, but also in reproductive biology, ranging from paracrine effect on the placenta to regulation of conseptus development and feral growth (7,8). Serum leptin levels are increased in normal pregnancies; however, they are higher in pre-eclamptics than normal pregnant women. The empirical evidence to support the independent association between serum leptin level and pre-eclampsia is lacking (7). The results of studies conducted so far on leptin and hsCRP correlation with hypertensive disorders of pregnancy, including mild and severe PE and CHTN, are contradictory. The present study was then designed to elucidate the role of serum hsCRP and leptin levels in different types of hypertensive disorders of pregnancy, aiming to establish whether early serum detection of these markers is worth for prediction and timely detection of the aforementioned disorders.

MATERIALS AND METHODS

In this cross-sectional study, we recruited a total number of 180 subjects from whom 120 were the cases of hypertensive disorders of pregnancy and 60 were normal pregnant women as controls (group A). The cases were subdivided into three separate groups comprising 40 cases of mild pre-eclampsia (group B), 40 cases of severe pre-eclampsia (group C) and 40 cases of chronic hypertension (group D). All the cases and controls were evenly matched for parity, BMI and gestational age. Exclusion criteria were gestational diabetes, infectious disease, premature rupture of membrane, any other medical disease, and being in labor phase. The cases were those admitted to Shiraz medical university affiliated hospitals (Hafez and Zeinabieh) during a two year period starting December 2007. The controls were normotensive women in the third trimester of their pregnancy.

They were referrals to CPDs with the gestational age of 28-40 weeks. They were monitored to have normal BP throughout the gestation. The case groups consisted of women admitted to hospitals during 24-40 weeks of gestation suffering hypertensive disorders of pregnancy as specified earlier. Preeclampsia was diagnosed when a blood pressure equal to or higher than 140/90 mmHg, at least at two occasions more than 6 hours apart and a proteinuria with positive dipstick test 1+ of higher than 300 mg 24hr were observed after the 20th week of pregnancy. Pre-eclampsia was classified as severe if diastolic blood pressure increased to at least 110 mmHg, proteinuria with positive dipstick test 2+ or more or higher than 2000 mg per day and the presence of headache, visual disturbances, upper abdominal pain, Oliguria (<30 ml/h), Hyperbilirubinemia, elevated serum creatinin levels (> 1 mg/dl), thrombocytopenia (< 100/000/mm^3), elevated aspartate or alanin aminotransferase levels occured. Chronic hypertension was diagnosed when a blood pressure higher than 140/90 mmHg at least at two occasions more than 6 hours apart and no proteinuria with

negative dip stick test, prior to 20th week of pregnancy occurred.

In all the subjects, fasting venus blood was drawn at am hours upon admission. In preeclamptic groups, blood samples were collected when the patients presented for evaluation before initiation of medical therapy. The controls were enrolled when they referred for their routine third trimester prenatal care at OPDs. The bloods of all the subjects were drawn from the ante-cubital vein in the lateral recumbent position after an overnight fasting without labor pain. Right after collecting the sample, the serum was separated by centrifugation and stored at -20 degrees centigrade till use. After re-warming the serum to room temperature, the serum levels of leptin and hsCRP were determined by specific ELISA. One way analysis of variance (ANOVA) with dunnett post hoc was applied to compare the data obtained from the four groups. Statistical analysis was performed using SPSS, Version 11.0.

RESULT

Of the total 180 subjects who were enrolled, 60 normal pregnant women were controls and the remaining were pregnancy hypertensive disorder cases. The demographic particulars of the groups are summarized in Table 1.

There were 54 primigravidas and 66 multigravidas in the study group versus 28 primigravidas and 32 multigravidas in the control group. Maternal age was 28.39 6.18 years (ranging 15-43 years) in the study group and 25.96 5.3 (ranging 15-34 years), 29.64 7.27 (ranging 19-41 years), 28.47 5.13 (ranging 19-37 years), and 30.94 6.68 (ranging 21.43 years) in the control, mild PE, severe PE and CHTN groups, respectively.

Gestational age was 34 3.4 weeks (ranging 26-40 weeks) in all the groups. Gestational age was 34 4.3 weeks (ranging 30-38 weeks), 34.76 3.8 weeks (ranging 30-38.66 weeks), 32.71 3.4 weeks (ranging 26-37 weeks), and 34.68 3.8 weeks (ranging 26-40 weeks) in the control, mild PE, Severe PE and CHTN groups, respectively.

The mean values for leptin were different in the four groups (P<0.0001). Leptin level was 28.30 19.55, 55.9 37.38, 67.19 34.43 and 55.48 38.08(pg/ml) in the control group, mild PE, severe PE and CHTN group, respectively. Leptin was significantly higher in the severe PE group compared to controls (P <0.001). This increase in mild PE and CHTN groups was insignificant. The mean SEM values for serum concentration of hsCRP across all the groups were not significantly different as were 3.11 1.31, 3.11 0.97, 3.05 1.33 and 2.64 1.78(pg/ml) in mild PE, severe PE, CHTN and control groups, respectively (P=0.256). (Table 2)

Figure 1

Table 1: Demographic data by enrollment date

	Controls	Mild PE	Severe PE	CHTN
Age(years)	25.96±5.30	29.69±7.27	32.71±3.4	30.94±6.68
GA (weeks)	34±4.3	34.76±3.9	32.71±3.4	34.6±3.8

GA: Gestational Age PE: Pre-edampsia CHTN: chronic Hypertension

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Figure 2

Table 2: Levels (pg/ml) of leptin and hsCRP across all the study groups

Type of HTN	Mild PE mean±SEM	Severe PE mean±SEM	Chronic HTN mean±SEM	Control mean±SEM	P.Value
Leptin	55.91±37.38	67.19±34.43	55.49±38.08	28.30±19.55	<0.001*
Hs CRP	3.12±1.31	3.43±0.97	3.05±1.34	2.64±1.78	NS

hsCRP: highly Sensitive C-Reactive protein

SEM: Standard Error of Mean

CHTN: Hypertension

NS: Non Significant

* P<0.001 (compared between Severe PE and control group)

DISCUSSION

Since maternal health and pregnancy outcome is drastically affected by hypertensive disorders of pregnancy, early detection and timely interventions to minimize the harm should be to our utmost attention and interest. Biomarkers such as hsCRP and leptin are suspected elements contributing to the pathogenesis of PE, and this is based on the shared etiopathophysiological role of such markers and inflammation. Since early identification of patients with increased risk for PE is one of the important goals in obstetrics, several studies have attempted to elaborate on the correlation between such inflammatory markers and presence of PE (2).

Endothelial dysfunction leads to elevated CRP and hsCRP is

shown to be more sensitive in establishing inflammation. Leptin level is also seen to be increased in systemic inflammatory processes. Similar to the studies on the relationship among these markers and PE as well as normal gestation, Belo. et al conducted a longitudinal study , using a highly sensitive CRP Immunoassay, no special trend for hsCRP over gestation was identified.However, H.Picklesimer et al showed that few women (17%) demonstrated a progressive increase in hsCRP throughout the gestation,

whereas 30% had the serum hsCRP decreased as gestational age increased. In this study, half of the women (50%) experienced fluctuating hsCRP in their normal course of pregnancy. The initial investigations which applied older assays with narrower discriminatory ranges described a progressive increase in CRP level with advancing the gestational age.

Leptin as a novel pro-inflammatory adipocyte-derived factor not only links the immune and inflammatory processes to neuroendocrine system but also it affects the hypothalamo-pituitary–gonadal axis, regulating gonadotropin-releasing hormone and luteinising hormone secretion, and appears to be a permissive factor in the onset of the puberty (10,11).It also plays an important role not only in modulating satiety related mechanisms but also in reproductive biology (20). Maternal levels arise from adipose stores and perhaps the placenta. Leptin is also shown to have a correlation with hypertensive disorders of pregnancy;however, these correlation trends are not in agreement across different studies we reviewed in literature. In the current study, we selected our hypertensive subjects from pregnant women in their third trimester of pregnancy and compared both their hsCRP and leptin serum level to those of normal pregnant cases recruited as controls. They all were matched for BMI. We divided the patients according to systolic and diastolic BP, epigastric pain, blurred vision, abnormal Liver Function Test and Oligourea, through which the patients were categorized into mild PE, severe PE and CHTN groups to be compared with controls.

Maternal serum hsCRP and leptin were inspected. Leptin was increased in PE groups and more significantly in the severe preeclamptics ($P<0.001$). The observed increase in the concentration of leptin in the present study further signifies the abnormal cytokine responses in severe PE and its possible involvement in the pathogenesis of this maternal syndrome. There is cumulative evidence that PE is a systemic inflammatory disease (21-39). In some previously done studies, a higher concentration of leptin has been reported during preeclampsia (4,8,9,19,22,44). Some authors believe that hyperleptinemia is a hallmark of mammalian pregnancy although both the role of leptin and the mechanisms known to be regulating its function remain specific in each subject (21-29, 43-45). Acromite et al suggest that serum leptin level does not add to the prediction of PE after measuring BMI of preeclamptic women (7,38). Being aware that serum leptin is closely correlated with serum insulin and BMI (44), we excluded women with diabetes from the study and meticulously adjusted BMI across groups.

In the current investigation, although the serum level of hsCRP showed to be elevated in hypertensive mothers, this increase was not statistically significant. The relationship between the levels of CRP and preeclampsia has already been studied. In some works, a higher concentration of CRP or hsCRP was reported during preeclampsia (2,43). In contrast to those studies which evaluated this relationship in one hypertensive condition (8,9,11-17,20,35,43,44), we examined different types of pregnancy hypertensive disorders, i.e. mild, severe PE and CHTN. Other studies have mainly considered CRP while we examined hsCRP as a more sensitive measure. To the best of our knowledge, this is the first study of a kind evaluating leptin and hsCRP in four separate groups including mild and severe PE, CHTN, and normal pregnancies.

Although normal pregnancy is associated with increased pro-inflammatory markers, it has been suggested that the cause of serum hsCRP elevation in pre-eclamptic patients might be a result of reduced plasma volume in these patients (2). BMI has a significant effect on elevation of CRP. This confounder as well as other causes contributing to the elevation of CRP such as smoking and presence of sexually transmitted diseases was taken into account in our study by adjusting the cases and controls by excluding the afflicted cases from enrollment. The serum levels of leptin and hsCRP in pregnant women with chronic HTN were slightly elevated in this study rather than previous investigations; however, there was still no significant change compared to the normotensive group.

CONCLUSION

Considering the relatively small number of patients enrolled in the current study, care must be taken in extrapolating the present findings to all patients with preclampsia and a larger

patient cohort may provide by far more insightful data. Determination of serum leptin level can be considered as a practical and non-invasive method for risk prediction of severe preeclampsia; however, there is a lack of evidence to support hsCRP level measurement for the some purposes.

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