

Leptin as an early pregnancy marker for pregnancy induced hypertension

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Objectives: To study the role of serum leptin as an early pregnancy marker for pre-eclampsia.

Methodology: A total of 1300 patients were selected for the study. 79 (6%) were lost to follow-up. Out of 1221 patients, 134 (10.9%) patients developed pre-eclampsia, 1087 (89.1%) remained normotensive. Patients included in the study had confirmed intrauterine pregnancy with ultrasound, either normotensive or $\geq 140/90$ mmHg, 24-hour urine proteinuria >300 mg or ratio of protein to creatinine >30 mg/mmol. Patients with pre-eclampsia in the previous pregnancy and twin pregnancy were not included in the study. Blood samples were taken at the gestational age of 16 weeks and serum leptin level was measured by

ELISA.

Result: Mean age of the pre-eclampsia group was 27.54 ± 4.50 years and for the normal pregnancy group was 27.65 ± 4.62 years. Mean leptin value in the pre-eclampsia group was 64.38 ± 12.77 ng/ml while in normal group it was 63.64 ± 33.58 ng/ml ($p > 0.05$). Cesarean rate was higher in the pre-eclampsia group (14.9%) as compared to normal pregnancy group (8.9%).

Conclusion: Serum leptin levels were found to be similar in the patients with preeclampsia and normotensive pregnant women. (Rawal Med J 201;41:342-345)

Keywords: Biomarkers, leptin, pre-eclampsia, proteinuria.

INTRODUCTION

Approximate 5-10% of pregnant women have hypertension; out of which 2% is due to preeclampsia.¹ Gestational hypertension before 34 weeks has been associated with increased maternal and perinatal mortality.² Pregnancy-induced hypertension (PIH) is closely associated with placental dysfunction, oxidative stress, inflammatory response and endothelial dysfunction.³ Leptin is an adipose-derived hormone and is found in higher concentration in obese women. Several studies have shown that level of leptin increases during pregnancy.^{4,5} Leptin has been found in higher concentration in women with pre-eclampsia as compared to normotensive pregnant women.^{6,7} On the other hand, some studies showed no change or decreased circulating leptin levels in patients with PIH.⁸ Leptin can serve as one of the early markers to identify pregnant women who might develop PIH. The early prediction will help in tailoring appropriate management of patients who are at a higher risk of developing PIH. The objective of our study was to determine the role of serum leptin level as an early

pregnancy marker for pre-eclampsia. Secondary objection was to compare BMI, age of mother, weight of baby and cesarean rate between pre-eclampsia and normotensive pregnancy group.

METHODOLOGY

We carried out this study at Shifa International Hospital, Islamabad, Pakistan from June 2012 to July 2015. Written informed consent was taken from all the participants. Pre-eclampsia was defined as systolic blood pressure of 140mmHg and/or diastolic blood pressure of 90mmHg or higher measured on at least two occasions over several hours, combined with proteinuria >300 mg total protein in a 24-h urine collection, or ratio of protein to creatinine >30 mg/mmol. With evidence of end organ damage it was labeled as severe pre-eclampsia. However, in our study, no differentiation was made between mild or severe pre-eclampsia. Eclampsia is a convulsive condition associated with pre-eclampsia.

Before measuring blood pressure patient arm was supported at the level of the heart.⁹ The participants

were advised to come for antenatal visits every 4 weeks. The frequency of the visits was increased as the participants approached the delivery date. Patients who already had pre-eclampsia in the previous pregnancy, twin pregnancy, and evidence of any previous medical disease were not included in the study. Convenience sampling was done to select the participants.

Blood samples were taken at the gestational age of 16 weeks and serum leptin concentrations were measured by enzyme-linked immunosorbent assay (ELISA; Human Leptin (LEP) ELISA KIT, CUSABIO). Statistical analysis was done by using SPSS 21. Independent t-test was applied to see if there was any significant difference in demographic profile and leptin values between the two groups.

RESULTS

A total of 1300 participants were selected for the study. Out of 1300; 79 (6%) were lost to follow up. Out of the remaining 1221 participants, 134(10.9%) developed pre-eclampsia, while 1087(89.1%) patients remained normotensive. The mean age of the pre-eclampsia group was 27.54 ± 4.50 years while that for the normotensive pregnancy group was 27.65 ± 4.62 years (Table 1). The mean leptin value in the pre-eclampsia group was found to be 64.38 ± 12.77 while the mean value in normotensive pregnancy group was found to be 63.64 ± 33.58 . The Caesarean rate was higher in the pre-eclampsia group as compared to normotensive pregnancy group.

Table 1. Demographic profile in pre-eclampsia and normal pregnancy group.

Variables	Pre-eclampsia Group	Normal Pregnancy Group
Age of mother (years)	27.54 ± 4.50	27.65 ± 4.62
Body Mass Index BMI (kg/m ²)	25.62 ± 7.31	25.8 ± 6.10
Weight of the baby (kg)	2.990 ± 0.294	2.995 ± 0.290
Cesarean_Rate_(n/%)	20(14.9%)	97(8.9%)

Independent t-test was applied to see if there was any significant difference in demographic profile and leptin values showed no statistically significant difference between the two groups ($p > 0.05$).

DISCUSSION

Leptin is a new placenta-derived human hormone released during pregnancy exerting some of its physiological roles.¹⁰ It also has pathophysiological significance in pregnancy-related disorders that are debatable in literature. The present study showed that plasma leptin levels changed during normal pregnant group and pre-eclampsia group. It has been proposed that leptin induces oxidative stress in cultured human endothelial cells.¹¹ Disequilibria between oxidation and antioxidation mechanisms involving neutrophils could lead to the aggression of endothelium, which is observed in pre-eclampsia patients.¹² Results of our study were showing not much difference in plasma leptin levels between normal pregnant group and pre-eclampsia group.

In present study plasma, leptin levels were 64.38 ± 12.77 ng/ml in the pre-eclampsia group while 63.64 ± 33.58 ng/ml in the normal pregnant group. Matrinez Abundis et al.¹³ study included 26 patients with pre-eclampsia and 32 normotensive pregnant patients while Sharma A et al.¹⁴ study included 54 pre-eclampsia and 50 normotensive pregnant patients as compared to our study, which included total 1221 participants. Out of these, 10.9% developed pre-eclampsia. Our results are similar to above studies. In contrast, another study¹⁵ showed that leptin levels were significantly higher in pre-eclampsia group as compared to normal group (Table 2). In another study from Pakistan concluded that serum leptin levels were significantly higher in severe pre-eclampsia as compared to mild pre-eclampsia.⁸

Table 2. Comparison between two studies in terms of Leptin values.

Current Study Results		Iftikhar et al. Study Results (ref 8)	
Serum leptin in pre-eclampsia group (ng/ml) n=134	Serum leptin in normotensive pregnant group (ng/ml) n=1087	Serum leptin in pre-eclampsia group (ng/ml) n= 45	Serum leptin in normotensive pregnant group (ng/ml) n=45
64.38 ± 12.77	63.64 ± 33.58	62.1 ± 23.8	26.8 ± 6.47

Body mass index (BMI) of mothers seen in our study was 25.62 ± 7.31 kg/m² in preeclampsia group,

and 25.8 ± 6.10 kg/m² compared to BMI documented by Sharma A et al,¹⁴ 23.1 ± 1.9 kg/m² (mild pre-eclampsia) 22.5 ± 1.3 kg/m² (severe preeclampsia), 22.7 ± 2.8 kg/m² (normotensive pregnancy). Comparison between variables like BMI of the mother, weight of baby after birth, cesarean rates and age of mother of our study with Sharma A et al. are shown in Table 3.

Table 3. Comparison of BMI, Age of Mother, Weight of Baby and Cesarean Rate in preeclampsia pregnancy between two studies.

Variables Compared	Current Study (n=134)	Sharma et al. Study (n=54)
BMI (kg/m ²)	25.62±7.31	23.1±1.9
Weight of baby (kg)	2.99±0.29	2.5±0.5
Cesarean Rates (%)	14.9%	14 %
Age of mother (years)	27.54±4.50	27.9±4.53

In our study, Caesarean rate was higher in the pre-eclampsia group as compared to normotensive pregnancy group. According to another study, pregnant women with the history of pre-eclampsia were 2.5 times more likely to have caesarean delivery ($p < 0.02$) while pregnant women with severe pre-eclampsia were 3.3 more likely to progress to caesarean delivery than those with mild pre-eclampsia ($p < 0.01$).¹⁶ The Caesarean rate was found to be 68.2% in a prospective cohort study of 500 pregnant women with severe preeclampsia.¹⁰ Higher rate can be explained because of the preference of the obstetrician to perform a caesarean section rather than the induction of labor for preeclampsia.¹¹ The elevated risk of fetal and maternal morbidity and mortality associated with pre-eclampsia is another reason of the high frequency of emergency caesarean section in this group.

A cohort study concluded that leptin value might act as the risk marker for predicting caesarean rate. This can be explained because of the association of high leptin value with the severity of pre-eclampsia.¹² Placental production of leptin is enhanced in response to hypoxia supports the idea that placental hypoxia or decreased perfusion in severe pre-eclampsia is reflected by raised plasma leptin levels. Since induction of many trophoblastic placental genes during hypoxia triggers placental production

of leptin may indicate hypoxic reactions of trophoblasts in pre-eclampsia.¹⁷

In parallel to human chorionic gonadotropin (hCG) secretion in pregnancy, placental leptin release is also increased irrespective of hypoxia. Hiroko et al.¹⁸ showed no significant differences in plasma leptin levels between the mild pre-eclampsia group and its control group (38.2 ± 4.8 ng/mL vs 33.8 ± 3.7 ng/mL). On the other hand, plasma leptin levels in the severe pre-eclampsia group (101.5 ± 14.9 ng/mL) were approximately 3-fold higher than those in its control group (control 37.8 ± 5.0 ng/mL) ($P < 0.0001$). Plasma leptin levels in the severe pre-eclampsia group were also significantly higher than those in the mild pre-eclampsia group ($P < 0.0001$).

The functional importance of raised placental leptin production in pre-eclampsia is not clear. Fetal growth in severe pre-eclampsia might be affected by satiety effect of raised plasma leptin levels. Pregnant ladies with increased plasma leptin levels have regularly normal appetite. Therefore, it seems that there is some resistance to the effect of leptin in pregnant ladies. Leptin application enhances temperature of the body and metabolic rate during pregnancy.¹⁷ Since leptin increases sympathetic outflow proposing that norepinephrine turnover to the brown adipose tissue is also enhanced by this placental hormone.¹⁹ There is also a raised sympathetic activity in pre-eclampsia patients correlating with levels of leptin.²⁰ Moreover, over one-week infusion with leptin increased arterial pressure signifying the probable input of raised plasma leptin in the maturity of hypertension in severe pre-eclampsia.²¹ However, controversy regarding pre-eclampsia and leptin levels during pregnancy still persists²² and further studies are required to confirm this probability.

CONCLUSION

Serum leptin levels were found to be similar in the patients with preeclampsia and normotensive pregnant women. However, controversy regarding pre-eclampsia and leptin levels during pregnancy still persists. Further studies are required to establish the role of leptin as an early pregnancy marker for pregnancy induced hypertension.

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