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Serum Leptin in Preeclampsia

Dr. Uma Debbarma[1], Dr. Ng Arunkumar Singh[1], Dr. Sangeeta Naorem[1], Dr. M. Amuba Singh[1], Dr. Arabil Reang[2], Dr. M. Rameswar Singh[3]

[1] *(Department of Biochemistry, RIMS, Imphal)*
[2] *(Department of Respiratory Medicine, RIMS, Imphal)*
[3] *(Department of Obstetrics and Gynaecology, RIMS, Imphal)*
Corresponding Author: Dr. Uma Debbarma

Abstract: ***Background:*** *Preeclampsia is a leading cause of maternal mortality in both developed and developing countries. Apart from a number of biomarkers for diagnosis of preeclampsia, leptin has recently been shown to be associated with the disease. Leptin is an adipose tissue derived protein. It helps in regulating energy balance by inhibiting hunger. Increased leptin levels has been suggested to be an independent risk factor for preeclampsia. The aim of this study was to determine serum leptin levels in preeclamptic women and to compare the findings between cases and controls.*

Materials and methods: *A case-control study was conducted in the Department of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, RIMS, Imphal. 30 preeclamptic women as cases and 30 pregnant women as controls were selected to form the study group. Serum leptin was estimated by leptin ELISA kit.*

Result: *The level of serum leptin was more in all the cases compared to the controls (11.64 ± 6.32 ng/ml and 4.85±2.46 ng/ml respectively)*

Conclusion: *This study confirms the association of high serum leptin levels with preeclampsia. It may be concluded that serum leptin can be used as a diagnostic marker in preeclampsia in addition to other conventional biomarkers. Further studies are required with larger sample size to evaluate the pathophysiology of leptin in preeclampsia*

Key words: *Leptin, preeclampsia, ELISA*

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I. Introduction

Preeclampsia (PE), a syndrome of pregnant women, is one of the leading cause of maternal and foetal morbidity and mortality.[1] It is a hypertensive disorder which develops in late pregnancy and is usually associated with placental hypoxia and dysfunction.[2] In PE, there is development of hypertension and proteinuria after 20 weeks of gestation in previously normotensive, non proteinuric pregnant women.[3] The syndrome is defined as a blood pressure of >140/90mmHg on two separate occasions, 4 hours apart or a single recording of a diastolic blood pressure of 110mmHg in association with proteinuria ≥1+ on dipstick testing.[4] Pre-eclamptic women are at increased risk for developing coagulation defects, pulmonary edema, cerebral hemorrhage, blindness, seizures, hepatic and/or renal failure and cardiovascular disease later in life while infants born to pre-eclamptic women are prone to prematurity and more likely to be small for gestational age.[5, 6] The cause is not yet clear. It includes immunological, genetic, environmental and placental abnormality. The final result of all these is endothelial dysfunction, characteristic of preeclampsia.[7] The pathogenesis of PE is thought to involve three steps: abnormal remodeling of the placental bed vasculature, placental ischemia, and endothelial cell dysfunction.[8] Abnormal vascular growth and impaired endothelial function in the placenta are associated with conditions of pregnancy such as PE, which results from inadequate trophoblast invasion of maternal spiral arteries during early gestation.[9] Preeclampsia is characterized by intense vasospasm affecting mainly the renal, uterine and cerebral vasculature that results due to increased vasopressor substance like angiotensin II, thromboxane A2, endothelin-I and a decrease in vasodilator substance such as nitric oxide and prostacyclin due to endothelial cell dysfunction.[10] Incidence of preeclampsia is about 5-7% of all pregnancies.[3]In India it is around 10% and around 2-5% in US.[11]According to the World Health Organization (WHO), its incidence is seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%).[12] It continues to be a leading cause of maternal mortality in both developed and developing countries.[13]As the only treatment for preeclampsia is delivery of the placenta, which is often preterm, there is a need to identify biomarkers for early prediction or to identify women with severe subtypes who require different clinical management.[14,15] Preeclampsia is very difficult to detect early and treat and hence complications usually result. Hypertension and proteinuria, which are

symptoms of preeclampsia form the diagnostic markers. The discovery of new serum markers might be helpful in identifying subjects at increased risk of developing preeclampsia. There are many biological molecules/markers implicated in preeclampsia including the adipokines, leptin and adiponectin. Leptin is a hormone that plays an important role in several physiological processes including the regulation of endocrine function, immune function, inflammation, reproduction, and angiogenesis.[16] In normal pregnancy, placental leptin expression is increased compared to non-pregnant women and suggested to support implantation, human chorionic gonadotrophin production, placental growth, amino acid uptake, and mitogenesis.[17] During pregnancy circulating maternal concentrations of leptin increase to maximum values in the second trimester, plateau in the third trimester and fall to below pre-pregnancy concentrations around birth.[18]Trophoblasts are responsible for the significantly increased plasma concentrations of leptin during the first two trimesters of normal pregnancies.[19, 20] In PE, the maternal plasma leptin level is possibly increased because of augmented placental production of hormones under hypoxic condition.[2] There is one hypothesis that leptin is increased as a result of placental stress so as to increase nutrient delivery to the fetus.[21] Although the precise mechanism of disorder remains elusive, it is usually associated with placental hypoxia and dysfunction, but according to new emerging studies, it is a complex polygenetic trait which involves maternal and foetal genes as well as environmental factors.[22]

Leptin is a 16 kilodalton (Kda) nonglycosylated polypeptide product of obese (Ob) gene, mainly produced and secreted by fat cells in proportion to fat mass.[23] The name leptin is derived from the Greek word "leptos" meaning thin because it leads to an increase in energy expenditure and acts on satiety signals in the hypothalamus reducing food intake.[24,25] It modulates pancreatic β-cell function resulting in improved peripheral insulin sensitivity.[26] Leptin contains 167 amino acids and circulates in blood at low levels (5-15ng/ml) in lean subjects.[27]The main source of leptin is adipose tissue but during pregnancy, leptin is also produced by placenta.[28] Circulating leptin level reflects adipose tissue size and also change with nutritional state.[29] Furthermore, it is considered as a pleiotropic hormone that regulates not only bodyweight but many other functions, including vascular function, bone and cartilage growth, immune system and systemic inflammatory response as well as the normal physiology of the reproductive system.[30,31] This anti-obesity hormone mainly acts by binding to specific central and peripheral receptorsin hypothalamus, adipose tissue, liver and pancreatic beta cells. It stimulates a negative energy balance by increasing energy expenditure and reducing food intake thus controlling body weight.[32] Leptin mediates its effects by binding to leptin receptors (LepRs) expressed in the brain and peripheral tissues.[29] Different variants of LepR have been described, but the long isoform of LepR (LepRb) is primarily responsible for leptin signalling. LepRb is strongly expressed in specific nuclei of the hypothalamus, a region of the brain that is involved in the control of appetite, and there it regulates energy homoeostasis and neuroendocrine function, among other functions.[33] It is regulated by 17 β-estradiol (E2) by both genomic and nongenomic regulatory pathways through nuclear estrogen receptor α and by an unknown membrane bound receptor respectively.[21] During pregnancy, E2 levels increase as a result of placental production that is of help in maintaining pregnancy and contributing to leptin production.[34]Maternal circulating leptin concentration is significantly higher in pregnancies complicated by PE than gestational matched controls.[35] In a longitudinal study by few workers, it has been shown that biochemical maternal hyperleptinaemia predates the development of PE and the clinical onset of which is associated with further rise in maternal leptin concentration.[36]The physiological role of leptin during pregnancy remains enigmatic. Pregnancy is a hypermetabolic state with an increase in maternal body fat and weight and an alteration in neuroendocrine parameters.[37] An increasing number of biochemical agents were evaluated as markers for predicting preeclampsia. None of them has been proved to be of clinical value yet. All the above mentioned studies were done mostly outside India and do not obviate the need for establishing normal physiology and pathophysiology in our population as geographic, racial and ethnic factors significantly affect the dynamics of every process in the normal and diseased human. Only a few studies on leptin in preeclampsia are on record globally and in northeast India no study has been done till now. Thus, this study is planned to determine the serum leptin levels in preeclamptic women and to compare the findings between cases and controls.

II. Materials And Methods

The study population consisted of 30 patients who were diagnosed as preeclampsia and admitted in antenatal ward, Regional Institute of Medical Sciences, Imphal. The control group consisted of 30 normal pregnant women. Prior to the commencement of the study, approval from the Research Ethics Board, RIMS, Imphal was obtained. Informed consent was taken from the participants before the study.

Study design: Case control study

Study location: The study was carried out in the Department of Biochemistry, RIMS, Imphal, in collaboration with the Department of Obstetrics and Gynaecology, RIMS, Imphal, Manipur, India.

Study duration: The study was carried out for a period of 24 months with effect from October 2018 to September 2020.

Sample size: 30 cases and 30 controls.

Inclusion criteria:

1. Patients considered as cases were those aged 18 yrs and above, who were diagnosed cases of preeclampsia admitted in antenatal ward and who were willing to participate in the study voluntarily.
2. Participants considered as controls were those with no proteinuria and were normotensive.

Exclusion criteria:

Patients having concurrent illness which might influence serum leptin level independently were excluded while selecting study group like,

- Chronic hypertension
- Diabetes mellitus
- Multiple pregnancy
- Renal disease
- Urinary tract infection
- Gestational diabetes mellitus
- Smokers
- Alcohol consumers
- Pregnant women who had any medical/surgical intervention.

Working definition:

Preeclampsia cases were diagnosed as defined by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.It was defined as a BP of >140 mmHg systolic or >90 mmHg diastolic in a woman, who was normotensive before 20 weeks gestation, accompanied by proteinuria (0.3 g/24 h, which correlates with ≥30 mg/dl or ≥1+ reading on dipstick in a random urine determination with no evidence of urinary tract infection).[3]

Procedure methodology:

Data were collected in pretested structured performa through interview. Subjects were interviewed after taking informed consent. Eligible participants were selected consecutively. To estimate the serum leptin level of each participant, 5 ml of venous blood was collected by venipuncture from antecubital vein. The blood collected in the plain vial was centrifuged for 10 minutes at 2000-3000 rpm within 30 minutes of collection. The serum was then collected in aliquots and stored immediately at <-20 ^{o}C till the analysis. Demographic profiles, systolic and diastolic blood pressure, weight, height and body mass index (BMI) were measured once at the beginning of the study. Leptin was measured by Human Leptin (LEP) ELISA as described by Porstmann T and Kiessig ST.[57] Cat No: K12-1560 manufactured by KinesisDx, 1179 W 29th Street, Los Angeles, CA 90007, USA.

Statistical analysis:

The data entry and analysis were performed using SPSS version 21.0 for windows (IBM Inc.,Armonk, NY, USA). Descriptive statistics like frequency, mean, proportion were used. Chi-square test, independent sample t test was applied whenever necessary. All comparisons were two-sided and p value <0.05 was taken as significant.

III. Results

The study was carried out in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences, Imphal. The study included 30 cases of preeclampsia and 30 pregnant women as controls. The results of this study are being depicted as follows:

Table no 1: Age-wise distribution of cases and controls (N=60)

Age in years	Cases n (%)	Controls n (%)	p- value
18-29 ≥30	14(46.7) 16(53.3)	16(53.3) 14(46.7)	0.6
Mean ± SD	29.93 ± 5.96	29.07 ± 3.91	0.5

Table 1 shows the number and percentage of cases and controls according to their age group. The two groups were divided into two categories according to their age. Maximum (53.3%) of the cases belong to the age group ≥30 years and maximum of the controls belong to the age group 18-29 (53.3%) years. Mean ± SD of the

age of cases and controls were 29.93 ± 5.96 years and 29.07 ±3.91 years respectively with p-value 0.5. So, both the groups were comparable with respect to age.

Table no 2: Distribution of cases and controls by religion (N=60)

Religion	Cases n (%)	Controls n (%)	p-value
Hindu Muslim Christian	19 (50.0) 8 (61.5) 3 (33.3)	19 (50.0) 5 (38.5) 6 (66.7)	0.42

In table 2, the number of cases and controls were presented according to the religion to which they belong. Maximum of the cases and controls belonged to Hindu religion (50.0%) with p-value 0.42. So both the cases and controls are comparable with respect to religion.

Table no 3: Distribution of cases and controls as per area of inhabitance (N=60)

Area of inhabitance	Cases n (%)	Controls n (%)	p-value
Rural Urban	12 (52.2) 18 (48.6)	11 (47.8) 19 (51.4)	0.7

In table 3, the number and percentage of cases and controls were presented according to their address or their area of inhabitance. 52.2% of the cases and 47.8% of the controls were from rural area. Whereas, 48.6% of the cases and 51.4% of the controls were from urban area. Both the cases and controls were comparable (p-value 0.7).

Table no. 4: Comparison between blood pressure among cases and controls (N=60)

Blood pressure	Cases Mean (±SD)	Controls Mean (±SD)	p-value
Systolic blood pressure (mmHg)	159.10 ± 16.32	115.73±5..47	0.000
Diastolic blood pressure (mmHg)	104.77±8.82	76.53 ± 3.96	0.000

In table 4, the mean systolic blood pressure in cases was 159.10 ± 16.32 mmHg whereas in controls it was 115.73±5.47 mmHg. Mean diastolic blood pressure in cases was 104.77±8.82 mmHg whereas in controls it was found to be 76.53±3.96 mmHg. The blood pressure was significantly higher in cases compared to controls (p-value 0.000).

Table no. 5: Comparison of body mass index among cases and controls (N=60)

Variable	Cases Mean (±SD)	Controls Mean (±SD)	p-value
Body mass index (BMI)	26.96 ± 3.52	21.37± 2.99	0.000

Table 5 shows the body mass index in cases and controls. The mean body mass index in cases and controls were 26.96 ± 3.52 kg/m^2 and 21.37 ± 2.99 kg/m^2 respectively. It was found to be significantly higher in cases compared to controls (p-value 0.000).

Table no. 6: Serum leptin levels in cases and controls (N=60)

Variable	Cases Mean ± SD	Controls Mean ± SD	p-value
Leptin (ng/ml)	11.64 ± 6.32	4.85±2.46	0.000

Table 6 shows the level of serum leptin in cases and controls. The mean serum leptin level in cases was 11.64 ± 6.32 ng/ml and in control it was 4.85±2.46 ng/ml. The level was significantly higher in cases than in controls with a p value 0.000.

Table no. 7: Correlation between Systolic blood pressure and serum leptin in cases and controls (N=60)

Variables		Cases (30)	Controls (30)
Systolic blood pressure	Pearson correlation p-value	0.05 0.77	-0.02 0.88

In table 7, the correlation was calculated between systolic blood pressure and serum leptin levels in cases and controls. A positive correlation (r = 0.05) was found in cases but not found to be statistically significant (p-value 0.77). In controls, a negative correlation was found between systolic blood pressure and serum leptin level.

Table no. 8: Correlation between diastolic blood pressure and serum leptin in cases and controls (N=60)

Variables		Cases (30)	Controls (30)
Diastolic blood pressure	Pearson correlation	0.20	0.02
	p-value	0.27	0.89

In table 8, when correlation was calculated between diastolic blood pressure and serum leptin levels in cases, a strong positive correlation was found with r value 0.20.
In controls, a weak positive correlation was found between diastolic blood pressure and serum leptin levels and it was statistically not significant (p-value 0.89).

Table no. 9: Correlation between body mass index and serum leptin in cases and controls (N=60)

Variables		Cases (30)	Controls (30)
Body mass index	Pearson correlation	0.64	0.03
	p-value	0.000	0.85

Table 9 showing a strong positive correlation between body mass index and leptin levels in cases. The findings were found to be statistically significant with r value 0.64 and p value 0.000. In controls, a weak positive correlation was found and it was found to be statistically not significant (p-value 0.85).

IV. Discussion

In the present study, an attempt has been made to estimate serum leptin level in preeclamptic patients and normal pregnant women. And also, to compare the findings between cases and controls and to find out correlation between the leptin level and pregnancy outcome.

In this study the maximum number of preeclamptic cases were in the age group of 30 years and above. Total number of patients in this age group was 16. This was followed by age group of 18-29 years with 14 cases. This finding was supported by the study conducted by Chan TF et al.[58] They found out that the incidence of preeclampsia and eclampsia in 20-24 years age group was the lowest. The relative risk of preeclampsia increased incrementally with the increase in age, as follows: aged <20 years, 1.02 fold; 25-29 years, 1.35 fold; 30-34 years, 1.79 fold; 35-39 years, 2.99 fold and ≥ 40 years, 5.13 fold. They concluded that advanced maternal age was associated with increased risk of preeclampsia.

The relationship between religion and incidence of preeclampsia was analysed and it was found that among the 30 cases, 19 patients belonged to the Hindu religion followed by 8 Muslim and 3 Christian. But this variation might simply be the result of the demographic variation according to religion among the local population.

In our study, 52.2% of the cases were from rural area. This could be due to the fact that the study had been undertaken in RIMS hospital which is a government hospital and caters to the need of all the poor people who constitute majority of the rural population. Another reason could be that the patients were being referred from primary health centres to a tertiary care centre for proper management. Similar study was conducted by Middendorp DV et al.[59]

Systolic blood pressure and diastolic blood pressure were significantly higher among the cases compared to the controls. The mean systolic and diastolic blood pressure in the cases were 159.10 ± 16.32 mmHg and 104.77±8.82 respectively. The findings of the study is in agreement with the study conducted by Tabassum H et al[60] among the Riyadh population. The mean systolic and diastolic blood pressure in their study among the cases were 167 mmHg and 98 mmHg respectively. In the present study when these variables were compared with serum leptin levels, it was found to be positively correlated.

In the present study the mean BMI of cases and controls were 26.96 ± 3.52 kg/m^2 and 21.37± 2.99 kg/m^2 respectively. when correlation was done, significant positive correlation was observed between serum leptin and BMI in preeclamptics (r= 0.64, p<0.01). These finding were in agreement with the study conducted by Kharb S et al[41] who opined that this might be due to weight gain in pregnancy. Leptin levels in preeclamptics

were independently related to maternal body mass index (BMI) in few studies. However, it might be appreciated that weight gain during pregnancy is solely not due to fat deposition as suggested by Highman TJ et al.[61]

It had been suggested that BMI was responsible for the increase in maternal leptin levels in preeclamptic women in several studies since adipose tissue is a source of leptin.[56] In pregnancy however, the body mass index does not accurately reflect fat accumulation because the fetus, the placenta, the amniotic fluid, increase plasma volume and available degree of extravascular fluid accumulation all increase maternal weight.[62] They also explained that hypoxia is involved in the regulation of leptin expression and may therefore contribute to elevated plasma leptin levels in pre-eclampsia. Elevated pro-inflammatory activity in preeclampsia promotes augmented leptin production, and proinflammatory cytokines (e.g. interleukin-1, interleukin-6) are involved in pathophysiology of preeclampsia and stimulatory effects of interleukin-1 and interleukin-6 on leptin production have been observed, suggesting that.

Cumin F et al[63] has opined that during pregnancy, maternal plasma leptin concentrations are elevated, and lacks the well-established correlation with body fat energy stores that are observed in non-pregnant women, indicating an alternative function for leptin during pregnancy and fetal development. Maternal and fetal plasma leptin levels are dysregulated in pathological conditions such as gestational diabetes, pre-eclampsia and intrauterine growth retardation, representing an effect or a cause of disturbances in the feto-placenta-maternal unit.

In the present study serum leptin levels were measured in both cases and controls. The mean leptin level in cases and controls were 11.64 ± 6.32 ng/ml and 4.85±2.46 ng/ml respectively. Our findings are in accordance with the results of Colcimen N and Sahin HG.[45] In their study, while comparing serum leptin levels among preeclamptic cases and controls, they found that the mean values of the marker were 9.6 ± 7.2 ng/ml in severely preeclamptic group, 5.4 ± 3.0 ng/ml in mildly preeclamptic group and 3.1± 3.1 ng/ml. The possible reason they mentioned was disordered renal function and decreased renal clearance may increase the leptin levels. Apart from this, decreased plasma volume in preeclampsia might increase the serum leptin by causing haemoconcentration.

Bouloumie A et al[64] and Ross R[65] have reported that leptin has a role in oxidative stress characterised by increased reactive oxygen compounds which have thought to have role in etiopathogenesis of preeclampsia. Leptin activates the formation of reactive oxygen compounds which are present on many cells. Leptin has been proposed to be a risk factor for many complications such as hypertension and atherosclerosis through vascular inflammation that results from accumulation of reactive oxygen compounds in endothelial cells.

Mise H et al[2] has suggested that placental ischemia also explains rapid increase in leptin concentration during late third trimester in preeclampsia. Placental hypoperfusion produces local hypoxia which consequently augments leptin gene expression in the placenta.

Vince GS et al[66] had found that inflammatory mediators increased plasma leptin concentration and in pre-eclampsia circulating concentration of the inflammatory cytokines such as TNF-α and IL-6 are increased. They concluded that there were several possible explanations for higher leptin concentrations in pregnancies complicated by preeclampsia. But the exact mechanism underlying the increase in circulating leptin concentration in preeclampsia awaits further clarification.

Increase in leptin concentration in preeclampsia could be due to placental ischemia. This could also be due to adaptive response of fetoplacental unit to impaired placental perfusion to meet the energy requirements of the fetus. Also during preeclampsia there is evidence of increased inflammatory mediators which increase the plasma leptin concentration. Placental pathological and pathophysiological changes occur in preeclampsia and it can be recommended that analysis of the biological activity of the products released by the placenta should be done which could provide a clue to the understanding placental response or adaptation.

In our study, it was seen that the number of preterm birth and low birth weight was more in preeclamptic women with high serum leptin level. The findings were found to be statistically significant. This is similar to the study conducted by Taylor BD et al[34] where they found that preeclamptic women were significantly more likely to have a preterm infant < 37 weeks gestation ($p < 0.0001$) and < 34 weeks gestation ($p=0.0038$). The possible reason might be endothelial dysfunction. There was increase risk of preterm labor with increasing severity of preeclampsia. To reduce the risk, termination of pregnancy was done to prevent and decrease maternal and fetal complications.

Leptin is an important physiological regulator of fetal growth and altered in pathological state of pregnancy such as diabetes and preeclampsia. Findings of the study done by Kharb S et al[41] has suggested that leptin is associated with rise in blood pressure and adverse pregnancy outcome in preeclampsia. Alterations in maternal-placental-fetal leptin exchange may modify the development of the fetus and contribute to the increased risk of developing diseases in adulthood. Their findings are in accordance with our present study.

However, there are some possible limitations in our study. Further studies with larger sample size are required to find the mechanisms responsible for this increase of leptin level in preeclamptics and role played by leptin in the development of preeclampsia.

V. Conclusion

The result of this study has shown that serum leptin level are more in all the cases compared to the controls. The increase in serum leptin level among cases and controls was correlated.

This is the first study of serum leptin among the diagnosed cases of preeclampsia in Northeast India. The study demonstrates that leptin could effectively help in diagnosis of the preeclampsia cases for effective treatment .

As the study pattern is a case control study, the future pattern of leptin levels among the patients in the follow up period could not be ascertained. If follow ups could be done, this could have helped to understand how long the leptin levels remain high in the postnatal period. Also, the patients were selected as diagnosed cases of preeclampsia when they had been hospitalised with acute symptoms after 20 weeks of gestation. But those who were prone to preeclampsia and were in early trimester (< 20weeks), were left out. The efficiency of leptin in diagnosing such cases could be a matter of interest for future researchers.

Nevertheless, it may be concluded that serum leptin can be used as a diagnostic marker in preeclampsia in addition to other conventional biomarkers. Further studies are required with larger sample size to evaluate the pathophysiology of leptin in preeclampsia.

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