

Leptin and Hyperlipidemia in Primigravida Preeclamptic Women and Normotensive Women

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ABSTRACT

Objective: To measure and compare serum levels of leptin and lipid profile parameters in primigravida women with PE and normotensive primigravida.

Study Design: Analytical cross-sectional study.

Place and Duration of Study: Department of Physiology and Cell Biology, University of Health Sciences, Lahore, from 2018 to 2020.

Methodology: Preeclamptic (PE, group A) and normal primigravida (PG, group B) with gestational age 30-36 weeks were recruited from tertiary care hospitals. After written and informed consent, blood samples were taken. Serum was separated and stored at -80°C until processed. CBC and lipid profile of each patient was also done using automated lab machines. Serum levels of leptin were calculated by ELISA. The data was entered and analysed in SPSS version 20.

Results: The mean serum levels of leptin (ng/ml) in PE (group A) were significantly raised compared to normotensive PG (group B) at 33.44 ± 12.91 and 4 ± 6.20 respectively ($p < 0.001$). The mean levels of TG (group A 242.40 ± 73.96 , group B 198 ± 43.73 , $p = 0.003$), LDL (group A 134.37 ± 33.61 , group B 115.70 ± 22.32 , $p = 0.004$), VLDL (group A 48.20 ± 15.06 , group B 39.52 ± 8.79 , $p = 0.002$), and cholesterol (group A 222.07 ± 44.78 , group B 290.77 ± 86.89 , $p = 0.001$), were significantly raised in patients of PE. The group A had significantly higher monocytes (5.90 ± 5.94) vs. group B (3.35 ± 0.94 , $p = 0.001$) and platelets (group A, 230.25 ± 73.27 , vs. group B 290.77 ± 86.89 , $p = 0.001$). No correlation was found between leptin and other study parameters.

Conclusion: Preeclamptic patients had significantly higher levels of leptin and hyperlipidemia independently. These findings can be utilised for the early detection of disease.

Key Words: Preeclampsia, Primigravida, Leptin, Lipid profile, Pregnancy, Cholesterol.

How to cite this article: Rana M, Iftikhar B, Khaliq S, Lone KP. Leptin and Hyperlipidemia in Primigravida Preeclamptic Women and Normotensive Women. *J Coll Physicians Surg Pak* 2022; **32(11)**:1410-1414.

INTRODUCTION

Preeclampsia (PE) is a disorder that involves multiple systems.¹ The signs and symptoms of PE include high blood pressure both systolic and diastolic, proteinuria, headache, oedema, nausea and vomiting, shortness of breath, and changes in vision.² The ultimate pathophysiologic abnormality is endothelial dysfunction along with exaggerated BP 140/90 mm Hg after 20 weeks of gestation and urinary loss of proteins >300mg/day.³ Worldwide approximately 5-7% of primigravida women develop PE in pregnancy.⁴ The incidence of PE is even higher in middle and low-income countries.⁵ PE and eclampsia account for 10-15% deaths in Pakistani pregnant women.⁶

Leptin is the most abundant adipokine produced by the adipose tissue. This polypeptide (167-amino acid) cytokine is also released from various other tissues such as the placenta, ovaries, mammary epithelium, bone marrow, and lymphoid tissues.⁷ Leptin plays multiple roles in the human body including energy metabolism, regulation of body weight, homeostasis of lipids and glucose, inflammation, bone physiology, reproduction, immunity, and tissue remodelling. Altered levels of this marker may cause severe and potentially injurious changes in body homeostasis.⁸ Leptin has vital roles in angiogenesis and blood pressure regulation leading to higher serum leptin concentrations in females with PE as compared to normal pregnant women.⁹ Serum leptin and leptin receptor expressions are raised in placentas from pathological pregnancies including PE.¹⁰ The significant positive association between LEPR variant c.668A>G and preeclampsia in Sudanese women also suggests the role of leptin in the development of preeclampsia.¹¹

In pregnancy, increasing energy demands of the growing fetus are met with the change in the metabolism from anabolism to catabolism and the lipids are used as the main source of

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Received: February 10, 2022; Revised: October 03, 2022;

Accepted: October 04, 2022

DOI: <https://doi.org/10.29271/jcpsp.2022.11.1410>

energy. This change is eventually associated with hyperlipidemia and potentially reflects the possible causes of maternal diseases of the cardiovascular system including PE, and both increased leptin levels and hyperlipidemia have been positively associated with PE.¹² Since limited data is available, the study was performed to establish any link between leptin, lipid profile, and PE for early detection and better management of this syndrome.

METHODOLOGY

The study was performed in the Department of Physiology and Cell Biology, University of Health Sciences, Lahore, from 2018-2020, an analytical cross-sectional study with consecutive purposive sampling technique. The study population was females with preeclampsia and with normal blood pressure of gestational age of 30-36 weeks from the Fatima Memorial Hospital, Lahore. The sample size was calculated by keeping the power of the study equal to 90 percent and the level of significance equal to 5 percent.

The study population was divided into two groups; group A comprised of patients of preeclampsia, and group B comprised of normal pregnant females. The calculated sample size for each group was 18 subjects. The inclusion criteria for group A was PG, maternal age between 20-26 years, diagnosed cases of PE as per guidelines of ACOG 2013 with gestational age of 30-36 weeks.¹³ The inclusion criteria for group B was PG, maternal age between 20-26 years, whose blood pressures were in normal range; systolic (115 ± 12 mmHg) and for diastolic (69 ± 9 mmHg) and gestational age of 30-36 weeks.¹⁴ Pregnant ladies with twin or multiple pregnancy GDM, PIH, smokers, and gestational age less than 30 weeks or more than 36 weeks, history of chronic hypertension, diabetes mellitus, kidney disease, arthritis, inflammatory bowel syndrome, other cardiovascular illness, or other chronic inflammatory disease, if present, were excluded.

After approval from UHS ethical review board, subjects were recruited from gynecological departments of tertiary care hospitals, who were admitted in wards and presented to the outpatient department keeping in view the exclusion and inclusion criteria as mentioned above.

Written and well informed consent was taken prior to data collection. Relevant information, clinical history, and demographic data (age, gender, address, and contact number) were taken. All the information taken from the subjects was recorded on the subject data sheet and consent form.

Ten millilitres of venous blood was taken by using an aseptic technique. About 3.5 ml of blood was saved in EDTA coated vacutainers for estimation of haemoglobin. The remaining blood was saved in non-coated vacutainers for isolation of blood serum. The samples were stored in icebox and transferred to the laboratory for further analysis. The serum was separated by centrifugation at 3000 revolutions per minute for 10 minutes. It was secured in properly labelled Eppendorfs and stored at -80°C for

analysis of other parameters later. CBC was measured by an automated CBC analyzer, Sysmex (XT-1800i).

Serum cholesterol was measured by using the enzymatic colorimetric (CHOD - PAP) method. Triglycerides, HDL, LDL, VLDL were measured in serum by using enzymatic colorimetric (GPO - PAP) method. Serum leptin concentration (ng/ml) was measured in serum by using Sandwich ELISA (Enzyme-Linked Immunosorbent Assay) kit commercially available from Human ELISA kit (International Immuno-Diagnostics, USA).

The data were analysed by IBM SPSS (Statistical Package for Social Sciences) 20 version. Mean \pm Standard Deviation (SD) was given for normally distributed quantitative variables, and Median \pm Inter Quartile Range (IQR) was given for non-normally distributed quantitative variables.

The normal distribution of data was checked by Shapiro-Wilk's test. For normally distributed variables, student "t" test was applied to compare various variables between the two groups. For non-normally distributed variables, the Mann-Whitney U test was used to compare various variables between two groups. Correlation between normally distributed variables was measured by using Pearson correlation (r) and correlation between non-normally distributed variables by using Spearman's rho correlation (rho). A $p \leq 0.05$ was considered statistically significant for all statistics.

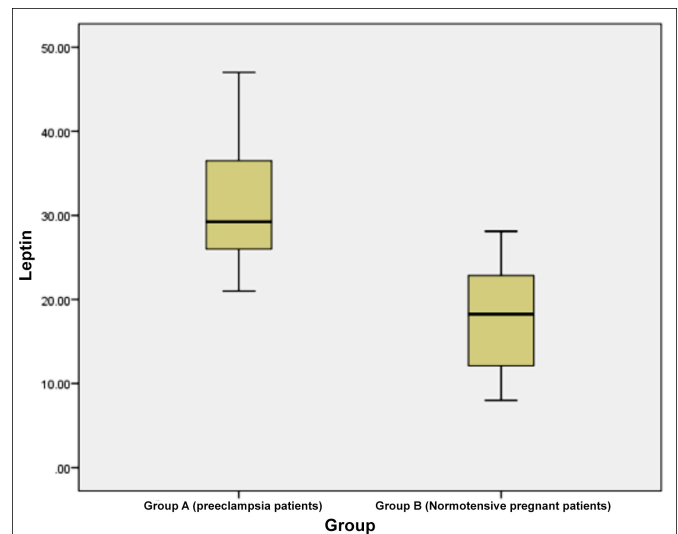


Figure 1: Serum levels of leptin (ng/ml) in group A and group B.

RESULTS

In this study, there was no significant difference of age in both groups ($p = 0.942^3$). The mean age of study participants in Group-A, and in Group-B were 23.07 ± 2.10 and 23.02 ± 2.11 years. In both groups, minimum and maximum age were 20 and 26 years respectively.

The mean gestational age of women in Group-A, and Group-B were 33.45 ± 2.30 and 34.45 ± 1.75 weeks. In both groups, minimum and maximum gestational age of women were 30 and 36 weeks respectively.

Table IA: Descriptive statistics for complete blood count.

Group	Hb (g/dl)		WBC (x10/L)		RBC (x10/L)		HTC (%)		MCV (fl)		MCH (pg)	
	A	B	A	B	A	B	A	B	A	B	A	B
N	40	40	40	40	40	40	40	40	40	40	40	40
Mean	10.14	10.38	10.52	9.48	3.95	3.80	30.54	30.84	75.67	75.32	26.92	26.20
SD	1.28	1.03	3.84	2.68	0.49	0.35	4.03	3.51	13.66	6.84	3.81	2.71
Median	10.20	10.30	10.30	9.03	3.96	3.78	30.80	30.35	77.35	74.65	26.70	26.00
Minimum	8.10	8.10	2.70	4.60	2.99	3.21	24.00	23.24	8.50	56.50	19.00	19.00
Maximum	16.00	12.40	20.00	15.90	5.80	5.01	48.40	36.60	104.00	92.40	36.70	31.70
p-value (normality)*	0.000	0.772	0.603	0.402	0.003	0.038	0.000	0.142	0.000	0.223	0.032	0.845
p-value	0.210 ^a		0.165 ^b		0.065 ^a		0.470 ^a		0.149 ^a		0.494 ^a	

Group-A: Declared patients of preeclampsia according to the ACOG (2013); Group-B: Normotensive pregnant females.

*Values generated According to Shapiro Wilk test; ^ap-value generated by Mann Whitney U test; ^bp-value generated by Independent sample t test; p-value ≤ 0.05 is considered statistically significant.

Table IB: Descriptive statistics for complete blood count.

Group	MCHC (%)		Platelet (x10/L)		Neutrophils (%)		Lymphocytes (%)		Monocytes (%)		Eosinophils (%)	
	A	B	A	B	A	B	A	B	A	B	A	B
N	40	40	40	40	40	40	40	40	40	40	40	40
Mean	34.83	33.80	230.25	290.77	65.02	67.55	28.75	27.65	5.90	3.35	1.42	1.22
SD	8.19	1.36	73.27	86.89	8.32	6.15	6.73	5.67	5.94	0.94	.549	.42
Median	34.00	33.75	234.00	298.0	68.00	68.00	27.00	27.50	5.00	3.00	1.00	1.00
Minimum	23.30	31.20	83.00	126.00	40.00	50.00	19.00	16.00	2.00	2.00	1.00	1.00
Maximum	83.80	37.90	374.00	492.00	75.00	82.00	46.00	42.00	40.00	6.00	3.00	2.00
p-value (normality)*	0.000	0.203	0.769	0.886	0.000	0.279	0.001	0.658	0.000	0.001	0.000	0.000
p-value	0.668 ^a		0.001 ^b		0.487 ^a		0.965 ^a		<0.001 ^a		0.084 ^a	

Group-A: Declared patients of preeclampsia according to the ACOG (2013); Group-B: Normotensive pregnant females.

*Values generated According to Shapiro Wilk test; ^ap-value generated by Mann Whitney U test; ^bp-value generated by Independent sample t test; p-value ≤ 0.05 is considered statistically significant.

Table II: Descriptive statistics for lipid profile in study groups.

Group	Cholesterol (mg/dl)		TG (mg/dl)		HDL (mg/dl)		LDL (mg/dl)		VLDL (mg/dl)		Total-Lipids (mg/dl)	
	A	B	A	B	A	B	A	B	A	B	A	B
N	40	40	40	40	40	40	40	40	40	40	40	40
Mean	222.07	195.72	242.40	198	39.22	40.50	134.37	115.70	48.20	39.52	886.55	789.45
SD	44.78	27.184	73.96	43.73	2.76	3.25	33.61	22.32	15.06	8.79	160.15	93.39
Median	212.50	193.50	228	191.50	39	41.00	130.50	111.00	45.50	38.50	843.50	771.50
Minimum	149	140.00	135	131.00	34	33.00	75	69.00	27	26.00	679	611
Maximum	332	265.00	421	326.00	45	46.00	212	166.00	84	65.00	1279	1056
p-value (normality)*	0.024	0.491	0.069	0.006	0.270	0.144	0.176	0.649	0.069	0.008	0.007	0.156
p-value	0.001 ^b		0.003 ^b		0.063 ^a		0.004 ^a		0.002 ^a		0.006 ^b	

Group-A: Declared patients of preeclampsia according to the ACOG (2013); Group-B: Normotensive pregnant female.

*Values generated According to Shapiro Wilk test; ^ap-value generated by Mann Whitney U-test; ^bp-value generated by independent sample t test; p-value ≤ 0.05 is considered statistically significant.

The mean height of women in Group-A, and Group-B were 1.51 ± 0.08 and 1.53 ± 0.04 metre and there was no significant difference of height in both groups ($p = 0.423$). The mean weight of women in Group-A, and Group-B were 73.87 ± 10.83 and 68.67 ± 7.92 Kg and there was a significant increase in the weight of Group-A ($p = -0.017$). The mean body mass index of Group-A and Group-B women were 32.06 ± 5.66 and 29.74 ± 3.64 and it was also significantly high in Group A ($p = 0.05$).

None of the patients in Group-A had history of hypertension, diabetes, gestational diabetes, acute/chronic inflammatory disease, renal disease, or any other disease. The same trend was seen for participants in Group-B.

In Group-A mean Leptin level was 33.44 ± 12.9 ng/ml and in Group-B it was 17.64 ± 6.20 ng/ml. A significant ($p < 0.001$) increase in Leptin value for the preeclamptic group was observed (Figure 1).

The complete blood count parameters showed no significant difference in both groups, except for monocytes and platelets. The monocyte count (%) was significantly high in Group-A ($p < 0.001$) compared with Group-B. The mean value of monocyte count for Group-A was 5.90 ± 0.94 and for Group-B was 3.35 ± 0.94 . The platelet count (x10/L) was significantly lower in Group-A mean value 230.25 ± 73.27 compared to Group-B mean value 290.77 ± 86.89 ($p < 0.001$). The mean Hb (g/dl) in Group-A was 10.14 ± 1.28 and in Group-B it was 10.38 ± 1.03 with no statistically significant difference in both groups ($p = 0.210$, Table IA and B).

Cholesterol, Triglycerides, LDL, and VLDL showed significant differences in both groups. Mean values of all these parameters except HDL were significantly higher in Group A women than that of Group B women. Further details can be seen in Table II.

DISCUSSION

PE is often regarded as a disease of theories because of its unknown pathogenesis. Leptin have fundamental roles in energy metabolism and angiogenesis and altered levels of leptin have fatal impact on body hemostasis.⁸ The role of leptin has been explored and various studies in the past have shown increased leptin levels in patients of PE. The increase in leptin levels occurs with an increase in systolic as well as diastolic blood pressure, and it can be taken as a marker of severity of PE independently or in the combination of other markers.¹⁵ The current study showed significantly increased levels of leptin in patients of PE compared to normotensive PG ($p < 0.001$), the findings of higher leptin levels have been found in various studies done in the past, hence, validating the role of leptin in the development of PE.¹⁶⁻¹⁸ There are many possible explanations of increased leptin levels in PE but the exact mechanism is still unknown.¹⁹

Studies have been done to explore the role of maternal adipose tissue as source of leptin production in PE but the relationship of higher leptin levels with BMI could not be established. However, there is a strong evidence which suggests that increased leptin levels in PE can be of placental origin.²⁰ The pathophysiological relation between BMI, PE, and obesity is complex and all these factors have an independent role in development of PE. These findings were found out in a study done on a cohort of 74 women with PE and 79 normotensive women.²¹ There was no significant correlation between BMI and leptin in both PE and normal pregnant women in the present study. This shows increased leptin production in PE may have source other than adipose tissue.

There are conflicting data on this topic and many other studies had opposite results showing no association or even lower levels of leptin in women with PE.²² These differences can be due to the differences in ethnicity, different environment, social customs, genetics, background nutritional history, and difference in study methodology *i.e.*, the differences in gestational age, maternal age, gravidity *etc.*²³ These findings put emphasis on the fact that studies should be done in each population as difference in ethnicity, environment, and genetics may lead to different results.

In the current study, it was found that cholesterol, triglycerides, HDL, LDL, VLDL, total lipids, and the ratio of cholesterol to other lipids fractions showed significant difference in both groups. Mean values of all these parameters except HDL were significantly higher in PE women compared to normal pregnant women. The similar findings have been stated by various studies done in the past.²⁴ When the possible correlation of leptin with lipid profile parameters was studied no significant relationship between these biomarkers and lipid profile parameters was found in both PE and control groups. However, the parameters of lipid profile

showed significant correlations with each other. The HDL has a significant negative correlation with the rest of the parameters of lipid profile. The dyslipidemia in PE (low levels of HDL and high levels of rest of the lipid profile parameters) has been found in multiple studies and put emphasis on the fact that it should be part of routine pregnancy investigation.²⁵

The limitation of the study was that it was a single-centred study done in the last trimester, it would be of great interest to elucidate at what gestational age the level of leptin rises in pregnant females who later develop PE. There should be prospective studies done both on mother and fetus to explore the further role of leptin and lipid profile.

CONCLUSION

The serum leptin and lipid profile parameters showed significantly raised values in patients with PE. Hence, one can conclude that obesity and leptin have a profound role in the development of preeclampsia and leptin and lipid profile can serve as possible markers of disease.

DISCLOSURE:

This study is part of the thesis project of M.Phil. Physiology and funded by the University of Health Sciences.

ETHICAL APPROVAL:

The Ethical Approval was given by the Ethical Committee of UHS, letter No. UHS/Education/126-17/26-04-2017.

PATIENTS' CONSENT:

Informed and written consent was taken from each patient.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

MR: Study design, data collection, analysis, interpretation, and drafting of research work.

BI: Contribution in data collection, acquisition, and drafting of work.

SK: Critical revision and final approval of the draft.

KPL: Conception of study design, critical revision, and analysis.

All the authors have approved the final version of the manuscript to be published.

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