ORIGINAL RESEARCH

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Serum Leptin as a Diagnostic Biomarker in Preeclampsia: A Prospective Controlled Study

Preeklampside Serum Leptin Seviyelerinin Tanısal Potansiyeli: Prospektif Bir Çalışma

Murat İbrahim Toplu[1], Erhan Aktürk[2], Başak Cıngıllıoğlu[3], Hamit Caner Uzun[4], Yasemin Damla Yenliç Kaya[5], Simten Genç[6], Veli Mihmanlı[1]

[1]University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Obstetrics and Gynecology, İstanbul, Turkey
[2]Medicana Zincirlikuyu Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
[3]Doha Clinic Hospital, Clinic of Obstetrics and Gynecology, Doha, Qatar
[4]Yuregir State Hospital, Clinic of Obstetrics and Gynecology, Adana, Turkey
[5]Medipol University Esenler Hospital, Department of Obstetrics and Gynecology, İstanbul, Turkey
[6]Private Practice, İstanbul, Turkey

Abstract

Objective: To compare serum leptin levels in preeclamptic pregnant women with those in healthy (normotensive) pregnant women and evaluate the potential of leptin as a diagnostic marker for preeclampsia.

Methods: This prospective study included 37 preeclamptic pregnant women and 37 healthy (normotensive) controls. Serum leptin concentrations were determined through the enzyme-linked immunosorbent assay method. Additionally, sociodemographic, clinical, and laboratory parameters were assessed. Receiver operating characteristic (ROC) curve analysis was performed to evaluate diagnostic performance.

Results: Mean serum leptin levels were significantly higher in the preeclampsia group (26.6±10.9 ng/mL) compared to the control group (10.8±5.3 ng/mL) ($p<0.05$). The area under the ROC curve was calculated as 0.928. A leptin threshold of 12.86 ng/mL yielded a sensitivity of 95% and a specificity of 70%, while a threshold of 15.36 ng/mL yielded 92% sensitivity and 79% specificity. Analysis of covariance confirmed that the differences in leptin levels remained statistically significant after adjusting for body mass index.

Conclusion: Serum leptin levels are significantly elevated in preeclamptic pregnancies, supporting its potential as a diagnostic biomarker. Further large-scale studies are needed to validate these findings and to investigate the mechanistic role of leptin in the pathogenesis of preeclampsia.

Keywords: Biomarker, hypertension, leptin, preeclampsia, pregnancy

Öz

Amaç: Preeklamptik gebelerde serum leptin düzeylerini sağlıklı (normotansif) gebelerle karşılaştırmak ve leptinin preeklampsi tanısındaki potansiyelini değerlendirmek.

Yöntem: Bu prospektif çalışmaya 37 preeklamptik gebe ile 37 sağlıklı (normotansif) gebe dahil edilmiştir. Serum leptin düzeyleri enzim bağlantılı immünosorbent analiz yöntemiyle ölçülmüştür. Demografik, klinik ve laboratuvar verileri toplanmış ve tanısal doğruluk alıcı çalışma karakteristiği (ROC) eğrisi analizi ile değerlendirilmiştir.

Bulgular: Serum leptin düzeyleri preeklampsi grubunda (26,6±10,9 ng/mL), kontrol grubuna (10,8±5,3 ng/mL) kıyasla anlamlı derecede yüksek bulunmuştur ($p<0,05$). ROC eğrisi altında kalan alan 0,928 olarak hesaplanmıştır. 12,86 ng/mL eşik değeri %95 duyarlılık ve %70 özgüllük sağlarken, 15,36 ng/mL eşiği %92 duyarlılık ve %79 özgüllük sağlamıştır. Vücut kitle indeksi farklarının etkisini kontrol etmek amacıyla yapılan kovaryans analizi, leptin düzeylerindeki farkların bağımsız olarak anlamlı olduğunu göstermiştir.

Sonuç: Preeklamptik gebeliklerde serum leptin düzeylerinin anlamlı şekilde yüksek bulunması, leptinin tanısal bir biyobelirteç olarak potansiyelini desteklemektedir. Bu bulguların daha büyük örneklemli çalışmalarla doğrulanması ve leptinin preeklampsi patogenezindeki rolünün aydınlatılması gerekmektedir.

Anahtar kelimeler: Biyobelirteç, gebelik, hipertansiyon, leptin, preeklampsi

Address for Correspondence: Murat İbrahim Toplu, University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Obstetrics and Gynecology, İstanbul, Turkey
E-mail: mitoplu@gmail.com **ORCID:** orcid.org/0000-0003-1358-9099
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Introduction

Preeclampsia (PE) is a multifactorial and complex condition unique to pregnancy, defined by the emergence of hypertension and proteinuria after 20 weeks of gestation (1). Globally, it impacts 2-8% of pregnancies, representing a significant contributor to maternal and fetal morbidity and mortality (2). The pathophysiology of PE involves a combination of maternal and placental factors, including abnormal placental development, immune dysregulation, and systemic endothelial dysfunction (3).

Leptin, a 16 kDa protein produced mainly by adipocytes, plays an important role in regulating energy balance and reproductive functions (4). During pregnancy, leptin is also produced by the placenta, with levels rising substantially as gestation progresses (5). In the context of PE, placental hypoxia and ischemia are believed to enhance leptin production, potentially contributing to the disease's pathogenesis (6). Preeclamptic pregnancies are associated with markedly increased leptin levels, indicating a possible relationship between leptin dysregulation and the pathogenesis of PE (7). However, the precise role of leptin in PE and its utility as a predictive biomarker remain areas for further investigation. This study aims to provide additional evidence for the potential utility of leptin as a diagnostic marker in PE.

Materials and Methods

Study Design and Participants

This prospective study was conducted at Okmeydanı Health Research and Training Center, now known as University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital. A total of 74 pregnant women participated, including 37 women diagnosed with PE and 37 normotensive controls. Ethical approval was granted by the Clinical Research Ethics Committee of Okmeydanı Health Research Center, and written informed consent was obtained from all participants. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (date: 27/01/2020, no: 48670771-514.10/15).

Inclusion and Exclusion Criteria

Participants were included if they were between 18 and 44 years old, had a singleton pregnancy, and were either diagnosed with PE according to the American College of Obstetricians and Gynecologists criteria or had an uncomplicated pregnancy for the control group (8). Exclusion criteria included multiple pregnancies, chronic hypertension, diabetes, thyroid disorders, and other systemic diseases.

Data Collection

Demographic data, obstetric history, and clinical measurements were collected from all participants. Blood pressure was measured using standardized techniques (9). Venous blood samples for leptin measurement were collected after an overnight fast at the time of hospital admission for delivery. Demographic and clinical characteristics were recorded for all participants.

Laboratory Analysis

Serum leptin levels were measured using the enzyme-linked immunosorbent assay method. Blood samples were collected, processed, and stored according to standardized protocols. The leptin assay was conducted in accordance with the manufacturer's instructions.

Statistical Analysis

Data were analyzed using SPSS version 25.0. Descriptive statistics, including mean and standard deviation, were used to summarize continuous variables, while frequencies and percentages were used for categorical variables. The Student's t-test and Mann-Whitney U test were employed to compare continuous variables, and chi-square or Fisher's exact tests were used for categorical variables. A p-value of less than 0.05 was considered statistically significant.

To account for differences in body mass index (BMI) between the preeclamptic and normotensive groups, an analysis of covariance (ANCOVA) was performed. This allowed for the adjustment of leptin levels by controlling BMI, providing a clearer comparison between the groups. Additionally, the diagnostic performance of serum leptin levels was evaluated using receiver operating characteristic (ROC) curve analysis.

Results

Participant Characteristics

The study included 74 pregnant women 37 diagnosed with PE and 37 normotensive controls. Table 1 presents the demographic and clinical characteristics of the participants. The two groups showed no significant differences in terms of age, gravida, or parity. The mean gestational age at the time of blood sampling was 36.5±2.6 weeks (median 37) in the PE group, whereas it was 39.5±1.1 weeks (median 39) in the control group, showing a statistically significant difference ($p<0.001$). However , the preeclamptic group had a significantly higher BMI compared to the control group ($p<0.05$).

Leptin Levels

Serum leptin levels were markedly elevated in the preeclamptic group, with a mean value of 26.6±10.9 ng/mL, compared to 10.8±5.3 ng/mL in the control group ($p<0.05$) (Table 2).

Diagnostic Performance

ROC curve analysis revealed an area under the curve (AUC) of 0.928 (95% confidence interval: 0.873-0.983, $p<0.001$), demonstrating excellent diagnostic accuracy for serum leptin levels. A threshold of 12.86 ng/mL provided 95% sensitivity and 70% specificity, while a higher threshold of 15.36 ng/mL yielded 92% sensitivity and 79% specificity (Table 3). Figure 1 illustrates the ROC curve.

BMI-adjusted Leptin Analysis

To evaluate the influence of BMI on serum leptin levels, an ANCOVA was conducted. The analysis revealed a statistically significant variation in leptin levels between preeclamptic and control groups after adjusting for BMI [$F(1, 71)=79.658$, $p<0.05$). Moreover, BMI itself exhibited a notable impact on leptin concentrations [$F(1, 71)=8.987$, $p=0.004$, partial eta squared=0.112]. These findings underscore the significant disparities in leptin levels between preeclamptic and normotensive pregnancies, regardless of BMI adjustments (Table 4).

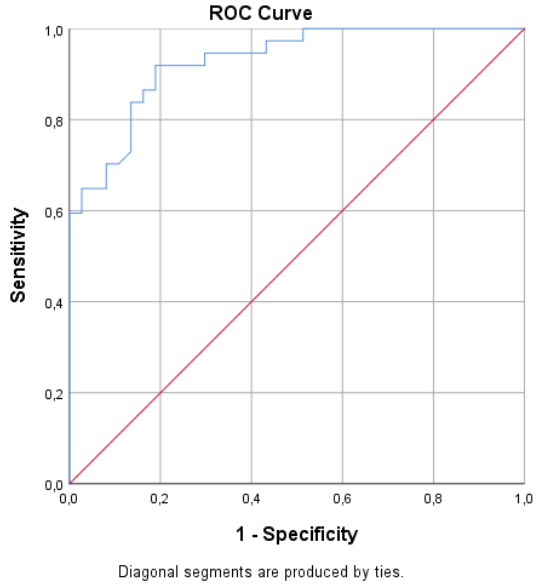

Figure 1. Receiver operating characteristic (ROC) curve for serum leptin levels

ROC curve for serum leptin levels in predicting preeclampsia. The area under the curve was 0.928 (95% confidence interval: 0.873-0.983, $p<0.001$). An optimal cut-off value of 12.86 ng/mL yielded 95% sensitivity and 70% specificity, while a higher threshold of 15.36 ng/mL provided 92% sensitivity and 79% specificity

Table 1. Demographic and clinical characteristics of the participants

Characteristic	Preeclamptic group (n=37)	Control group (n=37)	p-value
Age (years)	27.5±4.9	26.9±5.5	0.594
BMI (kg/m^2)	27.1±3.8	29.8±4.8	0.009
Gravida	2.8±1.4	2.4±1.3	0.462
Parity	1.1±1	0.9±1	0.444
Systolic BP (mmHg)	166.5±18.6	113.8±11.3	0.000
Diastolic BP (mmHg)	104.3±11.7	71.1±7.7	0.000

BMI: Body mass index, BP: Blood pressure

Table 2. Leptin levels

Group	Mean leptin levels (ng/mL)	Standard deviation	p-value
Preeclamptic (n=37)	26.6	10.9	0.000
Control (n=37)	10.8	5.3	0.000

Table 3. Diagnostic performance of leptin levels

Cut-off value (ng/mL)	Sensitivity (%)	Specificity (%)	AUC
12.86	95	70	0.928
15.36	92	79	0.928

AUC: Area under the curve

Table 4. ANCOVA results for BMI-adjusted leptin levels

Tests of between-subjects effects

Dependent variable: Leptin

Source	Type III sum of squares	df	Mean square	F	Sig.	Partial eta squared	Noncent. parameter	Observed power[b]
Corrected model	5253.959[a]	2	2626.980	39.881	0.000	0.529	79.762	1.000
Intercept	0.015	1	0.015	0.000	0.988	0.000	0.000	0.050
BMI	592.009	1	592.009	8.987	0.004	0.112	8.987	0.841
Preeclampsia status 1 PE/0 control	5247.115	1	5247.115	79.658	0.000	0.529	79.658	1.000
Error	4676.798	71	65.870					
Total	35771.807	74						
Corrected total	9930.757	73						

[a]: R squared =0.529 (adjusted R squared =0.516), [b]: Computed using alpha =0.05, ANCOVA: Analysis of covariance, BMI: Body mass index

Discussion

PE continues to rank among the primary contributors to maternal and perinatal morbidity and mortality. While its etiology and pathogenesis remain incompletely elucidated, current evidence suggests a multifactorial origin involving maternal and placental components, such as impaired placental development and endothelial dysfunction. This study highlights the significance, as a potential predictive marker for PE, of leptin, a hormone predominantly secreted by adipose tissue and additionally produced by the placenta during pregnancy.

Multiple studies have demonstrated the potential of serum leptin levels as a biomarker for early-onset PE. Taylor et al. (10) demonstrated in a large nested case-control study that serum leptin concentrations measured between 9 and 26 weeks of gestation were significantly elevated in women who later developed PE, independent of BMI and other confounders. Similarly, Hao et al. (11) conducted a longitudinal cohort study and found that leptin levels were consistently higher from the first trimester onwards in women who subsequently developed PE, surpassing traditional markers such as s soluble FMS-like tyrosine kinase receptor-1 and placental growth factor in early detection (10).

Beyond its role as a metabolic hormone, leptin is increasingly recognized as a pro-inflammatory cytokine-like mediator. It has been shown to stimulate the production of inflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha, which contribute to endothelial dysfunction, systemic inflammation, and abnormal placental development-key elements in the pathogenesis of PE. This mechanistic link may explain why leptin levels are elevated in preeclamptic pregnancies and supports the hypothesis that leptin actively participates in the disease process, rather than serving solely as a biomarker of adiposity or metabolic disturbance. Leptin's involvement in metabolic dysregulation and physiological imbalances during pregnancy underscores its pivotal role in the onset and progression of PE (12).

Our findings further support the potential role of leptin in PE pathogenesis, possibly via its influence on placental dysfunction and inflammatory pathways. This supports the hypothesis that leptin may act as a critical factor in the development of PE through its involvement in placental function and systemic inflammation (13). The ROC curve analysis in our study indicated a substantial AUC, confirming leptin's predictive value for PE at various cut-off points.

Other studies have reported consistent findings, further highlighting the significance of leptin in the pathophysiology of PE. Additionally, alterations in leptin dynamics and cellular metabolic pathways are believed to play a fundamental role in the mechanisms underlying hypertensive disorders in pregnancy, including PE (14).

Wang et al. (15) used an integrative approach combining bioinformatics tools with clinical sample analysis to identify leptin as a potential biomarker for PE. Their findings suggest that elevated leptin expression is strongly linked to PE and holds promise as both a diagnostic indicator and a therapeutic target (15).

Furthermore, a detailed review by Veiga et al. (16) confirmed that inflammatory markers, including leptin, are elevated in women with PE, reinforcing the potential of leptin as a biomarker for this condition.

Our findings on the diagnostic performance of serum leptin in PE are consistent with previous studies. El Shahat et al. (17) reported a cut-off value of 13.7 ng/mL for the diagnosis of PE with 91% sensitivity and 100% specificity, and a cut-off value of 22.5 ng/mL to predict severe cases, again with high diagnostic accuracy (AUC ~0.90). Similarly, Rao et al. (18) identified a threshold of 23.3 ng/mL, achieving 90% sensitivity and 88.3% specificity. Compared to previous studies, our study demonstrated a slightly lower diagnostic threshold (12.86 ng/mL) with higher sensitivity (95%) and acceptable specificity (70%), and an AUC of 0.928, indicating excellent discrimination. These findings suggest that serum leptin offers robust diagnostic utility across different populations and methodologies, reinforcing its value as a biomarker for PE.

Study Limitations

A notable strength of this study lies in its prospective design, enabling a precise evaluation of leptin levels in connection with PE. Furthermore, this research stands out as one of the few that accounts for BMI in the analysis of leptin levels, offering a more detailed understanding of its role in PE, independent of adiposity.

Nevertheless, this study has certain limitations. The relatively small sample size may restrict the generalizability of the results. Additionally, the research did not investigate longitudinal variations in leptin levels across different stages of pregnancy, which could offer deeper insights into the temporal dynamics of leptin's relationship with the onset of PE.

Moreover, it is noteworthy that the control group in our study exhibited a higher BMI compared to the PE group, which contrasts with existing literature, where higher BMI is typically associated with PE risk. This unexpected finding might be attributed to specific demographic or lifestyle characteristics of the study population and requires cautious interpretation.

Furthermore, the gestational age at the time of blood sampling was significantly lower in the PE group (median 37 weeks) compared to the control group (median 39 weeks). Given that serum leptin levels are known to increase with advancing gestational age, this discrepancy may have influenced the observed leptin concentrations and represents an additional limitation of our study.

Implications for Future Research

The results of this study suggest that serum leptin levels, especially when adjusted for BMI, may serve as a potential biomarker. Future investigations should prioritize large-scale, multicenter studies to confirm these findings. Moreover, research aimed at elucidating the mechanistic pathways by which leptin influences the pathogenesis of PE is strongly recommended.

Conclusion

PE remains a major obstetric challenge with complex and multifactorial pathophysiology that is yet to be fully elucidated. Among various biomarkers under investigation, leptin has emerged as a candidate involved in several key pathological pathways including placental dysfunction and systemic inflammation. In our study, significantly elevated serum leptin levels in preeclamptic pregnancies support its potential role in disease prediction.

Moving forward, our findings underscore the need for large-scale, multicenter studies to validate leptin's diagnostic performance across diverse populations. Future research should also focus on integrating leptin with other biochemical and clinical markers to develop robust predictive models for the early identification and risk stratification of PE.

Ethics

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (date: 27/01/2020, no: 48670771-514.10/15).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.İ.T., B.C., H.C.U., S.G., Concept: M.İ.T., E.A., Y.D.Y.K., V.M., Design: E.A., B.C., S.G., V.M., Data Collection or Processing: M.İ.T., B.C., S.G., V.M., Analysis or Interpretation: E.A., H.C.U., V.M., Literature Search: M.İ.T., E.A., Y.D.Y.K., S.G., Writing: M.İ.T., B.C., H.C.U., Y.D.Y.K., V.M.

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