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Investigation of serum neuroserpin levels in pregnant women diagnosed with pre-eclampsia: a prospective case-control study

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Abstract

Objective Neuroserpin, a serine protease inhibitor, is recognized for its anti-inflammatory and neuroprotective properties. Given the central role of inflammation and neurological involvement in the pathophysiology of preeclampsia, this study aimed to assess maternal serum neuroserpin levels in preeclamptic pregnancies and explore their association with disease severity.

Design Prospective case-control study.

Setting A tertiary referral center in Ankara, Türkiye.

Population Singleton pregnant women with a diagnosis of preeclampsia ($n=44$) and gestational age-matched normotensive pregnant women as controls ($n=44$).

Methods Participants were assigned to preeclampsia and control groups. Serum neuroserpin levels were quantified using enzyme-linked immunosorbent assay (ELISA). Subgroup analysis was conducted based on the clinical severity of preeclampsia. Statistical analysis included group comparisons, receiver operating characteristic (ROC) curve analysis, and correlation testing.

Main Outcome Measures The primary outcome was maternal serum neuroserpin level. Secondary outcomes included obstetric and neonatal parameters such as gestational age at delivery, delivery mode, NICU admission, and Apgar scores.

Results Serum neuroserpin levels were significantly reduced in the preeclampsia group compared to controls ($p=0.018$). Within the preeclampsia cohort, patients with severe disease exhibited even lower neuroserpin concentrations than those with mild preeclampsia. ROC curve analysis determined a neuroserpin cutoff value of ≤ 22.95 ng/mL for identifying preeclampsia (AUC: 0.647, $p=0.013$) and ≤ 14.7 ng/mL for severe preeclampsia (AUC: 0.740, $p=0.007$).

Conclusion Reduced maternal serum neuroserpin levels are associated with both the diagnosis and severity of preeclampsia. These findings highlight the potential role of neuroserpin in the disease's inflammatory mechanisms and support its utility as a candidate biomarker in clinical prediction models.

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Clinical trial registration Not applicable

Keywords Neuroserpin, Preeclampsia, Biomarker, Inflammation, Severe preeclampsia, ELISA

Introduction

Preeclampsia is a multisystem hypertensive disorder of pregnancy characterized by systemic inflammation, endothelial dysfunction, and a procoagulant state [1]. Although its global incidence varies, it affects approximately 2–5% of all pregnancies and remains a major contributor to maternal and perinatal morbidity and mortality worldwide [1]. The condition most commonly manifests in the third trimester, typically after 34 weeks of gestation; however, its early-onset form—developing before 34 weeks—is associated with more severe clinical outcomes and heightened risks for both mother and fetus [2, 3].

Despite extensive research, the precise pathophysiology of preeclampsia remains only partially understood [4, 5]. Central to its development is inadequate trophoblastic remodeling of maternal spiral arteries, which disrupts uteroplacental perfusion. This impaired placentation triggers a cascade of pathological events including aberrant inflammatory responses, oxidative stress, and the release of antiangiogenic factors into the maternal circulation [5–7]. Among the molecules implicated in this process are soluble endoglin (sEng), soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), and members of the transforming growth factor (TGF) family, particularly TGF-β1 and TGF-β3 [8–10]. These factors collectively impair trophoblast invasion and hinder the establishment of an effective placental vascular network, thereby compromising fetal oxygen and nutrient delivery [8–10]. Concurrently, oxidative stress in the placental microenvironment promotes the local production of metalloproteinases, angiogenic regulators, and proinflammatory cytokines, further exacerbating systemic inflammation [8–11].

Preeclampsia is also associated with maternal leukocyte activation, elevated levels of circulating leukocyte-derived microparticles, and transcriptional changes at the mRNA level [11]. These immunological alterations are reflected in elevated maternal serum levels of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10), which are known contributors to generalized endothelial dysfunction [12]. In recent years, considerable attention has been directed toward identifying novel biomarkers that could aid in elucidating the underlying inflammatory mechanisms of preeclampsia and serve as tools for early diagnosis and risk stratification.

Neuroserpin, a member of the serine protease inhibitor (serpin) family, is primarily secreted by neuronal axons and is known to regulate proteolytic enzymes such as tissue plasminogen activator (tPA) and plasminogen [13, 14]. Beyond its neurological functions, neuroserpin plays a critical role in neuronal growth, synaptic plasticity, and cellular maturation [13, 15, 16]. Emerging evidence also highlights its anti-inflammatory properties, particularly demonstrated in experimental models of transplant vasculopathy, where neuroserpin has been shown to attenuate immune activation and vascular injury [17].

Considering the pivotal role of inflammation and endothelial injury in preeclampsia, and given neuroserpin's demonstrated anti-inflammatory and neuroprotective effects, it is reasonable to hypothesize that neuroserpin may be involved in the pathogenesis of this condition. Accordingly, this study aims to evaluate maternal serum neuroserpin levels in pregnancies complicated by preeclampsia and to investigate their potential association with disease severity.

Materials and methods

Study design and setting

This prospective case-control study was conducted between September 25, 2024, and January 15, 2025, in the Departments of Obstetrics and Perinatology at a tertiary referral hospital in Ankara, Türkiye. The institution, with an annual delivery rate of approximately 12,500 births, provided an optimal setting for patient recruitment. Ethical approval was obtained from the hospital's research ethics committee (Approval No: AEŞH-BADEK-2024-842), and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Participants

Eligible participants were pregnant women aged between 21 and 45 years with singleton pregnancies, either with a diagnosis of preeclampsia or without any pregnancy complications. The diagnostic criteria for preeclampsia followed the guidelines of the American College of Obstetricians and Gynecologists (ACOG) [18].

Inclusion criteria

- Singleton pregnancy.
- Diagnosis of preeclampsia based on ACOG criteria.
- Healthy pregnancies matched for gestational age as controls.

Exclusion criteria

- Multiple gestations.

- Pre-existing maternal comorbidities (e.g., chronic hypertension, diabetes mellitus).
- Use of tobacco, alcohol, or illicit drugs during pregnancy.
- Prior corticosteroid or tocolytic therapy before blood sampling.
- Complications such as chorioamnionitis.
- Presence of fetal congenital or chromosomal anomalies.

Diagnostic criteria

Preeclampsia was defined as a systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg on two separate occasions at least four hours apart, accompanied by proteinuria after 20 weeks of gestation. In the absence of proteinuria, diagnosis was based on new-onset hypertension with at least one of the following features:

- Thrombocytopenia (platelet count < 100,000/μL).
- Elevated liver transaminases.
- Renal dysfunction (serum creatinine > 1.1 mg/dL or doubling from baseline).
- Persistent headache or visual disturbances.
- Pulmonary edema [18].

Group allocation

A total of 88 participants were enrolled and divided into two equal groups:

- Preeclampsia group ($n = 44$).
- Healthy pregnancy group ($n = 44$).

Control participants were selected based on gestational age matching, with the first eligible healthy pregnant woman attending routine prenatal care during the same week of gestation as each case.

Data collection

A statistical power analysis determined that a total of 88 participants (44 with preeclampsia, 44 controls) would be sufficient for this prospective case-control study, assuming a type I error (α) of 0.05, beta of 0.2, and statistical power of 0.80 [19]. After group allocation, maternal demographic and clinical data were retrieved from hospital medical records and included:

- Maternal age, body mass index (BMI), parity, smoking status, gestational age at sampling.
- Laboratory parameters: hemoglobin (Hb), platelet count (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and neuroserpin levels.
- Neonatal outcomes: birth weight, Apgar scores at 1 and 5 min, NICU admission, fetal sex, and mode of delivery.

Laboratory analysis

Fasting blood samples (≥ 3 mL) were collected after 10–12 h of fasting. Samples were stored under cold chain conditions for no more than two hours before centrifugation at 1000 rpm for 15 min. The resulting serum was aliquoted into Eppendorf tubes and preserved at – 80 °C until further analysis.

Serum neuroserpin concentrations were measured using a commercially available Human NSP ELISA Kit (Shanghai Coon Koon Biotech Co., Catalog No: CK-BIO-25312) utilizing a sandwich ELISA technique. The assay detection range was 8–25 ng/mL, with a sensitivity of 1.00 ng/mL. Measurements were performed using the Alisei Q.S. Analyzer (Next Level s.r.l., Italy).

Imaging

All participants underwent routine obstetric sonographic evaluations. Fetal biometric measurements and well-being assessments were conducted using the GE Voluson S10 Performance System (General Electric Company, USA), equipped with a 2–5 MHz transabdominal probe. A transvaginal probe (2.9–9.7 MHz) was employed when clinically indicated.

Statistical analysis

All statistical analyses were conducted using open-access statistical software.

- Normality of distribution was assessed using Shapiro-Wilk and Kolmogorov-Smirnov tests, supported by visual tools (histograms and Q-Q plots).
- Levene's test was used to assess homogeneity of variances.
- For comparisons between groups, the Student's t-test was applied to normally distributed variables, and the Mann-Whitney U test was used for non-parametric data.
- Categorical variables were compared using chi-square or Fisher's exact tests, as appropriate.
- Spearman's rank correlation analysis was used to evaluate associations between serum neuroserpin levels and clinical variables.
- Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic utility of serum neuroserpin concentrations for predicting preeclampsia and severe disease subtypes.

A p-value less than 0.05 was considered statistically significant.

Results

During the four-month study period, 53 pregnant women were initially diagnosed with preeclampsia. Following the application of predefined inclusion and exclusion criteria, 44 participants were deemed eligible and enrolled in the study. Among these, 14 individuals met the criteria for preeclampsia with severe features (Preeclampsia-SF).

As detailed in the methodology, a total of 88 participants were included through case-control matching, forming two equal groups: 44 pregnant women with preeclampsia and 44 healthy gestational age-matched controls. The preeclampsia group was subsequently stratified into two subgroups based on disease severity: mild preeclampsia and Preeclampsia-SF. Serum neuroserpin concentrations were then analyzed across all groups (Fig. 1).

Baseline demographic and perinatal characteristics of the study population are summarized in Table 1. There were no statistically significant differences between the preeclampsia and control groups in terms of maternal age, body mass index (BMI), parity, smoking status, or gestational age at the time of blood sampling. In contrast, significant differences were observed in gestational age at delivery, rate of cesarean section, and neonatal outcomes including birth weight, Apgar scores, and NICU admissions ($p < 0.001$ for all). Importantly, maternal serum neuroserpin levels were significantly lower in the preeclampsia group compared to the control group ($p = 0.018$).

Furthermore, Table 2 presents subgroup comparisons within the preeclampsia cohort, showing that neuroserpin levels were significantly lower in women with Preeclampsia-SF than in those with mild disease.

Spearman's correlation analysis was performed to evaluate the relationship between maternal serum neuroserpin levels and various maternal and perinatal variables (Table 3.). A weak negative correlation was identified between neuroserpin levels and maternal age ($r = -0.082$, $p = 0.447$), and a similarly weak inverse association was found with maternal AST levels ($r = -0.204$, $p = 0.057$), which approached but did not reach statistical significance. Positive but non-significant correlations were observed with BMI ($r = 0.067$, $p = 0.537$), parity ($r = 0.067$, $p = 0.539$), gestational age at delivery ($r = 0.186$, $p = 0.083$), and birth weight ($r = 0.161$, $p = 0.134$). Apgar scores at the 1st and 5th minutes also demonstrated weak, non-significant positive correlations ($r = 0.112$, $p = 0.298$ and $r = 0.049$, $p = 0.650$, respectively). ALT levels showed a negligible correlation with neuroserpin ($r = 0.064$, $p = 0.552$).

To assess the diagnostic value of serum neuroserpin for identifying preeclampsia, a receiver operating characteristic (ROC) curve analysis was conducted. The Youden index identified a cutoff value of ≤ 22.95 ng/mL, yielding a sensitivity of 86.4% and a specificity of 43.2%. The area under the curve (AUC) was 0.647 (95% CI: 0.538–0.746, $p = 0.013$), as shown in Fig. 2.

A separate ROC analysis was performed to determine the predictive utility of neuroserpin for identifying Preeclampsia-SF. The optimal cutoff value was found to be ≤ 14.7 ng/mL, yielding a sensitivity of 50.0% and a

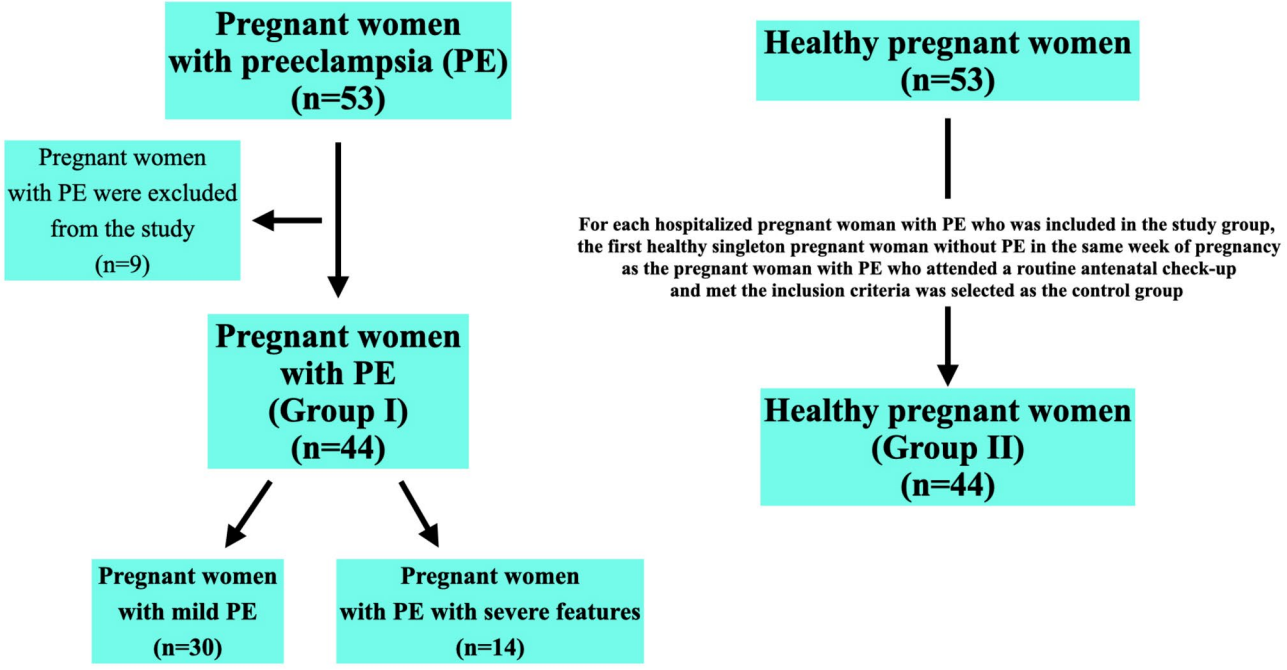

Fig. 1 Flowchart illustrating participant inclusion and subgroup classification

Table 1 Maternal characteristics and perinatal outcomes of the pregnant woman included in the study

	Preeclampsia Group ***n*** **= 44**	**Control Group** ***n*** **= 44**	***p***
Maternal age (year)	30 ± 6.10	28 ± 5.10	0.189
BMI at during test (kg/m^2)	28.0 (26.0–31.0)	27.3 (25.2–29.3)	0.116
Parity	0 (0–2)	0 (0–1)	0.252
Smoking	0 (0%)	2 (4.5%)	0.494
Blood sample collection time (week)	34 (29–36)	33 (28–36)	0.726
Delivery time (week)	35 (31–37)	39 (38–40)	**< 0.001**
CS	39 (88.6%)	19 (43.2%)	**< 0.001**
Female gender	21 (47.7%)	27 (61.4%)	0.284
Birth weight (g)	2080 (1608–2823)	3270 (3013–3540)	**< 0.001**
Apgar score at 1st minute	8 (7–9)	9 (9–9)	**< 0.001**
Apgar score at 5th minute	9 (8–10)	10 (10–10)	**< 0.001**
NICU admission	19 (43.2%)	2 (4.5%)	**< 0.001**
HB (g/dL)	12 (11.3–13.6)	11.9 (10.7–12.7)	0.276
PLT (x10^9/L)	232 (187–297)	227 (199–262)	0.845
ALT (U/L)	13 (9–25)	12 (8–16)	0.103
AST (U/L)	22 (16–36)	14 (12–18)	**< 0.001**
Creatinine (mg/dL)	0.6 (0.5–0.7)	0.5 (0.5–0.6)	**< 0.001**
Neuroserpin (ng/mL)	21.2 (19.3–22.6)	22.4 (19.8–24.9)	**0.018**

Abbreviations: ALT: alanine aminotransferase; Apgar: Appearance, Pulse, Grimace, Activity, and Respiration; AST: aspartate aminotransferase; BMI: Body mass index, CS: cesarean section; HB: hemoglobin; NICU: Neonatal Intensive Care Unit; PLT: platelet count.

Data are expressed as mean ± SD, median and interquartiles (Q1-Q3), or number (percentage) where appropriate.

A p value of < 0.05 indicates a significant difference. Statistically significant p-values are in bold.

Table 2 Maternal characteristics and perinatal outcomes of pregnant women with or without severe features of preeclampsia included in the study

	PE ***n*** **= 30**	**PE-SF** ***n*** **= 14**	***p***
Maternal age (year)	29 ± 5.90	31 ± 6.20	0.204
BMI at during test (kg/m^2)	29.3 ± 4.49	27.3 ± 2.49	0.120
Parity	0 (0–2)	1 (0–2)	0.611
Blood sample collection time (week)	34 (29–36)	34 (27–37)	0.724
Delivery time (week)	35 (31–37)	35 (31–38)	0.596
CS	26 (86.7%)	13 (92.9%)	N/A
Female gender	14 (46.7%)	7 (50.0%)	N/A
Birth weight (g)	2220 ± 969.9	1998 ± 1090.2	0.499
Apgar score at 1st minute	8 (8–9)	8 (6–9)	0.188
Apgar score at 5th minute	9 (8–10)	9 (8–10)	0.360
NICU admission	10 (33.3%)	9 (64.3%)	0.109
HB (g/dL)	12.8 ± 1.93	11.3 ± 1.60	0.050
PLT (x10^9/L)	262 ± 95.5	208 ± 76.0	0.071
ALT (U/L)	13 (10–27)	14 (7–26)	0.830
AST (U/L)	23 (17–30)	21 (16–39)	0.781
Creatinine (mg/dL)	0.6 (0.6–0.7)	0.6 (0.5–0.9)	0.856
Neuroserpin (ng/mL)	21.7 (20.6–22.9)	17.2 (12.7–22.0)	**0.011**

Abbreviations: ALT: alanine aminotransferase; Apgar: Appearance, Pulse, Grimace, Activity, and Respiration; AST: aspartate aminotransferase; BMI: Body mass index, CS: cesarean section; HB: hemoglobin; NICU: Neonatal Intensive Care Unit; PE: preeclampsia; PE-SF: preeclampsia with severe features; PLT: platelet count.

Data are expressed as mean ± SD, median and interquartiles (Q1-Q3), or number (percentage) where appropriate.

A p value of < 0.05 indicates a significant difference. Statistically significant p-values are in bold.

Table 3 Spearman's correlation between maternal serum neuroserpin levels and maternal-perinatal characteristics

	r	*p*
Maternal age (year)	-0.082	0.447
BMI (kg/m^2)	0.067	0.537
Parity	0.067	0.539
Delivery time (week)	0.186	0.083
Birth weight	0.161	0.134
Apgar Score at 1stminute	0.112	0.298
Apgar Score at 5th minute	0.049	0.650
ALT (U/L)	0,064	0.552
AST (U/L)	-0,204	0.057

Abbreviations: ALT: alanine aminotransferase; Apgar: Appearance, Pulse, Grimace, Activity, and Respiration; AST: aspartate aminotransferase; BMI: Body mass index; r: Spearman's rank correlation coefficient.

A p value of < 0.05 indicates a significant difference.

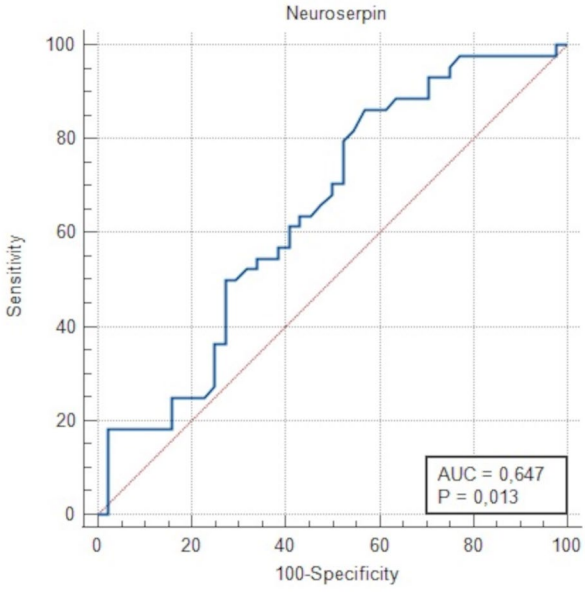

Fig. 2 ROC curve analysis illustrating the diagnostic performance of maternal serum neuroserpin levels for identifying preeclampsia, with a cutoff of ≤ 22.95 ng/mL

specificity of 96.7%. The corresponding AUC was 0.740 (95% CI: 0.586–0.861, $p = 0.007$), as depicted in Fig. 3.

Discussion

The present study demonstrated that maternal serum neuroserpin levels were significantly lower in women diagnosed with preeclampsia compared to gestational age-matched healthy pregnant controls. Moreover, neuroserpin levels were further decreased in those with severe clinical features (Preeclampsia-SF), suggesting a potential role of neuroserpin not only in the presence but also in the progression of the disease.

Preeclampsia is a multifactorial disorder characterized by systemic endothelial dysfunction, placental hypoperfusion, and a heightened inflammatory response. Its

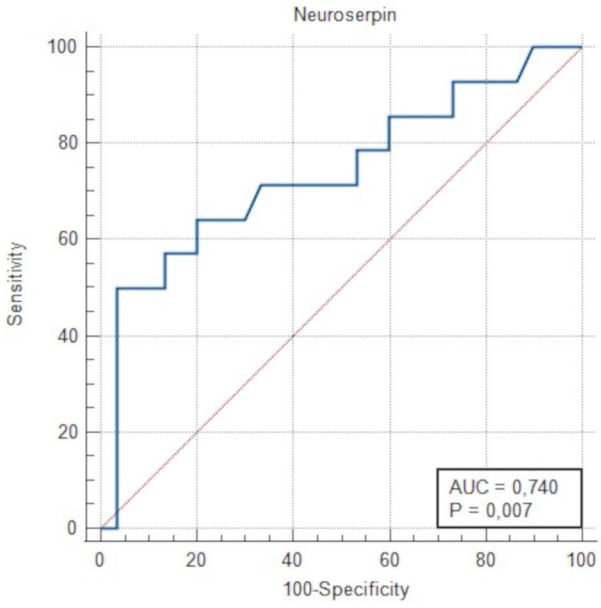

Fig. 3 ROC curve illustrating the predictive value of maternal serum neuroserpin levels for severe preeclampsia, with a cutoff of ≤ 14.7 ng/mL

pathophysiology involves impaired trophoblastic invasion of maternal spiral arteries, oxidative stress, and dysregulation of immune responses, notably an increase in pro-inflammatory cytokines alongside a reduction in regulatory anti-inflammatory mediators [20, 21]. These mechanisms culminate in the exaggerated systemic inflammation that underpins the clinical syndrome.

Neuroserpin, a serine protease inhibitor secreted by neurons and monocytes, is known to regulate proteolytic activity by inhibiting tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) [17, 22, 23]. Under physiological conditions, neuroserpin plays a neuroprotective role by attenuating tPA-mediated extracellular damage, especially during ischemic events [24]. Beyond its neurological functions, neuroserpin is expressed in peripheral tissues such as the heart, pancreas, and pituitary gland, where it contributes to broader processes including vascular remodeling and inflammatory regulation [17, 22, 25].

In experimental models, neuroserpin has been shown to exert anti-inflammatory effects. Notably, Munuswamy-Ramanujam et al. [17] demonstrated that neuroserpin administration reduced T cell infiltration and immune activation, thereby mitigating transplant vasculopathy. These findings support its potential utility as an immunomodulatory agent.

The clinical relevance of neuroserpin in pregnancy remains underexplored. To date, only two studies have investigated its role in pregnant populations. Silva et al. [26] identified altered neuroserpin levels in pregnant women with chronic *Toxoplasma gondii* infection, suggesting neuroimmune interactions involving IL-17 and

IL-33. More pertinently, Perucci et al. [19] reported decreased serum neuroserpin levels in early-onset severe preeclampsia and proposed that neuroserpin deficiency—alongside CXCL-16 and IL-17 A imbalances—may contribute to disease development. Our findings align with Perucci et al.'s results, confirming that lower serum neuroserpin concentrations are associated with both preeclampsia and its severity. Although Spearman correlation analysis did not reveal statistically significant associations between neuroserpin levels and maternal age, BMI, liver enzymes, or perinatal outcomes, the consistent trend of declining neuroserpin with increasing disease severity reinforces its potential role as a pathophysiological marker rather than a coincidental change.

The observed suppression of neuroserpin in preeclamptic pregnancies may reflect impaired physiological upregulation in response to inflammatory vascular stress. In healthy pregnancies, neuroserpin expression may serve as a compensatory mechanism to maintain endothelial integrity. Its reduction in preeclampsia could therefore facilitate unchecked vascular inflammation and endothelial dysfunction. Notably, this alteration appeared independent of maternal demographic factors, further supporting its mechanistic association with disease pathology.

Our findings also resonate with recent biomarker investigations. For instance, reductions in uterine sensitization-associated gene-1 (USAG-1), another inflammation-related molecule, have similarly been linked to preeclampsia severity [27]. Such studies emphasize the need to evaluate emerging serum biomarkers that could improve early diagnosis, risk stratification, and clinical decision-making.

Strengths and limitations

This study has several strengths, including its prospective design, rigorous inclusion criteria, and use of a gestational age-matched control group, which reduce potential confounders. It is the second study to examine neuroserpin in preeclampsia and the first to incorporate subgroup analysis based on disease severity. The use of standardized assay protocols and consistent sample processing adds further robustness to the findings.

Nonetheless, certain limitations should be acknowledged. The study's sample size, although statistically adequate, was relatively modest and limited to a single center. Furthermore, the cross-sectional design precludes assessment of longitudinal trends in neuroserpin levels across pregnancy or postpartum recovery.

Conclusion

In summary, this study provides novel evidence that decreased maternal serum neuroserpin levels are significantly associated with both the presence and severity of preeclampsia. The findings suggest that neuroserpin may serve as a candidate biomarker reflecting disease burden and inflammatory activity. Further large-scale, multicenter, and longitudinal studies are warranted to validate these results and to evaluate the clinical utility of neuroserpin in risk prediction, monitoring, and personalized management of preeclampsia.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
HB	Hemoglobin
Preeclampsia-SF	Preeclampsia with severe features
PlGF	Placental growth factor
PLT	Platelets
sEng	Soluble endoglin
sFlt-1	Soluble fms-like tyrosine kinase-1
TGF	Transforming growth factors
tPa	Tissue plasminogen activator
uPA	Urokinase-type plasminogen activator

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Author contributions

Conceptualization, BSU, FBF and KYY; methodology, FBF and SS; software, DK; validation, BSU and DK; formal analysis, SS and SO; investigation, BSU, FBF and SO; resources, SO and DK; data curation, DK; writing—original draft preparation, FBF; writing—review and editing, SS; visualization, KYY; supervision, KYY; project administration, BSU and FBF. All authors have read and agreed to the published version of the manuscript.

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Data availability

These shall be shown on request. The complete database is private, but it shall be available on request from the corresponding author following permission from Ankara Etlik City Hospital.

Declarations

Ethics approval and consent to participate

All patients and controls provided written informed consents in accordance with the Declaration of Helsinki. This study was approved by Ankara Etlik City Hospital's Scientific Research Assessment and Ethics Committee (September 25, 2024; AEŞH-BADEK-2024-842).

Consent for publication

This is not applicable.

Competing interests

The authors declare no competing interests.

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