Diagnostic and prognostic role of maternal serum prokineticin-1 in preeclampsia and adverse pregnancy outcomes

Merve Ayas Özkan[1], Aziz Kından[1], İslam Aslanlı[2], Kadriye Yakut Yücel[1]

[1]Clinic of Perinatology, University of Health Sciences Türkiye, Ankara Etlik City Hospital, Ankara, Türkiye
[2]Clinic of Obstetrics and Gynecology, University of Health Sciences Türkiye, Ankara Etlik City Hospital, Ankara, Türkiye

Abstract

Objective: Prokineticin-1 (PROK-1), known as endocrine gland-derived vascular endothelial growth factor, is an angiogenic peptide mostly produced in endocrine and placental organs. It is important for placental vascular remodeling and trophoblast control. This study sought to investigate the potential of maternal serum PROK-1 levels as a diagnostic or prognostic marker in preeclampsia (PE).

Material and Methods: This prospective case–control study included women diagnosed with PE and normotensive pregnant controls. Serum samples were collected at hospital admission, and PROK-1 concentrations were quantified using a commercial ELISA kit. Clinical characteristics and perinatal outcomes were compared between groups. Receiver operating characteristic analyses were used to assess the diagnostic and prognostic performance of PROK-1 for PE, disease severity, and composite adverse perinatal outcomes (CAPO).

Results: There were 45 women in the PE group and an equal number of controls. PROK-1 levels were significantly higher in PE than in controls [8.37 (10.51) vs. 4.89 (3.26) ng/mL, $p<0.001$). PROK-1 predicted PE with an area under the curve (AUC) of 0.721 (cut-off >5.40 ng/mL; sensitivity 75.6%, specificity 60.0%; positive predictive value 65.5%, negative predictive value 71.4%). Furthermore, severe PE cases had significantly higher PROK-1 levels than mild PE cases. PROK-1 predicted severe PE with an AUC of 0.716 (cut-off >9.80 ng/mL) and CAPO with an AUC of 0.673 (cut-off >6.53 ng/mL).

Conclusion: Maternal serum PROK-1 was elevated in PE and correlated with disease severity and adverse perinatal outcomes. Although inadequate as a stand-alone marker, PROK-1 may complement existing angiogenic biomarkers in multimarker prediction models. [J Turk Ger Gynecol Assoc. 2026; 27(1): 43-50]

Keywords: Preeclampsia, prokineticin-1, biomarkers, pregnancy outcome, angiogenesis

Received: October 17, 2025 **Accepted:** January 19, 2026 **Publication Date:** March 3, 2026

Introduction

Preeclampsia (PE) is one of the major hypertensive disorders of pregnancy and typically occurs after the 20th week of gestation, presenting with hypertension and various systemic symptoms (1). It is a multisystemic disorder that provides considerable health hazards to both the mother and the fetus, significantly contributing to maternal and perinatal morbidity and mortality globally (2,3). The global prevalence of PE is estimated to range between 2% and 8% of all pregnancies, though regional variations are common (1). PE is clinically categorized into early-onset (EO-PE), occurring prior to 34 weeks of gestation, and late-onset (LO-PE), which presents beyond 34 weeks (4). EO-PE is often more severe and predominantly associated with fetal complications, while LO-PE tends to be more frequent and more closely linked with maternal outcomes (5). Despite these clinical distinctions,

Address for Correspondence: *Merve Ayas Özkan*
e-mail: *merveayasozkan@gmail.com* ***ORCID:*** *orcid.org/0000-0002-2437-9719*

DOI: *10.4274/jtgga.galenos.2026.2025-10-12*

Cite this article as: *Ayas Özkan M, Kından A, Aslanlı İ, Yakut Yücel K. Diagnostic and prognostic role of maternal serum prokineticin-1 in preeclampsia and adverse pregnancy outcomes. J Turk Ger Gynecol Assoc. 2026; 27(1): 43-50*

both forms share a common underlying mechanism involving placental dysfunction. The predominant hypothesis for the pathophysiology of PE focuses on insufficient remodeling of the spiral arteries, resulting in placental hypoperfusion, ischemia, and eventual systemic endothelial dysfunction, associated with inflammatory activation (6). This cascade of events disrupts maternal vascular homeostasis and gives rise to the clinical manifestations of PE. Molecular pathways and biomarkers have been investigated to better understand this process and to identify early diagnostic indicators (7,8).

Prokineticin-1 (PROK-1) has emerged as a notable candidate molecule. PROK-1, often referred to as endocrine gland-derived vascular endothelial growth factor (VEGF), is an angiogenic peptide predominantly found in steroidogenic tissues, including the adrenal gland, ovary, testis, and placenta (9). Although not a member of the VEGF family, it exerts VEGF-like effects in endocrine tissues by promoting vascular growth and cellular proliferation (10). PROK-1 contributes to endometrial and placental angiogenesis and regulates cellular processes including proliferation, adhesion, and invasion (11). It plays an essential role in embryo implantation and trophoblastic invasion, two of the key events in early placental development (11,12). Dysregulation of PROK-1 expression, whether excessive or deficient, has been implicated in several pregnancy complications, suggesting that it may act as a sensitive indicator of placental health (13,14).

However, despite increasing biological evidence, the clinical utility of PROK-1 in PE remains unclear. Only a limited number of human studies have evaluated circulating PROK-1 levels in PE, and findings are inconsistent, with some reporting elevated levels while others found no significant difference between PE and healthy pregnancies. Moreover, most published work has focused solely on diagnostic comparison and has not examined the relationship between PROK-1, disease severity, or adverse perinatal outcomes. Therefore, there is a knowledge gap regarding whether maternal PROK-1 levels may provide diagnostic or prognostic value in PE, beyond currently used clinical parameters.

Given these uncertainties and the lack of consistent clinical evidence, PROK-1 may be a promising biomarker for the diagnosis and prognosis of PE due to its dual role as an angiogenic and trophoblast regulatory factor. Therefore, the objective of the present study was to measure maternal serum PROK-1 concentrations in women with PE, evaluate their diagnostic and prognostic performance, and investigate their potential association with adverse perinatal outcomes.

Material and Methods

This prospective case–control observational study was conducted in the perinatology clinic of a tertiary referral center between April 2024 and October 2024, in accordance with the STROBE guidelines for observational studies. The study protocol was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (approval number: 2024-252, date: 03.04.2024), and all procedures adhered to the Declaration of Helsinki.

During the study period, all women admitted to the perinatology clinic and evaluated for suspected PE were screened. No randomization procedures were used because this was an observational case–control design. Pregnant women aged 18–40 years who met the diagnostic criteria of the American College of Obstetricians and Gynecologists for PE were included in the case group (1). EO-PE was defined as diagnosis before 34 weeks, and LO-PE as diagnosis at or after 34 weeks of gestation (5). To minimize selection bias and ensure comparability between groups, the control group was composed of the next eligible healthy pregnant woman admitted to the clinic on the same day as each PE case, matched according to maternal age, gestational week, and body mass index (BMI). Exclusion criteria consisted of multiple current pregnancy, chronic maternal disease, fetal growth restriction diagnosed before PE, fetal congenital or chromosomal anomalies, placental pathology, chronic medication use, maternal smoking or alcohol consumption, and loss to follow-up.

The sample size was calculated using G*Power 3.0.10 with an alpha of 0.05 and a power of 0.80, indicating that a minimum of 42 participants was required. Maternal demographic characteristics (age, parity, BMI), gestational age at diagnosis, gestational age at blood sampling, gestational age at delivery, umbilical artery systolic/diastolic ratio (UA-S/D) and pulsatility index (UA-PI), biochemical parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, uric acid, 24-hour urine protein], birth weight, mode of delivery, neonatal outcomes and the presence of composite adverse perinatal outcomes (CAPO) were obtained from standardized electronic hospital records. CAPO was defined as the occurrence of at least one adverse outcome, including spontaneous preterm birth, fetal growth restriction, oligohydramnios or polyhydramnios, preterm premature rupture of membranes, fetal distress [Category III fetal heart rate tracing (15)], or the need for neonatal intensive care unit (NICU) admission.

For PROK-1 analysis, maternal venous blood samples were collected at the time of diagnosis, placed in EDTA tubes, centrifuged within 10 minutes, and stored at –80 °C until analysis. Serum PROK-1 levels were measured in duplicate using a commercially available human PROK-1 ELISA kit (E4173Hu), and results were expressed in ng/mL. The same laboratory protocol was used for all samples in both groups to ensure measurement consistency and reduce information

bias. Additional potential sources of bias were minimized by prospective participant selection, matching of controls, and the use of objective data extracted from electronic medical records.

Statistical analysis

All statistical analyses were performed using IBM SPSS, version 30.0 (IBM Inc., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess the normality of data distribution since each group included more than 30 participants. Normally distributed variables are presented as mean ± standard deviation and compared using the Student's t-test, whereas non-normally distributed variables are presented as median (25^{th}–75^{th} percentile) and compared using the Mann–Whitney U test. Categorical variables are expressed as frequencies and percentages and analyzed using Pearson's chi-square or Fisher's exact test, as appropriate. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic and prognostic performance of maternal serum PROK-1 levels for the prediction of PE, severe PE, and CAPO. Cut-off values were determined using the Youden index, and area under the curve (AUC) values are reported with 95% confidence intervals. No missing data were present in the study. A p-value <0.05 was considered statistically significant.

Results

A total of 90 pregnant women were included in the study, comprising 45 women with PE and 45 normotensive controls. The flowchart summarizing patient screening, exclusions, and final group distribution is presented in Figure 1. Maternal age, gravida, parity, and BMI did not differ between the groups (all p>0.05). In comparison to controls, the gestational week of diagnosis in the PE group was substantially earlier (median 33.2 weeks, p<0.001). The PE group had significantly increased UA-S/D and UA-PI (both p<0.001). Preeclamptic patients had significantly lower platelet counts (p=0.048), and their levels of AST, ALT, creatinine, and uric acid were all significantly higher than those of the control group (p<0.05 for all). The EO-PE had substantially earlier gestational weeks at diagnosis and sampling (both p<0.001) and higher UA-PI values (p=0.006) than the LO-PE when PE patients were stratified by PE subtype, whereas other maternal characteristics did not differ significantly (Table 1).

The perinatal and neonatal outcomes were markedly inferior in the PE cohort. The gestational age at delivery was significantly lower in the PE group compared to controls (36.1 vs. 39.0 weeks, p<0.001), and the mean birth weight was substantially diminished (2550 g vs. 3160 g, p<0.001). The incidences of preterm delivery (53.3% vs. 6.7%), low birth weight (<2500 g; 48.9% vs. 8.9%), and fetal growth restriction (22.2% vs. 0%) were markedly elevated in the PE group (all p<0.001). Neonates delivered by mothers with PE exhibited diminished Apgar scores at both one and five minutes (p=0.006 and p=0.003, respectively) and necessitated admission to the NICU more often (48.9% vs. 4.4%, p<0.001). CAPO were observed in 48.9% of the PE group and 6.7% of controls (p<0.001). Within PE subgroups, EO-PE was associated with higher rates of preterm delivery, low birth weight, fetal distress, NICU admission, and CAPO compared with LO-PE (p<0.05 for all) (Table 2).

The entire PE group had considerably higher median maternal serum PROK-1 levels than the controls [8.37 (10.51) vs. 4.89 (3.26), p<0.001]. PROK-1 concentrations were greater in the EO-PE and LO-PE groups than in the controls (p=0.006 and p=0.019, respectively), but there was no difference between the two PE sub-groups (p=0.467). Severe PE cases showed significantly higher PROK-1 levels than mild PE cases when analyzed by illness severity [10.75 (10.61) vs. 6.84 (6.75), p=0.014] (Table 3).

ROC analyses evaluating the diagnostic and prognostic value of PROK-1 are presented in a single composite figure (Figure 2). PROK-1 demonstrated significant diagnostic ability for PE (AUC 0.721, 95% CI 0.61–0.82, p<0.001) with an optimal cut-off value of >5.40 ng/mL (sensitivity 75.6%, specificity 60.0%). For predicting CAPO, the AUC was 0.673 (95% CI 0.55–0.79, p=0.004) with a cut-off >6.53 ng/mL. For assessing severity of PE, PROK-1 yielded an AUC of 0.716 (95% CI 0.56–0.86, p=0.006), with a cut-off of >9.80 ng/mL providing 70.0% sensitivity and 72.0% specificity. Summary performance metrics are presented in Table 4.

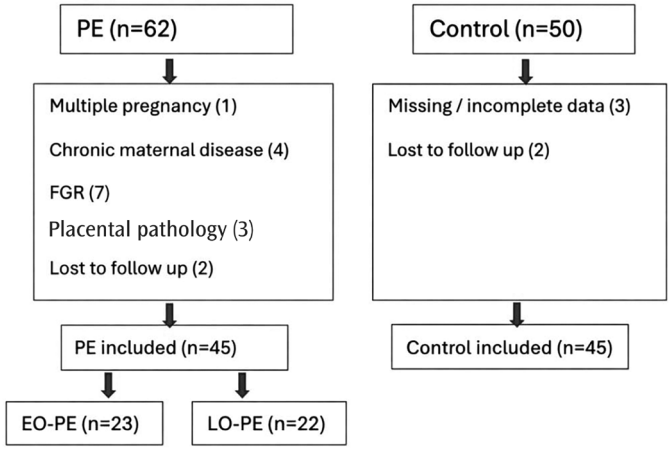

Figure 1. Flowchart of participant screening, exclusion criteria, and final group allocation. In this prospective case–control study, 62 women evaluated for preeclampsia and 50 healthy pregnant women were screened. After applying exclusion criteria, 45 women with preeclampsia and 45 normotensive controls were included in the final analysis EO-PE: Early-onset, LO-PE: Late-onset

Table 1. Maternal characteristics, Doppler findings, and biochemical markers in preeclampsia and control groups

	Total PE (n=45)	Total Control (n=45)	p-value	EO-PE (n=23)	LO-PE (n=22)	p-value
Maternal age (year)	32.1±5.8	29.5±5.2	0.062	32.4±6.0	31.9±5.6	0.781[a]
Gravida	2 (2)	2 (2)	0.320	2 (2)	2 (1)	0.267[b]
Parity	1 (2)	1 (1)	0.489	1 (2)	1 (1)	0.520[b]
Nulliparous	18 (40.0)	22 (48.9)	0.410[c]	7 (30.4)	11 (50.0)	0.173[c]
BMI (kg/m^2)	31.5 (5.8)	29.6 (5.4)	0.058[b]	31.1 (5.9)	32.8 (4.6)	0.142[b]
Gestational week at diagnosis	33.2 (5)	-	-	30.2 (5)	35.8 (2)	**<0.001**[b]
Gestation at sampling	33.2 (5)	33.5 (6)	0.318[b]	30.4 (5)	36.2 (2)	**<0.001**[b]
UA-S/D	3.0 (0.7)	2.3 (0.8)	**<0.001**[b]	3.3 (0.9)	2.6 (0.6)	**0.004**[b]
UA-PI	1.02 (0.25)	0.79 (0.21)	**<0.001**[b]	1.12 (0.27)	0.91 (0.22)	**0.006**[b]
Platelet count (10^9/L)	220 (68)	247 (74)	0.048[b]	212 (88)	229 (62)	0.521[b]
AST (IU/L)	24 (16)	16 (9)	**0.012**[b]	27 (18)	21 (13)	0.094[b]
ALT (IU/L)	19 (11)	12 (7)	**0.004**[b]	22 (13)	16 (9)	**0.046**[b]
Creatinine (mg/dL)	0.68 (0.15)	0.44 (0.09)	**<0.001**[b]	0.71 (0.16)	0.66 (0.12)	0.287[b]
Uric acid (mg/dL)	6.5 (2.2)	3.7 (1.1)	**<0.001**[b]	7.1 (2.3)	5.9 (1.8)	**0.041**[b]
24-hour urine protein (mg)	612 (1215)	-	-	748 (298)	482 (276)	0.081[b]

Data are expressed as n (%), mean ± standard deviation or median (interquartile range) where appropriate. A p-value of <0.05 indicates a significant difference and statistically significant p-values are in bold. EO-PE: Early onset preeclampsia, LO-PE: Late onset preeclampsia, BMI: Body mass index, UA-SD: Umbilical artery systolic/diastolic ratio, UA-PI: Umbilical artery pulsatility index, [a]: Student's t-test, [b]: Mann-Whitney U test, [c]: Pearson chi-square test, [d]: Fisher's exact test

Table 2. Perinatal and neonatal outcomes in preeclampsia subgroups compared to controls

	Total PE (n=45)	Total control (n=45)	p-value	EO-PE (n=23)	LO-PE (n=22)	p-value
Gestational age at delivery (week)	36.1 (3.2)	39.0 (2.1)	**<0.001**[a]	34.2 (3.9)	37.3 (2.0)	**<0.001**[a]
Preterm birth	24 (53.3%)	3 (6.7%)	**<0.001**[b]	18 (78.3%)	6 (27.3%)	**0.002**[b]
Mode of delivery Vaginal delivery Primary cesarean section Repeat cesarean section	 16 (35.5%) 21 (46.6%) 8 (17.8%)	 28 (62.2%) 10 (22.2%) 7 (15.6%)	0.005b	 6 (26.0%) 12 (52.1%) 5 (21.7%)	 10 (45.4%) 9 (40.9%) 3 (13.6%)	0.074[b]
Birth weight (gram)	2550 (1220)	3160 (580)	**<0.001**[a]	1810 (910)	2760 (780)	**<0.001**[a]
Low birth weight (<2500 gr)	22 (48.9%)	4 (8.9%)	**<0.001**[b]	17 (73.9%)	5 (22.7%)	**<0.001**[b]
FGR	10 (22.2%)	0 (0%)	**<0.001**[b]	8 (34.8%)	2 (9.1%)	**0.025**[b]
Premature rupture of membranes	4 (8.9%)	2 (4.4%)	0.403[b]	2 (8.7%)	2 (9.1%)	0.971[b]
Fetal Distress	9 (20.0%)	3 (6.7%)	0.083[b]	7 (30.4%)	2 (9.1%)	0.049[b]
Apgar score at 1st minute	8 (2)	9 (1)	**0.006**[a]	7 (3)	9 (1)	**0.002**[a]
Apgar score at 5th minute	9 (2)	10 (1)	**0.003**[a]	8 (2)	10 (1)	**0.001**[a]
RDS	12 (26.7%)	1 (2.2%)	**<0.001**[b]	9 (39.1%)	3 (13.6%)	0.064[b]
NICU admission	22 (48.9%)	2 (4.4%)	**<0.001**[b]	17 (73.9%)	5 (22.7%)	**<0.001**[a]
CAPO	22 (48.9%)	3 (6.7%)	**<0.001**[b]	17 (73.9%)	5 (22.7%)	**<0.001**[a]
Intrauterine fetal demise	1 (2.2%)	0 (0%)	0.312[b]	1 (4.3%)	0 (0%)	0.328[b]

Data are expressed as n (%), mean ± standard deviation or median (interquartile range) where appropriate. A p-value of <0.05 indicates a significant difference and statistically significant p-values are in bold. EO-PE: Early onset preeclampsia, LO-PE: Late onset preeclampsia, FGR: Fetal growth restriction, NICU: Neonatal intensive care unit, CAPO: Composite adverse perinatal outcome. [a]: Mann-Whitney U test, [b]: Pearson chi-square, [c]: Student's t-test, [d]: Fisher's exact test

Discussion

The main objective ofthe present study was to ascertain maternal serum PROK-1 concentrations in pregnancies affected by PE and to compare them with levels in healthy controls. A secondary objective was to assess the relationship between PROK-1 levels, meaures of PE severity, and pregnancy outcomes. Our findings demonstrated that maternal PROK-1 levels were significantly elevated in women with PE compared with normotensive pregnancies. The increase was most pronounced in severe PE cases and showed an additional association with CAPO. These findings suggest that PROK-1, a peptide with recognized angiogenic and trophoblastic regulatory roles, may play a clinically important role in the pathophysiology of PE. By integrating both severity and perinatal outcomes, this study has expanded the limited literature about PROK-1 and provides new insight into its clinical relevance.

During a typical pregnancy, extravillous trophoblasts infiltrate and restructure spiral arteries into low-resistance channels, facilitating optimal uteroplacental blood circulation. When this process fails, trophoblastic invasion becomes shallow and spiral artery remodeling remains incomplete, leading to placental hypoperfusion and ischemia. These events trigger systemic endothelial dysfunction and inflammation, both central to the development of PE (6,16).

PROK-1 is abundantly expressed in the placenta and functions as a key regulator of angiogenesis, vascular remodeling, and trophoblast activity (17). Physiologically, its expression peaks during the first trimester, which corresponds to the period of most intense vascular development, but then declines in later trimesters (17,18). This early elevation supports implantation and the establishment of placental circulation (17,19). PROK-1 has been shown to play an important role in the development of the normal placenta (20). Persistent elevation beyond the first trimester, however, may disrupt normal placental physiology. PROK-1 has been shown to inhibit extravillous trophoblast invasion and migration while promoting cell proliferation (17,18). These effects can lead

Table 3. Comparison of PROK-1 levels between preeclampsia subgroups and controls

Comparison Groups	Group	n	PROK-1 levels	p-value
Total-PE vs. control	**Total-PE**	45	8.37 (10.51)	**<0.001**[a]
	Control	45	4.89 (3.26)	
EO-PE vs. control	**EO-PE**	23	8.59 (8.45)	**0.006**[a]
	Control	23	4.89 (2.75)	
LO-PE vs. control	**LO-PE**	22	8.09 (6.44)	**0.019**[a]
	Control	22	4.93 (5.74)	
EO-PE vs. LO-PE	**EO-PE**	23	8.59 (8.45)	0.467[a]
	LO-PE	22	8.09 (6.44)	
Severe PE vs. Mild PE	**Severe PE**	20	10.75 (10.61)	**0.014**[a]
	Mild PE	25	6.84 (6.75)	

Data are expressed as n (%) or median (interquartile range) where appropriate. A p-value of <0.05 indicates a significant difference and statistically significant p-values are in bold. EO-PE: Early onset preeclampsia, LO-PE: Late onset preeclampsia, [a]: Mann-Whitney U Test, PROK-1: Prokineticin-1

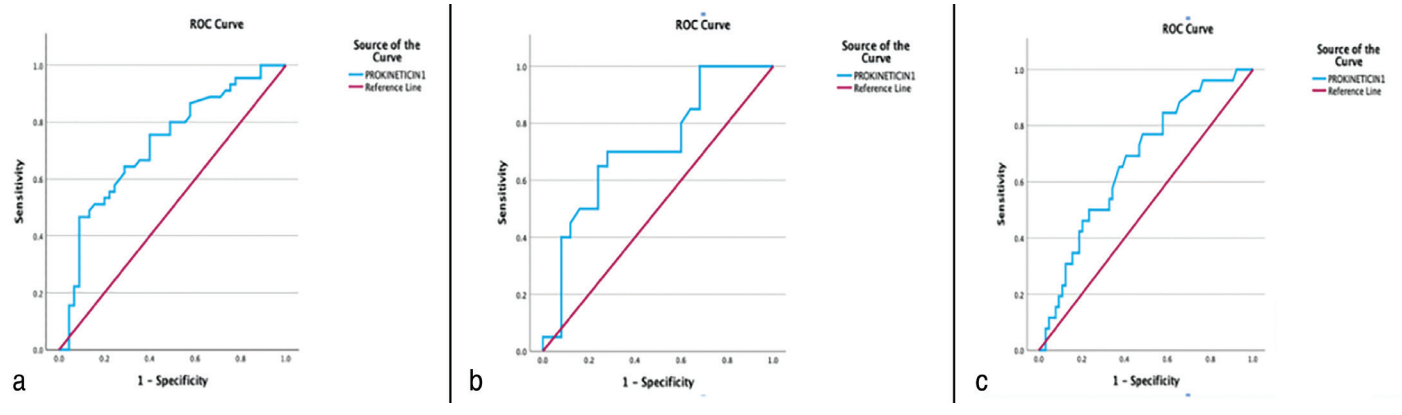

Figure 2. Composite receiver operating characteristic (ROC) curves of maternal serum prokineticin-1 levels for: (a) diagnosis of preeclampsia, (b) prediction of composite adverse perinatal outcomes, and (c) prediction of disease severity in preeclampsia

Table 4. Diagnostic and prognostic performance of PROK-1 for preeclampsia, adverse perinatal outcomes, and disease severity

	Cut-off*	Sensitivity	Specificity	AUC	%95 CI	p-value
Preeclampsia	>5.40	75.6%	60.0%	0.721	0.61-0.82	**<0.001**
Composite adverse perinatal outcomes	>6.53	65.5%	62.5%	0.673	0.55-0.79	**0.004**
Severe preclampsia	>9.80	70.0%	72.0%	0.716	0.56-0.86	**0.006**
*Cut-off values were found according to Youden index. AUC: Area under the curve, CI: Confidence Interval						

to inadequate vascular remodeling, a hallmark of PE. An experimental animal study reported that prolonged PROK-1 overexpression caused pregnancy-related hypertension (21), suggesting that sustained upregulation may contribute directly to PE pathogenesis. In line with these findings, our observation of higher maternal PROK-1 levels in diagnosed PE cases may provide indirect evidence of an earlier pathogenic role.

Previous studies also indicated that alterations in PROK-1 expression may influence pregnancy outcomes. Hoffman et al. (18) demonstrated that PROK-1 plays a central role in normal placentation, with significantly higher maternal levels observed in pregnancies affected by PE compared with healthy controls. Similarly, Inan and colleagues found that elevated first-trimester PROK-1 concentrations predicted subsequent PE and fetal growth restriction, whereas lower levels were linked to spontaneous preterm birth and gestational diabetes (22). Taken together, these findings highlight the importance of balanced PROK-1 activity for normal placental development, as both deficiency and excess may disturb homeostasis and contribute to obstetric complications.

However, not all investigations have arrived at uniform conclusions. Ulu et al. (19) found no significant difference in PROK-1 levels between preeclamptic and healthy pregnancies, while a trend towards elevated values was noted in severe PE. The study indicated that PROK-1 levels were generally lower in the mild PE cohort than in the severe PE cohort, but this difference was not significant (19). Differences in study design, patient selection, timing of sample collection, and assay sensitivity may explain these discrepancies. In our cohort, the higher PROK-1 concentrations among severe PE cases align more closely with the pathophysiologic mechanisms proposed in experimental data, supporting the hypothesis that PROK-1 upregulation may reflect endothelial and placental dysfunction.

Our results also revealed a significant association between PROK-1 and CAPO. Mechanistically, PROK-1 influences endothelial proliferation and vascular remodeling through specific PROK receptors, and its expression is enhanced under hypoxic conditions (23,24). These pathways may explain how elevated PROK-1 levels contribute to placental insufficiency and adverse fetal outcomes or may reflect the hypoxia present in palcenta and supplying vessels in existing PE. Due to the observational nature of our study, causal inference cannot be established. Further prospective, mechanistic and longitudinal research is required to determine whether PROK-1 acts as a driver of pathology or as a compensatory response to placental hypoxia.

From a diagnostic perspective, PROK-1 demonstrated moderate accuracy for distinguishing PE from normal pregnancy (AUC =0.721) and fair ability to predict severe disease and CAPO. Although its independent diagnostic performance remains limited, PROK-1 may enhance accuracy as part of a multimarker panel. Current evidence supports the utility of angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) in PE prediction and monitoring (8,25). The combination of a high sFlt-1/PlGF ratio with other emerging angiogenic markers, including PROK-1, could potentially improve predictive accuracy and clinical decision-making.

These findings highlight the potential role of PROK-1 as an adjunctive biomarker that may contribute to earlier risk stratification and improved clinical decision-making in pregnancies at risk for PE.

Study limitations

A key strength of our study lies in its prospective design and well-matched control group. Inclusion of both early- and LO-PE subtypes allowed subgroup comparisons and yielded consistent results across gestational stages. Moreover, beyond evaluating diagnostic potential, we also assessed PROK-1's association with disease severity and neonatal outcomes which added a prognostic dimension rarely explored in prior studies. Nonetheless, specific limits must be recognized. The study sample was modest and sourced from a single center, constraining generalizability. Serum PROK-1 levels were measured only at the time of diagnosis, preventing evaluation of temporal trends or early predictive value. Furthermore, given that PROK-1 alone provided only moderate diagnostic strength, it should likely be interpreted alongside other biochemical and clinical markers rather than as a stand-alone test.

Conclusion

Maternal serum PROK-1 levels were significantly elevated in pregnancies complicated by diagnosed PE and correlated with both disease severity and adverse perinatal outcomes. Although, diagnostic performance in isolation was moderate, PROK-1 may serve as a complementary marker when combined with established angiogenic biomarkers, such as sFlt-1 and PlGF. Integrating PROK-1 into multimarker predictive models may enhance the early identification and risk stratification of PE. Future multicenter and longitudinal studies with early gestational sampling that continues throughout pregnancy until delivery are needed to confirm clinical applicability and temporal changes throughout pregnancy, both normal and when affected by PE. This information would help to clarify whether elevated PROK-1 represents a causal factor or a secondary response to placental dysfunction.

Ethics

Ethics Committee Approval: *The study protocol was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (approval number: 2024-252, date: 03.04.2024), and all procedures adhered to the Declaration of Helsinki.*

Informed Consent: *All women had signed an informed consent that their data may be used in research studies.*

Footnotes

Author Contributions: *Surgical and Medical Practices: M.A.O., A.K., İ.A., K.Y.Y., Concept: M.A.O., K.Y.Y., Design: M.A.O., A.K., K.Y.Y., Data Collection or Processing: M.A.O., A.K., İ.A., K.Y.Y., Analysis or Interpretation: M.A.O., A.K., İ.A., Literature Search: M.A.O., A.K., İ.A., Writing: M.A.O.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. Gestational hypertension and preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020; 135: e237-e60.
2. Ives CW, Sinkey R, Rajapreyar I, Tita ATN, Oparil S. Preeclampsia-pathophysiology and clinical presentations: JACC state-of-the-art review. J Am Coll Cardiol. 2020; 76: 1690-702.
3. Backes CH, Markham K, Moorehead P, Cordero L, Nankervis CA, Giannone PJ. Maternal preeclampsia and neonatal outcomes. J Pregnancy. 2011; 2011: 214365.
4. Tranquilli AL. Early and late-onset pre-eclampsia. Pregnancy Hypertens. 2014; 4: 241.
5. Wójtowicz A, Zembala-Szczerba M, Babczyk D, Kołodziejczyk-Pietruszka M, Lewaczyńska O, Huras H. Early- and late-onset preeclampsia: a comprehensive cohort study of laboratory and clinical findings according to the new ISHHP criteria. Int J Hypertens. 2019; 2019: 4108271.
6. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges, and perspectives. Circ Res. 2019; 124: 1094-112.
7. Dayanan R, Bulan DD, Yucel KY. Diagnostic and prognostic role of thrombospondin-4 levels in pre-eclampsia: Association with onset type, severity, and perinatal outcome. Int J Gynaecol Obstet. 2025; 171: 345-52.
8. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016; 374: 13-22.
9. Masuda Y, Takatsu Y, Terao Y, Kumano S, Ishibashi Y, Suenaga M, et al. Isolation and identification of EG-VEGF/prokineticins as cognate ligands for two orphan G-protein-coupled receptors. Biochem Biophys Res Commun. 2002; 293: 396-402.
10. Corlan AS, Cîmpean AM, Jitariu AA, Melnic E, Raica M. Endocrine gland-derived vascular endothelial growth factor/prokineticin-1 in cancer development and tumor angiogenesis. Int J Endocrinol. 2017; 2017: 3232905.
11. Goryszewska E, Kaczynski P, Balboni G, Waclawik A. Prokineticin 1-prokineticin receptor 1 signaling promotes angiogenesis in the porcine endometrium during pregnancy†. Biol Reprod. 2020; 103: 654-68.
12. Chiang YT, Seow KM, Chen KH. The pathophysiological, genetic, and hormonal changes in preeclampsia: a systematic review of the molecular mechanisms. Int J Mol Sci. 2024; 25: 4532.
13. Cheng XX, Li MQ, Peng T. Novel ınsights into prokineticin 1 role in pregnancy-related diseases. Int J Med Sci. 2024; 21: 27-36.
14. Goryszewska-Szczurek E, Baryla M, Kaczynski P, Waclawik A. Prokineticin 1-prokineticin receptor 1 signaling in trophoblast promotes embryo implantation and placenta development. Sci Rep. 2021; 11: 13715.
15. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol. 2009; 114: 192-202.
16. Staff AC, Fjeldstad HE, Fosheim IK, Moe K, Turowski G, Johnsen GM, et al. Failure of physiological transformation and spiral artery atherosis: their roles in preeclampsia. Am J Obstet Gynecol. 2022; 226: S895-S906.
17. Alfaidy N. Prokineticin1 and pregnancy. Ann Endocrinol (Paris). 2016; 77: 101-4.
18. Hoffmann P, Saoudi Y, Benharouga M, Graham CH, Schaal JP, Mazouni C, et al. Role of EG-VEGF in human placentation: physiological and pathological implications. J Cell Mol Med. 2009; 13: 2224-35.
19. Ulu İ, Yıldırım Köpük Ş, Çekmez Y, Kıran G. Can prokineticin 1 be used as a biomarker in preeclampsia? The Journal of Gynecology - Obstetrics and Neonatology. 2022; 19: 1368-72.
20. Alfaidy N, Hoffmann P, Boufettal H, Samouh N, Aboussaouira T, Benharouga M, et al. The multiple roles of EG-VEGF/PROK1 in normal and pathological placental angiogenesis. Biomed Res Int. 2014; 2014: 451906.
21. Sergent F, Hoffmann P, Brouillet S, Garnier V, Salomon A, Murthi P, et al. Sustained endocrine gland-derived vascular endothelial growth factor levels beyond the first trimester of pregnancy display phenotypic and functional changes associated with the pathogenesis of pregnancy-ınduced hypertension. Hypertension. 2016; 68: 148-56.

22. Inan C, Varol FG, Erzincan SG, Uzun I, Sutcu H, Sayin NC. Use of prokineticin-1 (PROK1), pregnancy-associated plasma protein A (PAPP-A) and PROK1/PAPP-A ratio to predict adverse pregnancy outcomes in the first trimester: a prospective study. J Matern Fetal Neonatal Med. 2018; 31: 2685-92.
23. Hoffmann P, Feige JJ, Alfaidy N. Expression and oxygen regulation of endocrine gland-derived vascular endothelial growth factor/prokineticin-1 and its receptors in human placenta during early pregnancy. Endocrinology. 2006; 147: 1675-84.
24. Brouillet S, Hoffmann P, Benharouga M, Salomon A, Schaal JP, Feige JJ, et al. Molecular characterization of EG-VEGF-mediated angiogenesis: differential effects on microvascular and macrovascular endothelial cells. Mol Biol Cell. 2010; 21: 2832-43.
25. Dröge LA, Perschel FH, Stütz N, Gafron A, Frank L, Busjahn A, et al. Prediction of preeclampsia-related adverse outcomes with the sFlt-1 (Soluble fms-Like Tyrosine Kinase 1)/PlGF (placental growth factor)-ratio in the clinical routine: a real-world study. Hypertension. 2021; 77: 461-71.