Comparison of Serum Vascular Endothelial Growth Factor (VEGF) Levels Between Preeclamptic and Normotensive Pregnancies

Edgar Anthony Petra Sihite[1*], Johny Marpaung[2], Deri Edianto[3], Mohd. Rhiza Tala[4], Edwin Martin Asroel[5], Hilma Putri Lubis[6]

[1] Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, North Sumatera, Indonesia
[2] Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, North Sumatera, Indonesia
[3] Division of Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, North Sumatera, Indonesia
[4] Division of Urogynecology, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, North Sumatera, Indonesia
[5] Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, North Sumatera, Indonesia
[6] Division of Reproductive, Endocrinology and Infertility, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, North Sumatera, Indonesia

*Corresponding author: Edgar Anthony Petra Sihite
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara

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Abstract: Background: Preeclampsia is a hypertensive disorder of pregnancy that significantly contributes to maternal and fetal morbidity and mortality. Its pathogenesis is closely associated with angiogenic imbalance, particularly decreased levels of Vascular Endothelial Growth Factor (VEGF) due to increased anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), leading to systemic endothelial dysfunction. Objective: To compare serum VEGF levels between pregnant women with preeclampsia and normotensive pregnancies and to evaluate the diagnostic performance of VEGF as a predictor of preeclampsia. Methods: This analytical observational study with a case-control design included 40 subjects (20 preeclampsia and 20 normotensive pregnancies) at H. Adam Malik General Hospital and affiliated centers. Serum VEGF levels were measured using ELISA. Statistical analysis was performed using the Mann–Whitney test and Receiver Operating Characteristic (ROC) curve analysis ($p<0.05$). Results: Serum VEGF levels were significantly lower in the preeclampsia group compared to normotensive pregnancies (8.03±3.27 vs 39.78±24.39 pg/mL; $p<0.001$). Median values also showed consistent differences. ROC analysis demonstrated excellent diagnostic performance with an AUC of 1.000 ($p<0.001$). The optimal cutoff value of 14.9 pg/mL yielded 100% sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy.Conclusion: VEGF levels are significantly decreased in preeclampsia and demonstrate excellent potential as a reliable biomarker for predicting preeclampsia, supporting its use in early clinical assessment.

Keywords: preeclampsia, VEGF, angiogenesis, biomarker, pregnancy, endothelial dysfunction

INTRODUCTION

One of the key indicators used to assess the health status of a population in a country is the Maternal Mortality Ratio (MMR). In Indonesia, the MMR remains relatively high compared to other countries in the ASEAN region. According to the World Health Organization (WHO) in 2023, maternal mortality worldwide remains high, with approximately 260,000 women dying during and after pregnancy or childbirth. In Indonesia, based on population surveys, the MMR is reported to be 305 per 100,000 live births. Several factors contribute to the increased MMR, including the "four too" conditions: pregnancies that are too early, too frequent, too close, and too late. Proper pregnancy planning is one of the key strategies to reduce high-risk pregnancies and potentially lower maternal mortality rates.[1]

Preeclampsia (PE), small-for-gestational-age (SGA) infants, preterm birth, and recurrent miscarriage are complications occurring in approximately 17–29% of all pregnancies.[2] Preeclampsia is a multifactorial disease, and its pathogenesis cannot be attributed to a single factor such as genetic, immunological, or environmental causes; rather, it results from a complex interaction of multiple factors.[3] Preeclampsia is defined as a pregnancy complication occurring after 20 weeks of gestation, characterized by new-onset hypertension and proteinuria in previously normotensive women.[4]

The preeclamptic placenta releases large amounts of anti-angiogenic factors, particularly soluble fms-like tyrosine kinase-1 (sFlt-1), into the maternal circulation. This factor binds to pro-angiogenic molecules such as Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PlGF), resulting in an anti-angiogenic state.[4] Preeclampsia is therefore characterized by elevated plasma sFlt-1 levels and decreased circulating VEGF and PlGF levels.[5]

Maintaining VEGF levels within a physiological range is essential for a healthy pregnancy. However, imbalance in VEGF levels increases the likelihood of pathological conditions, particularly in pregnant women.[6] In normal pregnancy, cytotrophoblast cells aggregate and attach the embryo to the uterine wall. Extravillous cytotrophoblasts subsequently invade the decidual interstitium and maternal spiral arteries, establishing pathways that allow the fetus to obtain nutrients and oxygen while removing metabolic waste products.[7] During pregnancy, the human placenta undergoes both angiogenesis and vasculogenesis.[8]

VEGF and PlGF belong to the family of endothelial growth factors with strong angiogenic and mitogenic activity, enhancing vascular endothelial permeability.[9] VEGF serves as a key regulator of both physiological and pathological angiogenesis by promoting endothelial cell proliferation and neovascularization.[9] It is predominantly expressed on the surface of placental syncytiotrophoblasts and invasive chorionic trophoblast cells. VEGF is highly expressed in blood vessels during early pregnancy and is abundant in trophoblast cells.[10] VEGF (particularly VEGF-A) plays a crucial role in endothelial cell proliferation, migration, and angiogenesis, mediated through its receptors VEGFR-1 (Flt-1) and VEGFR-2 (kinase insert domain receptor/KDR). VEGFR-1 is particularly important in pathological angiogenesis.[3]

A study by Mochan et al. demonstrated that maternal serum VEGF concentrations in preeclamptic women (170.53 ± 36.55 pg/mL) were significantly lower than in normotensive pregnant women (254.61 ± 47.39 pg/mL; p<0.0001).[8] Similarly, Nabweyambo et al. reported significantly lower plasma VEGF and PlGF levels in preeclamptic women compared to normal pregnancies (median VEGF: 0.71 pg/mL [IQR 0.38–1.11] vs 1.20 pg/mL [0.64–1.91]; PlGF: 2.20 pg/mL [1.08–5.86] vs 84.62 pg/mL [34.00–154.45]). Using a VEGF cutoff value of 0.4594 pg/mL, sensitivity and specificity for predicting preeclampsia were 56% and 69%, respectively.[4] Tang et al. demonstrated that serum VEGF levels in patients with pregnancy-induced hypertension (PIH), mild preeclampsia, severe preeclampsia, and control groups were 24.58±3.54, 20.17±2.74, 17.52±1.95, and 33.51±3.47 μg/L, respectively. Compared with the control group, VEGF levels were significantly lower in all hypertensive groups (p<0.05). Furthermore, VEGF levels were significantly lower in mild and severe preeclampsia compared to PIH, and further decreased in severe preeclampsia compared to mild cases (p<0.05).[6]

Abnormal expression of VEGF family proteins and mRNA has important clinical value for the early diagnosis of preeclampsia.[11] Decreased VEGF concentration is associated with increased disease severity, and the risk of developing preeclampsia increases by approximately 1.4-fold for every 1 pg/mL decrease in maternal serum VEGF levels.[9] This study aims to compare serum VEGF concentrations between pregnant women with preeclampsia and normotensive pregnant women at Prof. Dr. CPL Hospital, Universitas Sumatera Utara, Medan.

METHODS

Study Design and Setting

This analytical observational study with a case-control design was conducted at Adam Malik General Hospital and affiliated hospitals in Medan, Indonesia, from August to November 2025.

Population and Sampling

The study included pregnant women diagnosed with preeclampsia and normotensive pregnant women. Subjects were recruited using consecutive sampling. Inclusion criteria included confirmed gestational age and diagnosis of preeclampsia based on standard clinical criteria. Exclusion criteria included chronic diseases, infections, and incomplete data. A total of 40 subjects were included, consisting of 20 preeclampsia cases and 20 normotensive controls.

Variables and Measurements

The primary independent variable in this study was serum Vascular Endothelial Growth Factor (VEGF) level, while the dependent variable was pregnancy status, categorized as preeclampsia and normotensive pregnancy. Preeclampsia was diagnosed

based on standard clinical criteria, defined as new-onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) occurring after 20 weeks of gestation, accompanied by proteinuria or evidence of maternal organ dysfunction. Serum VEGF concentrations were measured using the enzyme-linked immunosorbent assay (ELISA) method according to the manufacturer's protocol. The results were expressed in picograms per milliliter (pg/mL).All laboratory examinations were performed at the Clinical Pathology Laboratory of Universitas Sumatera Utara to ensure standardization of measurement procedures. In addition to the primary variable, baseline characteristics including maternal age, gestational age, and parity were recorded from medical records and patient interviews to describe the study population and assess potential confounding factors.

Data Analysis

Data were analyzed using SPSS. Normality was assessed using the Kolmogorov–Smirnov test. Differences between groups were analyzed using the Mann–Whitney test. ROC curve analysis was performed to determine the diagnostic value of VEGF. Statistical significance was set at $p<0.05$.

RESULTS AND DISCUSSION

Demographic Characteristics

Table 1. Demographic Characteristics

Characteristics	Preeclampsia (n = 20)	Normotensive (n = 20)
Age, n (%)		
20–29 years	8 (40)	11 (55)
≥30 years	12 (60)	9 (45)
Body Mass Index (BMI), n (%)		
Normal weight	5 (25)	4 (20)
Overweight	7 (35)	3 (15)
Obese	8 (40)	13 (65)
Systolic Blood Pressure, mmHg		
Mean ± SD	163.6 ± 16.07	114.15 ± 9.18
Median (Min–Max)	167.5 (140–190)	117.5 (100–129)
Diastolic Blood Pressure, mmHg		
Mean ± SD	97.75 ± 9.46	78.3 ± 8.9
Median (Min–Max)	100 (75–118)	80 (60–94)
Gestational Age, weeks		
<37 weeks	8 (40)	0
≥37 weeks	12 (60)	20 (100)
Parity, n (%)		
Primigravida	9 (45)	5 (25)
Secundigravida	5 (25)	8 (40)
Multigravida	5 (25)	6 (30)
Grandemultigravida	1 (5)	1 (5)

Characteristics	Preeclampsia (n = 20)	Normotensive (n = 20)
Education, n (%)		
Higher education	4 (20)	7 (35)
Senior high school	16 (80)	13 (65)
Occupation, n (%)		
Employed	5 (25)	5 (25)
Unemployed	15 (75)	15 (75)
History of Abortion, n (%)		
With curettage	3 (15)	3 (15)
Without curettage	1 (5)	0
None	16 (80)	17 (85)

The age distribution showed that the majority of participants in the preeclampsia group were aged ≥30 years (60%), whereas more than half of the normotensive group were aged 20–29 years (55%). Advanced maternal age is associated with increased risk of PE, likely due to pre-existing cardiovascular risk factors and reduced vascular adaptability to pregnancy stress. This is consistent with the angiogenic imbalance in PE, characterized by elevated soluble fms-like tyrosine kinase-1 (sFlt-1) and decreased free Vascular Endothelial Growth Factor (VEGF), contributing to endothelial dysfunction.[12,13] Although differences in VEGF and PlGF levels may occur independently of age, age may act as a modifier that exacerbates endothelial dysfunction and disease severity.[2,14]

Based on body mass index (BMI), obesity was the most prevalent category in both groups, accounting for 40% in the preeclampsia group and 65% in the normotensive group. While some studies reported no significant BMI differences between PE and normotensive groups ($p=0.607$; $p=0.172$)[5,13], others demonstrated significantly higher BMI in PE patients compared to controls ($p<0.0001$; $p<0.01$).[8] Mean systolic blood pressure was significantly higher in the preeclampsia group (163.6 ± 16.07 mmHg; median 167.5, range 140–190) compared to the normotensive group (114.15 ± 9.18 mmHg; median 117.5, range 100–129). Similarly, mean diastolic blood pressure was elevated in the preeclampsia group (97.75 ± 9.46 mmHg) compared to the normotensive group (78.3 ± 8.9 mmHg).

Regarding pregnancy characteristics, 40% of participants in the preeclampsia group delivered preterm (<37 weeks), whereas all normotensive participants delivered at term (≥37 weeks). The preeclampsia group was predominantly primigravida (45%), while the normotensive group was mostly secundigravida (40%). Nulliparity is a recognized moderate risk factor for PE, with a relative risk of approximately 2.1 and up to a threefold increase in risk.24,25,28 This is thought to be related to inadequate maternal immunological adaptation to fetal antigens, resulting in abnormal trophoblast invasion and angiogenic imbalance.[15,16]

Educational level was comparable between groups, with most participants having a senior high school background (80% vs 65%). Employment status was identical in both groups (25% employed, 75% unemployed). A history of abortion was also similar, observed in 20% of the preeclampsia group and 15% of the normotensive group.

Comparison of Serum VEGF Levels Between Preeclampsia and Normotensive Groups

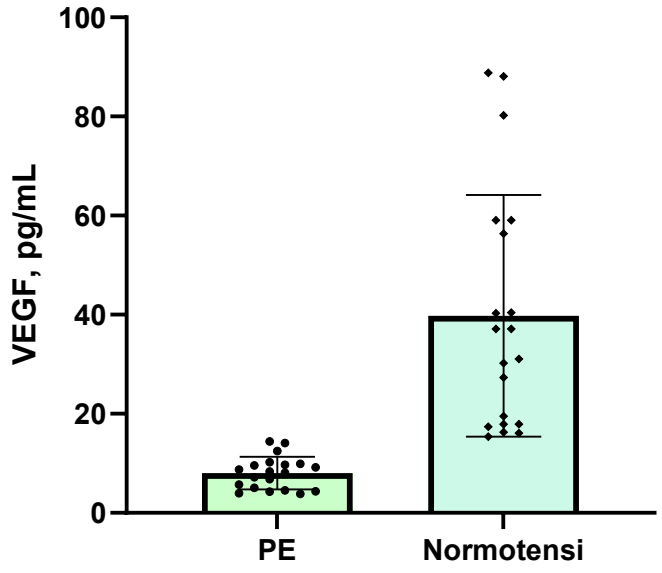
The analysis demonstrated a significant difference in VEGF levels between the preeclampsia and normotensive groups. The mean VEGF level in the preeclampsia group was 8.03 ± 3.27 pg/mL, which was substantially lower than that observed in the normotensive group (39.78 ± 24.39 pg/mL). This difference remained consistent when assessed using median values, with 8.21 pg/mL (range 3.87–14.4) in the preeclampsia group compared to 34.1 pg/mL (range 15.4–88.8) in the normotensive group. The Mann–Whitney test yielded a p-value < 0.001, indicating that the reduction in VEGF levels in the preeclampsia group was statistically highly significant compared to the normotensive group.

Table 2. Comparison of Serum VEGF Levels Between Preeclampsia and Normotensive Groups

Variable	Preeclampsia (n = 20)	Normotensive (n = 20)	p-value
VEGF (pg/mL)			
Mean ± SD	8.03 ± 3.27	39.78 ± 24.39	<0.001*
Median (Min–Max)	8.21 (3.87–14.4)	34.1 (15.4–88.8)	

**Mann Whitney*

Figure 1. Comparison of Serum VEGF Levels Between the Preeclampsia and Normotensive Groups



Previous studies evaluating Vascular Endothelial Growth Factor (VEGF) levels in normal pregnancies compared to preeclampsia (PE) consistently demonstrate that reduced free and functional VEGF is a hallmark of PE pathophysiology. Multiple clinical studies have reported significantly lower circulating VEGF (and PlGF) levels in preeclamptic patients compared to

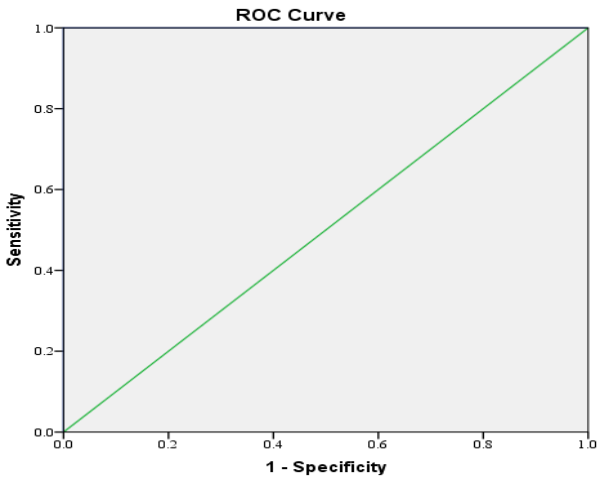
normotensive pregnancies.[8-10] This reduction is often proportional to disease severity, with more severe PE associated with lower VEGF levels.13,14,17 For example, one study reported VEGF levels of 17.52±1.95 µg/L in severe PE compared to 33.51±3.47 µg/L in controls.[10] Similarly, a study from Iran showed significantly lower VEGF levels in PE patients (15.50±8.87 pg/mL) compared to controls (45.94±12.77 pg/mL; p<0.001).[9] Decreased VEGF has also been associated with adverse perinatal outcomes, including low birth weight and poor Apgar scores.[10,17]

The primary mechanism underlying reduced functional VEGF in PE is angiogenic imbalance driven by placental dysfunction. The pathophysiology begins with uteroplacental malperfusion, leading to placental hypoxia and ischemia.[10,11,18] In response, the placenta releases excessive anti-angiogenic factors, particularly soluble fms-like tyrosine kinase-1 (sFlt-1), a circulating form of the VEGF receptor.[11,12,20,21]sFlt-1 acts as a decoy receptor by binding circulating VEGF and PlGF, thereby reducing their bioavailability and preventing interaction with endothelial receptors.9,11,15,28 This depletion of free VEGF results in endothelial dysfunction, vasoconstriction, hypertension, and the clinical manifestations of PE.[7,20,22]

Diagnostic Performance Of VEGF In Predicting Preeclampsia

To evaluate the diagnostic performance of VEGF in predicting preeclampsia, Receiver Operating Characteristic (ROC) curve analysis was performed. The ROC analysis demonstrated that VEGF levels exhibited perfect discriminative ability in distinguishing preeclampsia cases from normotensive pregnancies. The Area Under the Curve (AUC) was 1.000 (SE = 0.000; p < 0.001), with a 95% confidence interval ranging from 1.000 to 1.000. This finding indicates that VEGF was able to perfectly discriminate between individuals with preeclampsia and those without preeclampsia within this sample.

Figure 2. Diagnostic Performance Of VEGF In Predicting Preeclampsia



Graph 1. Line Graph for Determining the Optimal Cut-off Value of VEGF as a Predictor of Preeclampsia

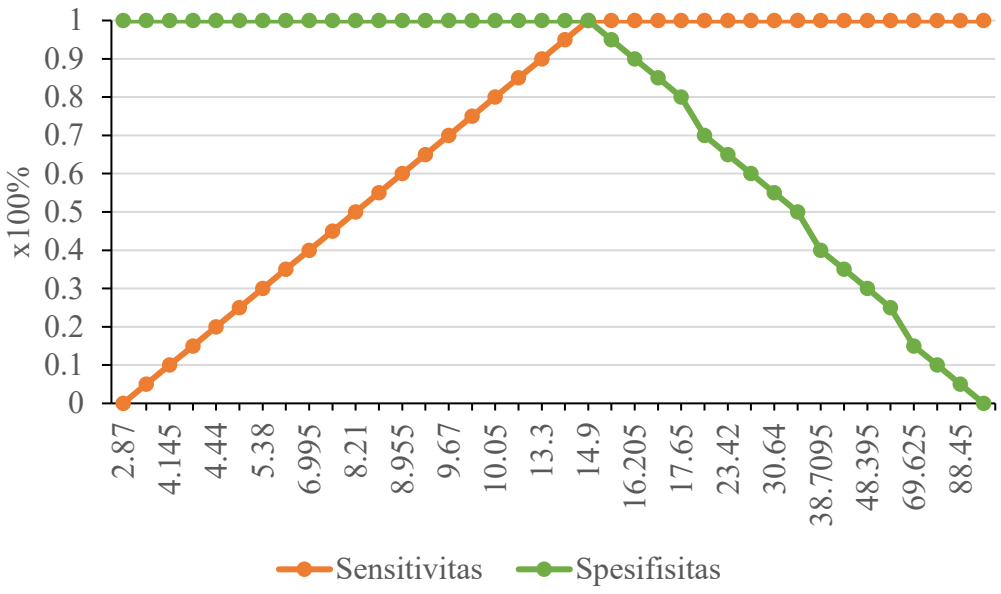


Table 3. Diagnostic Accuracy of VEGF as a Predictor of Preeclampsia

Variable	Preeclampsia		Sensitivity	Specificity	NPV	PPV	Diagnostic Performance
	(+)	(-)					
VEGF							
< 14,9	20	0	100%	100%	100%	100%	100%
≥ 14,9	0	20					

**Mann Whitney*

Based on a VEGF cut-off value of 14.9 pg/mL, this biomarker demonstrated perfect diagnostic performance within the study sample. All preeclampsia cases (20/20) had VEGF levels below 14.9 pg/mL, whereas all subjects in the normotensive group (20/20) had VEGF levels equal to or above this threshold.

Accordingly, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy each reached 100%. These findings indicate that, within this sample, a VEGF level <14.9 pg/mL was able to identify all cases of preeclampsia without any false-negative or false-positive results.

The ROC analysis in this study demonstrated that VEGF has excellent discriminative ability in distinguishing preeclampsia (PE) from normotensive pregnancies. These findings are consistent with previous studies. Tandon et al. (2017) reported an AUC of 73.8% (95% CI: 63.5–89.0) with a cut-off of 14.04 pg/mL, sensitivity of 88.6%, and specificity of 61.8%, indicating good diagnostic capability of VEGF in identifying hypertensive disorders of pregnancy.6 Furthermore, lower VEGF levels have been shown to correlate negatively with disease severity, including higher systolic and diastolic blood pressure.19 A decrease of 1 pg/mL in serum VEGF has been associated with a 1.4-fold increased risk of PE, highlighting its prognostic value.[9,10]

However, other studies have reported more modest diagnostic performance. A study in Uganda showed an AUC of 0.66, sensitivity of 0.56, and specificity of 0.69, suggesting limitations of VEGF as a standalone biomarker.16 Consequently, alternative markers such as the soluble fms-like tyrosine kinase-1 to Placental Growth Factor (sFlt-1/PlGF) ratio have been widely investigated.[7,11,19,22]A cut-off value ≤38 has demonstrated a negative predictive value of 99.3% for ruling out PE within one week.[11,22,23] More advanced predictive models combining angiogenic biomarkers with clinical factors, uterine artery Doppler, and other markers (e.g., PAPP-A) have achieved detection rates up to 96.3% for early-onset PE.2,31 Additional biomarkers such as soluble endoglin (sEng)[2], CRP[3], and endoplasmic reticulum stress markers (e.g., GRP78)[12] have also been proposed to enhance prediction and understanding of PE pathogenesis. Pathophysiologically, elevated sFlt-1 binds VEGF and PlGF, reducing free VEGF availability and leading to systemic endothelial dysfunction, vasoconstriction, glomerular endotheliosis, proteinuria, and hypertension in PE. However, further studies comparing VEGF with other angiogenic and anti-angiogenic factors are warranted. Measurement of sFlt-1 may be more sensitive, as its elevation precedes the decline in free VEGF levels.

Clinical Implications

The findings of this study suggest that serum VEGF has strong potential as a clinically useful biomarker for the early detection and prediction of preeclampsia. The significant reduction of VEGF levels in preeclamptic pregnancies, along with its excellent discriminative performance in this study, highlights its value in identifying patients at higher risk of developing the condition. Early identification of high-risk pregnancies is crucial, as it enables closer monitoring, timely intervention, and prevention of severe maternal and fetal complications.

Limitations

This study has several limitations. First, the relatively small sample size and case-control design may limit statistical power, introduce selection bias, and reduce generalizability, particularly as the study was conducted in a tertiary referral hospital setting. Second, VEGF levels were measured only once after 20 weeks of gestation, without serial assessment or differentiation between free and total VEGF, and without inclusion of other key angiogenic biomarkers such as PlGF, sFlt-1, and sEng, limiting comprehensive evaluation of angiogenic imbalance.

CONCLUSION

Baseline characteristics between the preeclampsia and normotensive groups were comparable, indicating that demographic factors did not significantly influence group differences. Serum VEGF levels were significantly lower in the preeclampsia group (8.03 ± 3.27 pg/mL) compared to normotensive pregnancies (39.78 ± 24.39 pg/mL; $p < 0.001$), reflecting reduced angiogenic activity in preeclampsia. ROC analysis demonstrated excellent diagnostic performance of VEGF, with an AUC of 1.000 ($p < 0.001$), and at

a cut-off value of 14.9 pg/mL, achieving 100% sensitivity, specificity, and overall accuracy. These findings suggest that VEGF has strong potential as a predictive biomarker for preeclampsia in this study population.

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