Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

# Maternal Serum GDF15 and Neuropilin-1 as Diagnostic Biomarkers of Third-Trimester Preeclampsia: A Case-Control Study

**Qasim Wathiq Abdulsadah[1*], Thana Mohammed Juda[1], Hanan Khudhair Al Kadhim[2]**

1. *Department of Biochemistry, College of Medicine, University of Babylon, Babylon, Iraq*
2. *Department of obstetrics and Gynecology, College of Medicine, University of Babylon, Babylon, Iraq*

**Article Info**

10.24200/jogcr.12.1.8

**Received:** 2026/04/02
**Accepted:** 2026/05/20
**Published Online:** 01 Nov. 2026

**Corresponding Information:**
**Qasim Wathiq Abdulsadah,**
Department of Biochemistry, College of Medicine, University of Babylon, Babylon, Iraq

**Email:** watheiqq@gmail.com

**ABSTRACT**

**Background & Objective:** Cellular stress and endothelial dysfunction peak during late gestation; however, the combined diagnostic value of Growth Differentiation Factor 15 (GDF15) and Neuropilin-1 (NRP1) has not been thoroughly investigated. To evaluate the concurrent diagnostic efficacy of maternal serum GDF15 and NRP1 in identifying preeclampsia during the third trimester.

**Materials & Methods:** This case-control study included 60 women with preeclampsia and 60 matched normotensive controls at more than 28 weeks of gestation. Serum GDF15 and NRP1 concentrations were measured using Enzyme-Linked Immunosorbent Assay (ELISA). Diagnostic performance was assessed using receiver operating characteristic (ROC) curve analysis.

**Results:** Serum GDF15 (725.2±208 vs. 523.7±112 pg/mL) and NRP1 (15.75±6.54 vs. 9.34±2.4 ng/mL) levels were significantly elevated in patients with preeclampsia compared with controls (P<0.0001). NRP1 demonstrated superior diagnostic accuracy (AUC=0.88; 76% sensitivity (95% CI: 63.2-86.0%); 87% specificity (95% CI: 75.8-94.1%)) compared with GDF15 (AUC=0.80; 70% sensitivity (95% CI: 56.8-81.2%); 79.4% specificity (95% CI: 67.3-88.5%)). A moderate positive correlation was observed between the two biomarkers (r=0.547, P<0.001). Neither marker is significantly distinguished severe from non-severe preeclampsia.

**Conclusion:** GDF15 and NRP1 show promise as complementary biomarkers for detecting preeclampsia, reflecting distinct pathophysiological pathways related to cellular stress and angiogenic dysregulation. Although they demonstrated high diagnostic potential for identifying the presence of the disease, their utility in stratifying disease severity appears limited.

**Keywords:** Pre-eclampsia, Growth differentiation factor 15, Neuropilin-1, Pregnancy trimester

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## 1. Introduction

Pre-Eclampsia (PE) is a life-threatening, pregnancy-specific disorder unique to humans and a leading cause of maternal and neonatal morbidity and mortality **(1)**. It is estimated to complicate approximately 2-8% of pregnancies worldwide **(2)**, representing one of the most common medical complications of pregnancy. Women who experience PE face a reduced life expectancy, alongside heightened risks of stroke, cardiovascular disease, and diabetes. Moreover, infants born from pre-eclamptic pregnancies carry higher risks of preterm birth, perinatal death, neurodevelopmental disabilities, and cardiovascular as well as metabolic diseases later in life **(3)**. Although PE most commonly manifests during the third trimester or within six weeks postpartum, the diagnosis may be established at any point during pregnancy **(4)**. The primary criteria for the clinical diagnosis of PE comprise new-onset hypertension and proteinuria; alternatively, in the absence of proteinuria, new-onset hypertension accompanied by any of the following features: thrombocytopenia, elevated liver transaminases, pulmonary edema, new-onset renal insufficiency, or cerebral or visual disturbances **(5)**. The principal risk factors for PE include pre-existing chronic kidney disease, a history of chronic hypertension, multifetal gestation, pre-pregnancy BMI≥25 kg/m², maternal hyperglycemia, primiparity, and a family history of hypertension **(6,7)**.

The pathophysiology of PE involves abnormal placentation, systemic endothelial dysfunction, and an exaggerated inflammatory response **(8,9)**. A central feature is defective trophoblast invasion into the maternal spiral arteries during early placentation.

Insufficient remodeling of these spiral arteries leads to relative placental ischemia, generating excessive Reactive Oxygen Species (ROS) and triggering oxidative stress **(10)**. This activation promotes the expression of Growth Differentiation Factor 15 (GDF15), also designated Macrophage Inhibitory Cytokine-1 (MIC-1), within trophoblast cells; it is subsequently released into the maternal circulation as an early marker of placental injury **(11)**. Studies have demonstrated that GDF15 levels are significantly elevated prior to the clinical manifestation of PE, indicating considerable predictive utility **(11)**. Conversely, hypoxia and oxidative dysfunction result in down-regulated expression of Neuropilin-1 (NRP1) a transmembrane protein functioning both as a coreceptor for vascular endothelial growth factor and as an immune-regulatory mediator thereby impairing angiogenesis and exacerbating placental malperfusion **(12,13)**.

Although GDF15 is a well-established marker of placental mitochondrial stress **(11)** and NRP1 is essential for endothelial regulation **(14)**, these biomarkers have primarily been evaluated independently or restricted to predicting early pregnancy outcomes. Consequently, a critical research gap remains regarding their concurrent diagnostic utility during the third trimester, a period when the combined burden of cellular stress and endothelial dysfunction reaches its clinical peak **(15)**.

To address this gap, the aim of this study was to evaluate the simultaneous diagnostic efficacy of maternal serum GDF15 and NRP1 in identifying PE during the third trimester. Specifically, the novelty of our research lies in the simultaneous measurement of these two biomarkers for a diagnostic, rather than predictive, assessment of third-trimester PE within an Iraqi population.

## 2. Materials and Methods

### Study Design

This case-control study was conducted at the Babylon Teaching Hospital for Women and Children in the Babylon Governorate, central Iraq, between September 2025 and January 2026. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and national research committees, as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Sample Size Calculation

The sample size for this study was determined based on feasibility and the availability of matched participants during the study period, rather than a formal a priori power calculation. A total of 120 participants (60 preeclamptic women and 60 matched normotensive controls) were enrolled. This sample size was considered adequate to evaluate the diagnostic efficacy of the biomarkers and to compare their performance using Receiver Operating Characteristic (ROC) curve analysis.

### Participant Selection

The study population consisted of pregnant women in their third trimester (gestational age >28 weeks). The case group included women diagnosed with PE, while the control group comprised normotensive pregnant women matched for both gestational and chronological age. PE was defined as new-onset hypertension (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) and proteinuria after 20 weeks of gestation. Cases were further classified into severe and non-severe (mild) according to the American College of Obstetricians and Gynecologists (ACOG) guidelines. Severe PE was diagnosed by the presence of "severe features," such as BP ≥160/110 mmHg, thrombocytopenia, impaired liver function, progressive renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances **(16)**.

Exclusion criteria were rigorously applied to ensure a homogeneous study sample. Participants were excluded if they had pre-existing medical conditions that could confound the results, including glomerular diseases, chronic liver or kidney disease, heart failure, or other conditions associated with proteinuria. Additionally, women with pregnancy-related complications such as gestational diabetes, chronic hypertension, or multifetal pregnancies were excluded. Patients with a prior diagnosis of PE, those who were severely ill, or those carrying a fetus with a congenital malformation incompatible with life, as confirmed by ultrasonography, were also excluded from the study.

### Data and Sample Collection

A comprehensive medical history was obtained from each participant, followed by a general and obstetric examination. Clinical data including Body Mass Index (BMI), maternal age, urban or rural residency, urinary protein levels, and blood pressure at presentation were extracted from the patients' medical records.

For biochemical analysis, whole blood samples were collected from all participants. The samples were then centrifuged at 2500 rpm for 5 minutes to separate the serum. The resulting serum was aliquoted and stored at -40°C until analysis to preserve sample integrity.

### Biochemical Analysis

Serum concentrations of GDF15 and NRP1 were measured using commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kits. Specifically, the Human GDF15 Immunoassay (Catalog No. E0037Hu) and the Human NRP1 Immunoassay (Catalog No. E2101Hu), both from R&D Systems, were employed. All assays were conducted in strict accordance with the manufacturers' instructions and protocols.

### Statistical analysis

Statistical analyses were conducted using GraphPad Prism 9. Continuous variables are reported as mean±SD and range. The Shapiro-Wilk test was utilized to evaluate the normality of data distribution. Because the data for both GDF15 and NRP1 were found to be normally distributed, comparisons between two groups were analyzed using an independent-samples t-test. Receiver Operating Characteristic (ROC) curve analysis was employed to assess the diagnostic performance of the biomarkers. The DeLong method was used to calculate the area Under the Curve (AUC) with 95% Confidence Intervals (CI). Optimal cut-off values were determined using Youden's index (J=Sensitivity+Specificity-1). Correlation analysis was performed using Pearson's correlation coefficient. All hypothesis tests utilized a two-tailed significance level of $\alpha=0.05$, and P-values<0.05 were considered statistically significant.

## 3. Results

Table 1 presents a comparative analysis of baseline demographic, clinical, and biochemical characteristics between the control (n=60) and PE (n=60) groups. There were no statistically significant differences in maternal age, rural versus urban residence, or Body Mass Index (BMI) between the two cohorts (P>0.05). However, the PE group demonstrated significantly higher systolic and diastolic blood pressures (P<0.0001 for both), along with a significant reduction in platelet counts (P<0.0001) and elevated levels of blood urea (P=0.0038), Aspartate Aminotransferase (AST) (P<0.0001), and Alanine Aminotransferase (ALT) (P<0.0001).

Dipstick analysis (Table 2) revealed that all PE cases exhibited proteinuria, whereas 95% of controls tested negative. Among patients with PE, 40% had ++ proteinuria and 33.3% had +++ proteinuria, with severe cases being more likely to present with higher grades.

Maternal serum levels of GDF15 were significantly elevated in women with PE (725.2±208 pg/mL) compared with healthy controls (523.7±112 pg/mL; P<0.0001). Similarly, NRP1 concentrations were significantly higher in the PE group (15.75±6.54 ng/mL) than in the control group (9.34±2.4 ng/mL; P<0.0001), as illustrated in Figure 1.

Subgroup analysis revealed no statistically significant differences in the levels of either biomarker between severe and non-severe PE (Table 3). Specifically, the mean GDF15 levels were 767±253 pg/mL in the non-severe group and 686±181 pg/mL in the severe group (P=0.1866). Additionally, NRP1 levels were 17.00±9.50 ng/mL in the non-severe group and 13.98±8.62 ng/mL in the severe group (P=0.0988).

**Table 1. Comparative Analysis of Demographic, Clinical, and Biochemical Characteristics of the Study Groups**

| Variable | Control (n=60) | Preeclampsia (n=60) | P-value |
|---|---|---|---|
| **Demographic and Clinical Parameters** | | | |
| **Age (years), Mean±SD** | 26.0±4.4 | 24.9±5.04 | 0.723 |
| **Rural Residence, n(%)** | 20(40%) | 31(52%) | 0.2218 |
| **Urban Residence, n(%)** | 40(60%) | 29(48%) | |
| **Body Mass Index (kg/m²), Mean±SD** | 28.65±1.89 | 29.75±3.08 | 0.18 |
| **Systolic Blood Pressure (mmHg), Mean±SD** | 114.00±3.71 | 147.18±10.55 | <0.0001 |
| **Diastolic Blood Pressure (mmHg), Mean±SD** | 75.25±3.76 | 92.03±6.63 | <0.0001 |
| **Hematological and Renal Parameters** | | | |
| **Platelets (×10⁹/L), Mean±SD** | 257.25±39.91 | 219.17±56.48 | <0.0001 |
| **Blood Urea (mmol/L), Mean±SD** | 3.17±0.83 | 4.59±2.1 | 0.0038 |
| **Serum Creatinine (mg/dL), Mean±SD** | 0.70±0.15 | 0.77±0.28 | 0.304 |
| **Hepatic Function Parameters** | | | |
| **Aspartate Aminotransferase (U/L), Mean±SD** | 22.95±4.60 | 32.95±11.97 | <0.0001 |
| **Alanine Aminotransferase (U/L), Mean±SD** | 25.20±5.59 | 31.95±12.83 | <0.0001 |
| **Prothrombin Time (seconds), Mean±SD** | 12.61±1.16 | 13.12±1.62 | 0.047 |
| **Partial Thromboplastin Time (seconds), Mean±SD** | 27.28±3.47 | 27.78±3.49 | 0.4334 |

Independent-samples t-tests were utilized, and a P-value of less than 0.05 was considered statistically significant.

**Table 2. Distribution of dipstick test results for proteinuria among all participants.**

| Urinary Protein | Non severe PE (n=26) | Severe PE (n=34) | PE (n=60) | Control (n=60) |
|---|---|---|---|---|
| **-ve** | 0 | 0 | 0(0.0%) | 57(95.0%) |
| **Trace** | 6(23.0%) | 0 | 6(10.0%) | 3(5.0%) |
| + | 5(19.2%) | 2(5.9%) | 7(11.7%) | 0 |
| ++ | 10(38.6%) | 14(41.2%) | 24(40.0%) | 0 |
| +++ | 5(19.2%) | 15(44.1%) | 20(33.3%) | 0 |
| ++++ | 0 | 3(8.8%) | 3(5.0%) | |

Negative (-ve) Note: P<0.0001, determined by Chi-square test

**Table 3. Comparison of Biomarkers in Non-severe versus Severe Preeclampsia**

| Biomarker | Non-severe PE (n=26) | Severe PE (n=34) | P-value |
|---|---|---|---|
| **GDF.15** | 767±253 pg/mL | 686±181 pg/mL | 0.1866 |
| **NRP1** | 17.00±9.50 ng/mL | 13.98±8.62 ng/mL | 0.0988 |

**Table 4. Correlation Analysis Using Pearson's Correlation Coefficient**

| NRP1 | 1 | | | | | | |
|---|---|---|---|---|---|---|---|
| **GDF.15** | 0.547<br>P<0.001 | 1 | | | | | |
| **ALT** | -0.039<br>P=0.787 | -0.074<br>P=0.611 | 1 | | | | |
| **AST** | -0.080<br>P=0.580 | -0.132<br>P=0.362 | 0.112<br>P=0.393 | 1 | | | |
| **Urea** | -0.199<br>P=0.166 | 0.080<br>P=0.583 | -0.039<br>P=0.767 | 0.086<br>P=0.517 | 1 | | |
| **S. creatinine** | -0.160<br>P=0.267 | -0.111<br>P=0.442 | 0.066<br>P=0.618 | -0.011<br>P=0.934 | 0.004<br>P=0.977 | 1 | |
| **systolic** | -0.164<br>P=0.255 | -0.234<br>P=0.102 | 0.045<br>P=0.734 | 0.129<br>P=0.326 | 0.067<br>P=0.611 | -0.053<br>P=0.687 | 1 |
| **diastolic** | -0.328<br>P=0.013 | -0.264<br>P=0.06 | -0.179<br>P=0.172 | 0.116<br>P=0.37 | 0.151<br>P=0.24 | 0.072<br>P=0.58 | 0.572<br>P<0.001 |
| | NRP1 | GDF.15 | ALT | AST | Urea | S. creatinine | systolic |

Note: Correlation strength is defined as follows: |r|>0.7 = strong; 0.4-0.7 = moderate; 0.2-0.4 = weak; <0.2=very weak.

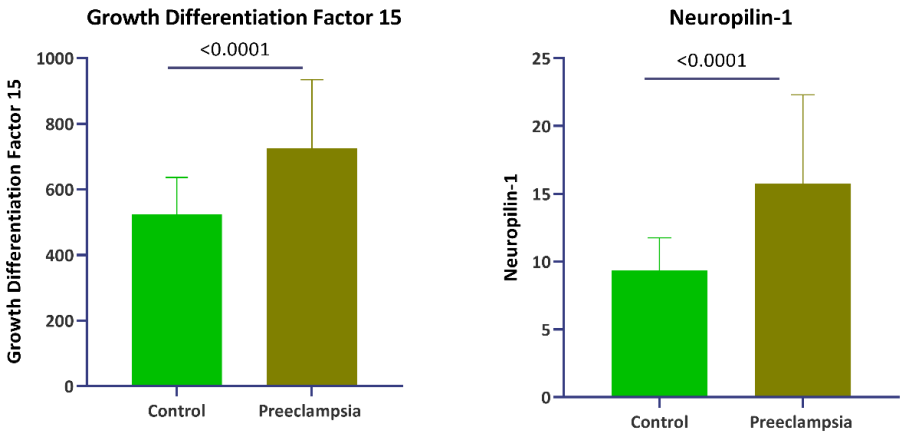



**Figure 1. Bar Chart of Serum Levels of Growth Differentiation Factor 15 and Neuropilin-1 in Control and Preeclampsia Groups**

Receiver Operating Characteristic (ROC) curve analysis demonstrated good diagnostic accuracy for both biomarkers. GDF15 yielded an Area Under the Curve (AUC) of 0.80 (95% CI: 0.70-0.88), with an optimal cutoff value of>625.9 pg/mL, resulting in a sensitivity of 70% (95% CI: 56.8-81.2%) and a specificity of 79.4% (95% CI: 67.3-88.5%) (P<0.0001). Notably, NRP1 exhibited superior diagnostic performance, with an AUC of 0.88 (95% CI: 0.79-0.94) at a cutoff value of >11.06 ng/mL, achieving a sensitivity of 76% (95% CI: 63.2-86.0%) and a specificity of 87% (95% CI: 75.8-94.1%) (P<0.0001).

Pearson correlation analysis (Table 4) demonstrated a moderate positive correlation between GDF15 and NRP1 (r=0.547, P<0.001). No significant correlations were found between these biomarkers and liver enzymes, renal parameters, or blood pressure indices.

## 4. Discussion

The current study demonstrates that maternal serum concentrations of GDF15 and NRP1 are significantly elevated in Iraqi women with PE during the third trimester of pregnancy. These elevations reflect the dual pathophysiological hallmarks of this multisystem disorder: placental stress responses and severe vascular endothelial dysfunction. By establishing a concurrent diagnostic panel of these two biomarkers, this research addresses a critical gap in late-gestation diagnostic strategies, advancing the evolving landscape of PE prediction and diagnosis described in recent literature.

The significant elevation of GDF15 observed in our preeclamptic cohort (725.2±208 pg/mL vs. 523.7±112 pg/mL in controls) aligns with its established role as a stress-responsive cytokine expressed by the placenta under hypoxic and inflammatory conditions. This finding is consistent with recent research by Cruickshank et al., who demonstrated that circulating GDF15 increases prior to the diagnosis of PE, serving as a promising biomarker linked to mitochondrial dysfunction and oxidative stress **(17)**. Furthermore, Liu et al., highlighted the dysregulation of maternal serum cytokine profiles, including GDF15, as early indicators of the inflammatory cascade characteristic of PE **(18)**. However, the trajectory of GDF15 throughout gestation remains debated; while our third-trimester data support an elevation during active disease, some earlier studies, such as Wertaschnigg et al., reported reduced GDF15 levels in the third trimester compared with matched controls **(19)**. These discrepancies likely arise from variations in sampling timing, population characteristics, and the specific pathophysiological phenotypes of PE studied, underscoring the need for standardized, longitudinal assessments.

Our study demonstrated that maternal serum NRP1 levels were significantly elevated in the PE group compared with healthy controls (15.75±6.54 ng/mL vs. 9.34±2.4 ng/mL), exhibiting strong diagnostic performance (AUC=0.88). This finding strongly supports recent results reported by Tosun et al., who also observed significantly increased maternal plasma NRP1 levels in preeclamptic pregnancies and proposed it as a promising diagnostic marker **(13)**. The systemic elevation of NRP1 presents an intriguing pathophysiological paradox. Although local placental expression of NRP1 is often downregulated in fetal growth restriction and PE **(20,21)**, the systemic increase observed in our study and by Assani et al., suggests a compensatory maternal response aimed at counteracting the severe anti-angiogenic state driven by excess soluble Fms-Like Tyrosine kinase-1 (sFlt-1) **(22)**. Moreover, as an essential co-receptor for VEGF and Placental Growth Factor (PlGF), the shedding of NRP1 from injured placental and endothelial cells into the maternal circulation may directly reflect the extent of endothelial damage, thereby linking local tissue injury with systemic biomarker elevation **(23)**.

A notable finding in our cohort was the absence of significant differences in GDF15 and NRP1 levels between severe and non-severe PE cases. This suggests that, although these biomarkers are highly sensitive and specific for detecting the presence of the disease, they may not reliably stratify the risk of progression to severe clinical manifestations. The moderate positive correlation between GDF15 and NRP1 (r=0.547) in our study supports the hypothesis that these markers reflect overlapping but distinct pathophysiological pathways with GDF15 indicating cellular stress and NRP1 indicating angiogenic dysregulation thereby providing complementary diagnostic value rather than prognostic severity scaling.

The contemporary approach to diagnosing PE increasingly emphasizes integrating molecular biomarkers with traditional clinical signs. The 2021 International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines have advanced toward incorporating anti-angiogenic biomarkers into the diagnostic framework **(24)**. While the sFlt-1/PlGF ratio remains the gold standard for clinical application **(22)**, our findings suggest that a panel combining stress-responsive cytokines (GDF15) and alternative Angiogenic Regulators (NRP1) may enhance diagnostic accuracy, particularly in the third trimester, when the combined burden of cellular stress and endothelial dysfunction peaks. As highlighted by Riano-Moreno et al., **(25)**, no single test currently possesses the absolute specificity and sensitivity required for standalone routine use; therefore, the concurrent measurement of distinct mechanistic markers, as demonstrated in this study, represents a crucial advancement.

Beyond our biomarker findings, this study confirmed the classical systemic manifestations of PE, including markedly elevated blood pressure, thrombocytopenia, proteinuria, and hepatic and renal dysfunction. These results reinforce the concept of PE as a multisystem disorder rather than a purely hypertensive condition, which is consistent with numerous well-established studies **(26,27)**. Furthermore, the presence of severe proteinuria (+++ or higher in one-third of cases) underscores the renal burden of the disease, whereas elevated AST and ALT levels indicate hepatocellular injury aligning with the spectrum of PE complications ranging from HELLP syndrome to fulminant hepatic dysfunction **(28)**.

### Limitations and Future Directions

This study has several limitations. First, the sample size was determined based on feasibility rather than a formal a priori power calculation, which may limit the generalizability of the findings. The single-center design also does not account for regional or ethnic variability in biomarker expression, and the cross-sectional design precludes the assessment of longitudinal changes in GDF-15 and NRP-1 throughout gestation. Additionally, the absence of placental tissue analysis restricts the interpretation of the divergence between local and systemic angiogenic signaling. The lack of long-term maternal and neonatal follow-up data also prevents the evaluation of these biomarkers' predictive value for adverse outcomes. Future research should prioritize large-scale, multicenter longitudinal studies to characterize the temporal dynamics of GDF-15 and NRP-1 across gestation. Furthermore, integrating these evaluated biomarkers with established indices, such as the sFlt-1/PlGF ratio, within multi-omics frameworks will be essential for developing comprehensive, AI-driven predictive models capable not only of diagnosing PE but also of accurately stratifying maternal and fetal risk.

## 5. Conclusion

This study identified GDF-15 and NRP-1 as complementary biomarkers reflecting distinct pathophysiological mechanisms in third-trimester PE. NRP-1 demonstrated superior diagnostic performance (AUC=0.88) compared with GDF-15 (AUC=0.80), suggesting its potential utility in clinical diagnosis. However, the inability of either biomarker to stratify disease severity indicates that diagnostic and prognostic assessments require distinct biomarker panels. These findings support the integration of GDF-15 and NRP-1 into comprehensive diagnostic algorithms for PE, while highlighting the need for multicenter validation studies and further investigation into their combined utility with established angiogenic markers to optimize clinical decision-making.

## 6. Declarations

## Acknowledgments

The authors thank all the pregnant women who kindly participated in this study. We also express our gratitude to the administrative staff of Babylon Teaching Hospital for Women and Children, as well as the dedicated medical and nursing personnel, for their invaluable assistance in making this study possible.

## Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Ethics Committee of the University of Babylon, College of Medicine (Reference No. 5-75, date: 18/9/2025). Additionally, the Institutional Review Board of Fujian Medical University approved the study. All participants provided written informed consent prior to enrollment, after being fully informed about the aims and procedures of the study.

## Authors' Contributions

Conceptualization: QWA and TMJ; Methodology: QWA, TMJ; Validation: QWA, TMJ; Formal

Analysis: QWA; Investigation: QWA, TMJ; Resources: QWA; Data Curation: QWA; Writing-Original Draft Preparation: QWA and HKA; Writing-Review & Editing: All authors; Visualization: HKA; Supervision: TMJ; Project Administration: QWA; Funding Acquisition: QWA and TMJ.

### Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Conflict of Interest

No conflicts of interest to declare.

### Use of Artificial Intelligence:

Applied artificial intelligence to enhance sentence structure and clarity.

## Fund or Financial Support

None.

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**How to Cite This Article:**

Abdulsadah QW, Juda TM, Al Kadhim HK. Maternal Serum GDF15 and Neuropilin-1 as Diagnostic Biomarkers of Third-Trimester Preeclampsia: A Case-Control Study. J Obstet Gynecol Cancer Res. 2027;12(1):8-15.

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