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# Placental Growth Factor as a Predictor of Severity of Preeclampsia in Iraqi Women

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**Abstract**

Pre-eclampsia is a serious pregnancy complication marked by high blood pressure, typically exceeding 140/90 mmHg, that often emerges after the 20th week of pregnancy. It may be pronounced if there is a high risk for the mother or fetus. The importance of the placental growth factor (PlGF) in predicting preeclampsia has been established by earlier research. However, the study aims to evaluate the predictive accuracy of serum Placental growth factor in determining the severity of disease. The study involved 90 pregnant Iraqi women who developed preeclampsia after 24 weeks of gestation. Based on the magnitude of their hypertension biochemical parameters and, other symptoms, the women were categorized into two groups: 45 moderate cases and 45 severe cases. They were aged between 27-29 years and were selected from the Al-Elwiya Teaching Hospital for Maternity from April to June 2024. Both blood pressure and proteinuria were assessed. Furthermore, a blood sample was obtained from each patient in order to evaluate the serum levels of PlGF using ELISA in addition to hematological and biochemical parameters. The severe PE group exhibits a statistically significant ($p \leq 0.05$) increase in both systolic and diastolic blood pressures when compared to the moderate group. Moreover, there is a statistically significant ($P \leq 0.01$) difference in platelet count, Aspartate amino Transferase (AST), Alanine amino Transferase (ALT), serum Creatinine and blood urea between the PE groups. In severe cases of PE, the presence of proteinuria on the urine dipstick at a level of 2+ or higher was found to be highly significant ($P \leq 0.01$) when compared to moderate cases. Notably, PlGF levels showed no significant variation between the different pre-eclampsia groups. This is not surprising, given that pre-eclampsia is a complex condition that affects multiple systems, making it challenging to accurately predict the severity of the disease. The results indicate PlGF is unable to differentiate between cases of moderate and severe PE. Further investigation is required to determine the predictive efficacy of PlGF in relation to the severity of the disease, taking into account the type of disease and gestational week.

**Keywords:** PlGF, preeclampsia, proteinuria, hypertension.

## عامل نمو المشيمة كمتنبئ لشدة تسمم الحمل لدى النساء العراقيات

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**الخلاصة**

تسمم الحمل (PE) هو مرض خاص بالحمل يتميز بأرتفاع ضغط الدم الشرياني بمقدار 140/90 ملم زئبقي. وعادة ما يظهر بعد الاسبوع ال20 من الحمل. وقد يكون شديدًا أذا كان هناك خطر كبير على الأم او الجنين. لقد تم اثبات أهمية عامل نمو المشيمة (PlGF) في التنبؤ بتسمم الحمل من خلال الأبحاث السابقة. بينما, تهدف الدراسة الى تقييم الدقة التنبؤية لعامل نمو المشيمة في المصل في تحديد شدة المرض. شملت الدراسة 90 أمرأة عراقية حامل أصبن بتسمم الحمل بعد الاسبوع ال24 من الحمل. بناءً على شدة ارتفاع ضغط الدم والمعايير الكيميائية الحيوية والأعراض الأخرى، تم تقسيم النساء إلى مجموعتين: 45 حالة متوسطة و45 حالة شديدة. تراوحت اعمارهن بين 27 و 29عاماً وتم اختيارهن من مستشفى العلوية التعليمي للولادة من ابريل الى يونيو 2024. تم تقييم كل من ضغط الدم ونسبة البروتين في البول. وعلاوة على ذلك، تم الحصول على عينة دم من كل مريضة من أجل تقييم مستويات PlGF في المصل باستخدام ELISA بالإضافة إلى المعايير الدموية والكيميائية الحيوية. تظهر مجموعة PE الشديدة فرق معنوي ($p \leq 0.05$) في كل من ضغط الدم الانقباضي والانبساطي عند مقارنتها بالمجموعة المعتدلة. علاوة على ذلك، هناك فرق معنوي كبير ($p \leq 0.01$) في عدد الصفائح الدموية و Aspartate amino Transferase (AST), Alanine amino Transferase (ALT), الكرياتينين و يوريا الدم بين مجموعتي PE. في الحالات الشديدة من PE، وجد أن وجود البروتين في البول على شريط اختبار البول بمستوى 2+ أو أعلى كان ذا فرق معنوي كبير ($p \leq 0.01$) عند مقارنته بالحالات المتوسطة . والجدير بالذكر أن مستويات PlGF لم تظهر أي اختلاف كبير بين مجموعتي تسمم الحمل المختلفة. وهذا ليس مفاجئًا، نظرًا لأن تسمم الحمل هو حالة معقدة تؤثر على أجهزة متعددة، مما يجعل من الصعب التنبؤ بدقة شدة المرض. تشير النتائج إلى أن PlGF غير قادر على التمييز بين حالات تسمم الحمل المتوسطة والشديدة. هناك حاجة إلى مزيد من التحقيقات لتحديد فعالية PlGF التنبؤية فيما يتعلق بشدة المرض، مع الأخذ بعين الاعتبار نوع المرض وأسبوع الحمل.

## 1. Introduction

Pre-eclampsia (PE) is a pregnancy-specific disorder that involves multiple organ systems and affects approximately 2-10% of expectant mothers [1]. It is a major cause of morbidity and mortality among mothers and neonates [2]. This condition is diagnosed after 20 weeks of pregnancy with arterial hypertension of 140/90 mmHg or higher, regardless of the presence of proteinuria or the occurrence of other new symptoms [3, 4]. Symptoms like elevated liver transaminases, thrombocytopenia, high serum creatinine levels, pulmonary oedema, visual or cerebral issues, epigastric pain, headache, and seizures help diagnose the condition [5, 6]. Moreover, albumin may serve as a valuable disease marker for the early management of established cases leading to preeclampsia and eclampsia [7].

PE is now universally recognized to be a heterogeneous condition [8], with at least two recognized primary subtypes: early-onset PE (preeclampsia associated with birth before 34 weeks of gestation) and the late-onset form, which manifests from 34 weeks of gestation to term [9]. Hypertension, resulting from increased resistance in the arteries of mothers with PE, can compromise blood flow to various organs such as the brain, placenta, liver, and kidneys [10].

PE is categorised as mild or severe based on the severity and accompanying symptoms [11]. Severe PE is commonly defined as preeclampsia linked to any of the following: Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg, thrombocytopenia, abnormally elevated blood concentrations of the liver, severe persistent right upper quadrant or epigastric pain unresponsive to medication, renal insufficiency (serum creatinine

concentration > 1.1), pulmonary oedema, and new-onset visual disturbances [12]. It can really get complex when other conditions get mixed in, like strokes, eclampsia, or posterior reversible encephalopathy syndrome. Those types of complications can make the situation a lot more involved, peripartum cardiomyopathy, maternal morbidity, acute kidney injury, reversible cerebral vasoconstriction syndrome, placental abruption, stillbirth, low birth weight, perinatal death, and HELLP (Hemolysis, Elevated Liver Enzymes, and Low Platelets) syndrome [13-15]. The severe consequences of preeclampsia that require intensive care unit (ICU) admission [16].

An imbalance between angiogenic and antiangiogenic substances, which are in charge of neo angiogenesis, fetal development, and spiral artery remodelling, is a major contributor to the pathophysiology of PE [17]. There is a theory suggesting that endothelial dysfunction affects the pathophysiology of PE. Changes in vascular endothelial growth factor (VEGF) production, a biomarker of endothelial dysfunction, are linked to this condition, regardless of whether they are increased, decreased, or remain normal [18]. The main mediator of angiogenesis is the homodimeric vasoactive glycoprotein known as VEGF. Angiogenesis, or the formation of new blood vessels, is the source of numerous physiological and pathological processes [19]. Additionally, the National Institute for Health and Care Excellence in the United Kingdom has emphasized the utility of this biomarker and suggested its use in the treatment of women who exhibit signs and symptoms suggestive of preeclampsia [20].
PlGF, a member of the vascular endothelial cell growth factor family [21], is crucial for morphogenesis and maturation of the placental vascular system [22]. The placental trophoblast is the primary source of PLGF during pregnancy, although various other tissues also express it, such as the villous trophoblast [23]. Normal PlGF concentrations typically range from around 141 pg/mL at approximately 30 weeks of gestation to 23 pg/mL at term, fluctuating with gestational age [24]. Lower serum and urine PlGF levels have been observed in women with PE at the time of diagnosis and even before symptom onset [25]. However, some studies suggest that the test sensitivity of PlGF may not be sufficient for reliably identifying cases of preeclampsia in clinical settings [26].
Future studies that investigate the use of serum PlGF in preeclampsia may address the knowledge gaps identified by this study. Furthermore, the objective of PIGF-based tests is to accurately predict the delivery date by assessing the perinatal outcome and incorporating additional clinical data to assist decision-making.

## 2. Materials and Methods

### *2. 1. Samples Collection*

A research investigation was conducted on a cohort of 90 pregnant females diagnosed with preeclampsia after 24 weeks of gestation until prenatal care at the Al-Elwiya Teaching Hospital for Maternity in Baghdad-Al-Rusafah between April and June 2024. Data regarding age, mode of delivery, body mass index (BMI), gestational age, maternal complications after delivery, fetal assessment, and outcome were collected through a questionnaire designed to investigate the condition, while those with diabetes, chronic renal diseases, and chronic hypertension were excluded from the study. The participants were split into two groups: 45 with moderate preeclampsia and 45 with severe preeclampsia, based on hypertension severity, biochemical parameters, and other symptoms and complications.

### *2.2. Sample Preparation*

Blood samples were collected, with 5 ml of venous blood placed in disposable plain plastic tubes. The samples were left to clot at room temperature before being centrifuged at 3,000 rpm for 15 minutes. The serum was isolated, stored in an Eppendorf tube at -20 °C, and

then used for measuring creatinine, urea, ALT and AST that were estimated by enzymatic colorimetric method by using multi chemical fully automated chemistry analyser (BioREX Mannheim/MALAYSIA). Placental growth factor levels were assessed by using kit supplied by (SunLong Biotech Co., LTD/China) and it based on sandwich an enzyme-linked immunosorbent assay (ELISA) technology, while proteinuria in the urine sample was measured through a dipstick test.

*2.3 Ethical clearance*

The ethical committee of the College of Science, University of Baghdad, authorized the study protocol (Ref: CSEC/0424/0040) on April 22, 2024.

*2.4 Statistical Analysis*

The study utilized the Statistical Analysis System- SAS (2018) program User's Guide. statistical version 9.6$^{th}$ ed. SAS. Inst. Ins. Cary. N.S. USA. to analyze the impact of different groups on study parameters, using T-tests for means comparison and chi-square tests for percentage comparison.

## 3. Results

*3.1. GA on Admission Show Significant Difference Among PE Cases, but There were no Differences in Age, BMI, or GA at delivery.*

The study included 45 pregnant women with moderate PE and 45 pregnant women with severe PE, their mean ages were (27.56 ±3.08 years) and (29.80 ±4.22 years), and their BMIs were (28.75 ±1.37) and (29.17 ±1.42), respectively. All groups exhibited no significant differences in their mean values. Also, GA on delivery was increased in the moderate PE (38.21 ±5.85) compared to the severe PE (34.71 ±5.02) without a statistically significant difference. while there was a highly significant (P≤0.01) difference in GA on admission between moderate PE (36.71 ±2.69) and severe PE (33.71 ±2.94), as shown in table 1.

**Table 1:** Comparison of age, BMI, and gestational age at admission and delivery regarding moderate and severe PE

| Variables | Mean ± SD | | T-test | P-value |
|---|---|---|---|---|
| | Moderate | Severe | | |
| Age (year) | 27.56 ±3.08 | 29.80 ±4.22 | 2.778 NS | 0.112 |
| BMI (kg/m$^2$) | 28.75 ±1.37 | 29.17 ±1.42 | 0.813 NS | 0.313 |
| GA on admission (week) | 36.71 ±2.69 | 33.71 ±2.94 | 1.557 ** | 0.0002 |
| GA on delivery | 38.21 ±5.85 | 34.71 ±5.02 | 7.216 NS | 0.0947 |

** (P≤0.01) , NS: Non-Significant.

Abbreviations: BMI, body mass index; GA, Gestational age

*3.2. An Increase in Blood Pressure Indicates a More Severe Form of Preeclampsia.*

The severe PE group had higher mean diastolic and systolic blood pressures (168.78 ±13.07 mmHg and 110.71 ±8.06 mmHg, respectively) than the moderate group (143.22 ±10.95 mmHg and 90.33 ±7.41 mmHg). Thus, there was a significant difference between the two groups as shown in table 2.

**Table 2:** Comparison of blood pressure alterations between the moderate PE and severe PE groups

| Parameters | Mean ± SD | | T-test | P-value |
|---|---|---|---|---|
| | Moderate | Severe | | |
| SBP (mm Hg) | 143.22 ±10.95 | 168.78 ±13.07 | 16.538 * | 0.03665 |
| DBP (mm Hg) | 90.33 ±7.41 | 110.71 ±8.06 | 12.863 * | 0.03091 |

* (P≤0.05).

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure

*3.3. Hb, HCT, and White Blood Cell Counts are not Relevant to The Severity of the Condition, Platelet Count is Significantly Decreased in Severe Cases.*

Table 3 shows the Hb, HCT, WBCs, and PLT count data for the groups under study. A striking exception to the overall lack of significant differences was the PLT count, which revealed a highly significant distinction (P<0.01) between the moderate and severe pre-eclampsia groups, highlighting a notable disparity between these two conditions.

**Table 3:** Comparison of haematological parameters between the moderate PE and severe PE groups

| Parameters | Mean ± SD | | T-test | P-value |
|---|---|---|---|---|
| | Moderate | Severe | | |
| Hb (g/dL) | 11.81 ±0.82 | 11.71 ±0.96 | 0.561 NS | 0.741 |
| HCT (%) | 37.54 ±1.79 | 36.82 ±3.28 | 1.723 NS | 0.406 |
| WBC (x $10^3$/ml) | 10.73 ±1.65 | 10.63 ±1.98 | 1.367 NS | 0.881 |
| PLT (x $10^3$/ml) | 218.24 ±29.71 | 181.87 ±33.05 | 23.354 ** | 0.0026 |

** (P≤0.01), NS: Non-Significant.

Abbreviations: Hb, haemoglobin; HCT, hematocrit; WBC, white blood cell; PLT, platelet count.

*3.4. Elevations in AST, ALT, Serum Creatinine, and Blood Urea are Associated with The Severity of Preeclampsia.*

As for the serum level of AST, ALT, urea, and creatinine, there was a highly significant (P≤0.01) increase in patients with severe PE (36.42 ±3.76 IU/L), (24.28 ±5.13 IU/L), (4.08 ±0.71 nmol/L) (0.778 ±0.12 mg/dl) respectively compared to patients with moderate PE (22.39 ±2.92 IU/L) (13.11 ±1.57 IU/L) (2.79 ±0.86 nmol/L) (0.576 ±0.13 mg/dl) respectively, as shown in table 4.

**Table 4:** Comparison of biochemical parameters between the moderate PE and severe PE groups

| Parameters | Mean ± SD | | T-test | P-value |
|---|---|---|---|---|
| | Moderate | Severe | | |
| AST (IU/L) | 22.39 ±2.92 | 36.42 ±3.76 | 4.062 ** | 0.0001 |
| ALT (IU/L) | 13.11 ±1.57 | 24.28 ±5.13 | 4.301 ** | 0.0001 |
| Blood urea (nmol/L) | 2.79 ±0.86 | 4.08 ±0.71 | 0.581 ** | 0.0001 |
| S. Cr (mg/dl) | 0.576 ±0.13 | 0.778 ±0.12 | 0.0699 ** | 0.0001 |

** (P≤0.01).

Abbreviations: AST, Aspartate aminotransferase; ALT, alanine aminotransferase; S.Cr, serum creatinine

*3.5. Increased Proteinuria Contributes to Severe Cases of Preeclampsia.*

With regard to proteinuria, a notable increase was observed in severe PE with a significant difference compared to moderate PE, as shown in table 5.

**Table 5:** Comparison of Proteinuria between the moderate PE and severe PE groups

| Parameter | | Moderate NO(%) | Severe NO(%) | P-value |
|---|---|---|---|---|
| Proteinuria + | -VE | 11(24.44%) | __ | 0.0001 ** |
| | Trace | 16(35.56%) | __ | 0.0001 ** |
| | + | 12(26.67%) | 18(40.00%) | 0.395 NS |
| | ++ | 6(13.33%) | 17(37.77%) | 0.0218 * |
| | +++ | __ | 10(22.22%) | 0.0045 ** |

** (P≤0.01), * (P≤0.05), NS: Non-Significant.

Abbreviations: -VE, negative

*3.6. PlGF Level is Almost Similar in Cases with Moderate and Severe Preeclampsia.*

Regarding PlGF level, results showed a non-significant difference between Pregnant females with moderate PE and those with severe PE, as presented in table 6

**Table 6:** Serum placental growth factor in patients with moderate PE and severe PE pregnant women

| Parameters | Mean ± SD | | T-test | P-value |
|---|---|---|---|---|
| | Moderate | Severe | | |
| PlGF (pg/ml)) | 16.17 ±0.2.56 | 16.81 ±1.85 | 2.568 NS | 0.620 |

NS: Non-Significant.

Abbreviations: PlGF, placental growth factor.

*3.7. Elevated Probability of ICU Admission, IUD Delivery, and Cesarean Section in Severe Preeclampsia.*

There was a highly significant (P≤0.01) difference in ICU and both types of delivery mode (including VD and CS), and also a significant (P≤0.05) difference in IUD between the two studied groups, as presented in table 7.

**Table 7:** The distribution of intensive care unit, mode of delivery, and intrauterine death between the groups with moderate PE and severe PE

| **Factors** | | **Moderate No (%)** | **Severe No (%)** | **P-value** |
|---|---|---|---|---|
| **ICU** | | 5 (12.50%) | 32 (71.11%) | 0.0006 ** |
| **Mode of Delivery** | VD | 28 (62.22%) | 11 (24.44%) | 0.0074 ** |
| | CS | 17 (37.78%) | 34 (75.56%) | 0.0089 ** |
| **IUD** | | 0 (0.00%) | 7 (15.56%) | 0.028 * |

* (P≤0.05), ** (P≤0.01).

Abbreviations: ICU, intensive care unit; VD, vaginal delivery; CS, cesarean section; IUD, intrauterine death

## 4. Discussion

The analysis revealed no significant difference in age and BMI between moderate preeclampsia and severe preeclampsia, in accordance with the findings of Cleary-Goldman *et al*. [27] who found no evidence linking the mother's age to hypertension-related issues such as preeclampsia and gestational hypertension. Furthermore, according to Odegard *et al*. [28], there was an inconsistent correlation between maternal weight and the clinical subtypes of mild, moderate, and severe PE. Regarding the topic of reduced gestational age upon admission and at delivery in cases of severe PE, which agrees with another study that reported for women with preeclampsia, the probability increases with lower gestational ages at delivery; this may minimize perinatal morbidity and mortality [29].

The arterial blood pressure of pregnant women with severe PE increased significantly; this finding is consistent with research by Nirupama *et al*. [30] that found that high blood pressure during pregnancy raises the risk of PE.

The findings of this investigation on WBC, Hb, and HCT corroborated with those of a different study carried out by Stevanović *et al*. [31]. Furthermore, it was observed that there were no statistically significant variations in WBC, Hb, or HCT between the two study groups. While there is a pronounced decline in platelet counts in study cases of severe PE, this discovery is in line with a study by Freitas *et al*. [32] that found that the development and severity of PE are influenced by platelet counts. The placenta of preeclamptic women has been seen to have significant degenerative alterations in both trophoblastic and endothelial cells. The increase of platelets in the capillary lumen served as a representation of these alterations [33]. Neiger *et al*. [34], however, reported showed that there was no statistically significant variation in platelet counts between those with moderate and severe preeclampsia.
This study found that, compared to moderate PE, severe PE had significantly higher values of biochemical markers. These serve as essential indicators for predicting when preeclampsia complications will manifest. The acquired results were consistent with the research of Hussein *et al*. [35], who discovered liver and kidney function in preeclamptic pregnancies are crucial indicators for early detection of preeclampsia complications, potentially reducing the likelihood of illness development. Because hypoxia-induced stress mediators damage the developing placenta's endothelial cells, preeclampsia causes a decrease in GFR. This, in turn, leads to increased protein loss and damage to the filtration apparatus and cells, ultimately changing renal function [36, 37]. In addition, pathophysiological abnormalities, including generalized vasospasm, abnormal lipid metabolism, vascular endothelial dysfunction, and insulin resistance, may impact the liver and lead to partially elevated liver enzymes prior to the development of preeclampsia [38].
Furthermore, there was a correlation observed between the severity of the illness and rises in proteinuria outcomes. This finding aligns with the study by Lei *et al*., which recommends that proteinuria should be included as one of the monitoring indicators for patients with preeclampsia [36]. Stevanović *et al*. achieved a similar result, demonstrating that proteinuria is one of the primary markers used to diagnose preeclampsia. It is caused by damage to the endothelium of the renal glomeruli, which is one of the indicators of extensive endothelial damage during pregnancy [31]. However, according to Özkara *et al*. [37], it is impossible to measure how severe preeclampsia is based on the level of proteinuria.

The present study suggests that there is no substantial disparity in PlGF levels between the groups with moderate and severe PE. These findings indicate that PIGF is not a reliable predictor for identifying groups at risk of developing PE. Therefore, the findings align with

the study conducted by Torry *et al*. [38], which concluded that there was no significant difference in serum placenta growth factor levels between women with mild to moderate preeclampsia and those with severe preeclampsia. Robinson *et al*. [39] found that the concentration of PlGF was lower in patients with mild PE compared to those with severe PE, as opposed to other studies. Furthermore, Chau *et al*. [22] found that the ability of PlGF and other angiogenic markers to predict outcomes is likely restricted by a variety of underlying causes, which contributes to the varying clinical manifestations of preeclampsia. Heazell *et al*. [40] conducted a study that found inadequate evidence to support the use of placental biomarkers for predicting prenatal outcomes. Additional research has indicated that the impact of PlGF on blood pressure is observable when analyzing all pregnancies, regardless of whether they involve mild or severe preeclampsia. However, this effect becomes undetectable when specifically examining women with severe features of preeclampsia [41-43]. According to another study, the use of PlGF-based biomarker testing may not have a significant impact on other clinical outcomes, such as the need for maternal hospital admission and adverse effects for the baby [44]. Further investigation provides evidence that various stimuli, including growth factors, hormones, inflammatory cytokines, and hypoxia, which are all present during implantation and placenta development, and may increase the expression of PlGF, as well as environmental and genetic factors, influence the variability of placental growth factor [45, 46]. Due to the limited involvement of defective placentation in the development of late-onset disease, PlGF seems to have a low level of predictability for late-onset disease. Additionally, the levels of PlGF fluctuate depending on the stage of pregnancy [47-49]. It's conceivable that the extent of endothelial cell dysfunction or damage is not accurately captured by clinical measures, potentially leading to an incomplete picture of the diseases severity, which could explain these results. Based on the previous observation, it is desirable to combine the study of biological and biochemical markers with clinical assessments of preeclampsia severity.

This study indicates that many women who have severe PE need to be admitted to an intensive care unit. This observation may be related to the morbidity and mortality associated with pregnant mothers with hypertension who are admitted to the intensive care unit. In addition, about 51 women in the present study underwent cesarean sections; the majority of these had severe PE. The results observed were consistent with the research by Sukmawati *et al*. [50], who reported that cesarean deliveries were more common in cases with severe PE than vaginal deliveries, and a study done by Majeed *et al*. [51] showed that preterm birth, low birth weight, cesarean section (CS), and various maternal and neonatal complications were significant anxieties for pregnant women with PE. According to this study, there are 7 (15.56%) intrauterine deaths in severe PE cases. The study done by Espinoza *et al*. [52] observed that preeclampsia's aberrant uteroplacental blood flow negatively impacts the fetus's health.

## 5. Limitation, Weaknesses and Strength of the Study

This study has certain limitations and weaknesses. Firstly, it was conducted in a hospital, and more clinical cases were needed to improve accuracy. In addition, the parameters were only studied in maternal blood; future studies should include a placental tissue sample. On the other hand, two important aspects of the study's strength are its use of detailed clinical records to provide diagnostic criteria for PE and its sufficient amount of blood samples, which enhanced estimation and precision and improved the statistical test's power.

## Conclusion

The study concluded that blood pressure, proteinuria, platelets, ALT, AST, serum creatinine, and blood urea levels are used to assess the severity of preeclampsia. Nevertheless, placental growth factor lacks the ability to distinguish between moderate and severe cases of preeclampsia. Given the uncertainty, it's hard to predict just how severe the illness might end up being.

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## 8. Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## 10. Author Contribution

The author admits full responsibility for the following aspects: conception and design of the study, collection of data, analysis and interpretation of results, and preparation of the manuscript.

"Conflict of interest: The authors have no conflicts of interest to declare."

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