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# Changes in Blood Coagulation Parameters and Platelet Indices in Pregnancies with Gestational Hypertension and Preeclampsia

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**ABSTRACT**

**Background:** Hypertensive disorders of pregnancy impact approximately 10% of pregnancies worldwide. During pregnancy, there are changes in the expression of coagulation and fibrinolytic proteins that promote clot formation. While a normal pregnancy is associated with increased coagulation, women with preeclampsia experience even greater coagulation. Aim of the study: To assess the potential of blood coagulation parameters and platelet indices as predictors for preeclampsia. **Material and Methods:** The study included 97 age-matched pregnant women, 78 of which had gestational hypertension and 19 had preeclampsia and its severe forms. The study compared demographic data, clinical characteristics, blood clotting parameters and platelet measurements of all participants. **Results:** Patients with preeclampsia had slightly elevated coagulation parameters such as activated partial thromboplastin time, prothrombin time activity percentage, and prothrombin time. We found a statistically significant difference in prothrombin time activity percentage (106.6 ± 3.457; 95.07 ± 2.165, p = 0.0166). However, patients with preeclampsia had significantly lower levels of international normalized ratio (0.975 vs. 1.048, p = 0.019), fibrinogen (314.2 mg/dL vs. 344.5 mg/dL, p = 0.0247), and platelet count (234.2 ± 19.59 × 104/μL vs. 280.8 ± 8.63 × 104/μL, p = 0.0214) than women with gestational hypertension. We found no statistically significant differences between the groups regarding mean platelet volume and platelet distribution width. **Conclusions:** Platelet count is a promising method for diagnosing preeclampsia due to its simplicity. Mean platelet volume, activated partial thromboplastin time, and prothrombin time increased in women with preeclampsia, indicating a hypercoagulable state in the third trimester in these patients. Prothrombin time activity percentage increased significantly and could be a potentially parameter in predincting preeclampsia.

**Keywords:** preeclampsia, gestational hypertension, coagulation, platelet indices

## INTRODUCTION

Hypertensive disorders of pregnancy (HDP) impact approximately 10% of pregnancies worldwide. These disorders, which affect multiple systems, include chronic hypertension with superimposed preeclampsia, gestational hypertension, preeclampsia, and eclampsia. The majority of HDP cases occur in low- and middle-income countries.1 The complications of gestational hypertension and preeclampsia include abruptio placentae, intrauterine growth retardation, premature delivery, and intrauterine death. Maternal complications include acute liver or renal failure, HELLP syndrome, disseminated intravascular coagulopathy, pulmonary edema, liver hemorrhage, and sepsis.[1,2] Maternal and perinatal mortality rates are elevated when HDP is left untreated.[3]

Gestational hypertension is a condition in which a pregnant woman who previously had normal blood pressure, exhibits a systolic blood pressure of 140 mmHg or higher, or a diastolic blood pressure of 90 mmHg or higher, or both, on two separate occasions at least 4 h apart after the 20th week of pregnancy. Severe gestational hypertension is indicated by a systolic blood pressure of 160 mmHg or higher, a diastolic blood pressure of 110 mmHg or higher, or both.[4]

Preeclampsia, often referred to as the "disease of theories", is marked by hypertension, indicated by a blood pressure of 140/90 mmHg or higher along with proteinuria of more than 0.3 g per day, edema, and other associated symptoms. It can manifest as early as the 20th week of pregnancy. In some cases, preeclampsia can occur without proteinuria or signs of maternal liver dysfunction, acute kidney injury, hemolysis, neurological features, or thrombocytopenia, which highlights the variability and complexity of preeclampsia as a condition.[5,6]

The complete understanding of the pathophysiology of HDP remains unclear.[1] The pathogenesis of preeclampsia is thought to involve various factors. One of these factors is the abnormal invasion of uterine arteries by cytotrophoblasts, which can lead to inadequate remodeling of the uterine vasculature. Endothelial dysfunction is also believed to play a role in preeclampsia. It involves impaired function of the endothelial cells lining blood vessels, leading to vasoconstriction, increased permeability, and altered production of vasoactive substances. Additionally, preeclampsia is associated with endothelial cell activation, intravascular inflammation, and syncytiotrophoblast stress.[7,8]

During pregnancy, there are changes in the expression of coagulation and fibrinolytic proteins that promote clot formation. While normal pregnancy is associated with increased coagulation, women with preeclampsia experience even greater coagulation compared to those with normal pregnancies.[9]

Maternal inflammatory reactions and immune dysfunction significantly impact the coagulation and fibrinolytic systems in patients with preeclampsia. In normal pregnancies, maintaining an appropriate increase in blood coagulation is crucial to prevent postpartum hemorrhage and minimize complications. However, in patients with preeclampsia, this delicate balance is disrupted, leading to microthrombosis, which obstructs blood flow in the placenta and various organs.[5]

Platelets play a vital role in hemostasis, providing rapid protection against bleeding. Platelet indices obtained from the complete blood count, including platelet distribution width (PDW), mean platelet volume (MPV), platelet-large cell ratio (P-LCR), and plateletcrit (PCT), provide information about platelet characteristics and can be helpful in assessing platelet function and bone marrow activity. MPV is a measure of the average size of platelets, while PDW indicates the degree of variation in platelet size, PCT represents the volume of platelets in a given blood volume, and P-LCR reflects the percentage of larger platelets in the blood.[10,11]

Recent research has indicated a correlation between elevated MPV and severe inflammatory processes. Additionally, various indices, such as PDW, soluble vascular endothelial growth factor, and D-dimer, have been identified as ideal indicators for preeclampsia.[5] The aim of this study was to assess the potential of blood coagulation parameters and platelet indices as predictors for preeclampsia.

## MATERIAL AND METHODS

### Study design and patient groups

We carried out a prospective, single-center cohort study between January 1, 2020 and December 31, 2022. The study included 97 age-matched pregnant women, who met the inclusion criteria and had gestational hypertension, or preeclampsia and its severe forms. The patients were divided into two groups based on diagnostic criteria. The first group comprised 78 patients with gestational hypertension, while the second group included 19 patients with preeclampsia and its severe forms (14 patients with preeclampsia, 3 with incomplete HELLP syndrome, and 2 with eclampsia). The gestational hypertension and preeclampsia groups included pregnant patients between the ages of 15 and 45 years who were diagnosed after 20 weeks of gestation.

Patients with systemic infection, fever, chorioamnionitis, chronic systemic diseases during pregnancy (e.g., ne-

phropathy, renal or hepatic dysfunction), thyroid disease, previous pregnancy with preeclampsia, autoimmune disease, cholestasis of pregnancy, and fetal anomalies were excluded from the study.

### Clinical and laboratory parameters

Demographic and clinical data were recorded: age, body mass index (BMI), symptoms, medical hystory, platelet indices, and blood coagulation parameters. The measured laboratory parameters included activated partial thromboplastin time (aPTT), international normalized ratio (INR), platelet count (PLT), Quick time (PTs), prothrombin time activity percentage (PTp), MPV, fibrinogen, and PDW. The venous blood samples were prevailed from the records before the 20th week of gestation and on the day of hospitalisation. Platelet-related parameters (PLT, PDW, and MPV) were measured from venous blood samples collected in EDTA-containing tubes and analyzed using a RAYTO 7600 automatic blood cell analyzer. For the measurement of coagulation parameters (APTT, PTs, PTp, INR, and fibrinogen) plasma was separated from the venous blood samples collected in sodium citrate-containing tubes, and the measurements were performed with a RAYTO2201 C automatic coagulation instrument and appropriate reagents.

### Statistical analysis

Statistical analysis was carried out using Prism 5.0 software (GraphPad, San Diego, CA, USA). Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are expressed as percentage (%). Two-sample t-tests were used for comparing continuous variables between two groups. The statistical significance level was set at a p value of $<0.05$.

### Ethics

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the "Elena Doamna" Clinical Hospital of Obstetric and Gynecology, Iași, Romania.

## RESULTS

### Baseline characteristics

The baseline characteristics of study participants are presented in Table 1. Women with preeclampsia had significantly higher systolic and diastolic blood pressure levels than women with gestational hypertension ($p < 0.0001$ and

**TABLE 1.** The demographic and clinical data of the participants

| | Gestational hypertension (n = 78) | Preeclampsia (n = 19) | 95% CI | $R^2$ | p value |
|---|---|---|---|---|---|
| General information | | | | | |
| Age (years) | 27.78 ± 0.73 | 24.58 ± 1.52 | –0.11 to 6.5 | 0.037 | 0.057 |
| BMI (kg/m$^2$) | 27.82 ± 0.65 | 27.21 ± 1.30 | –2.30 to 3.51 | 0.002 | 0.680 |
| Blood pressure | | | | | |
| SBP (90–140 mmHg) | 155.30 ± 1.35 | 168.70 ± 2.35 | –19.31 to –7.49 | 0.176 | <0.0001 |
| DBP (60–90 mmHg) | 96.24 ± 1.16 | 103.90 ± 1.86 | –12.74 to –2.66 | 0.089 | 0.003 |
| Medical history | | | | | |
| Obesity | 0.34 ± 0.05 | 0.16 ± 0.09 | –0.05 to 0.42 | 0.026 | 0.114 |
| Diabetes mellitus | 0.05 ± 0.02 | 0.11 ± 0.07 | –0.18 to 0.069 | 0.008 | 0.386 |
| Clinical characteristics | | | | | |
| Mild hypertension | 0.47 ± 0.05 | 0.53 ± 0.12 | –0.31 to 0.20 | 0.002 | 0.688 |
| Severe hypertension | 0.19 ± 0.04 | 0.47 ± 0.12 | –0.50 to –0.07 | 0.067 | 0.011 |
| Headache | 0.15 ± 0.04 | 0.42 ± 0.12 | –0.47 to –0.07 | 0.069 | 0.010 |
| Vaginal bleeding | 0.02 ± 0.01 | 0.11 ± 0.07 | –0.18 to 0.021 | 0.025 | 0.120 |
| Vertigo | 0.14 ± 0.04 | 0.21 ± 0.10 | –0.25 to 0.12 | 0.006 | 0.458 |
| Primigravida | 0.58 ± 0.05 | 0.79 ± 0.10 | –0.46 to 0.03 | 0.030 | 0.089 |
| RI MCA/UA <1 | 0.02 ± 0.01 | 0.16 ± 0.09 | –0.24 to –0.02 | 0.056 | 0.019 |
| Fetal morphology scan | 0.61 ± 0.05 | 0.58 ± 0.12 | –0.21 to 0.28 | 0.001 | 0.773 |
| Miscarriage | 0.27 ± 0.05 | 0.21 ± 0.10 | –0.17 to 0.28 | 0.003 | 0.003 |
| Multiple pregnancies | 0.03 ± 0.02 | 0.05 ± 0.05 | –0.12 to 0.06 | 0.003 | 0.037 |

RI MCA/UA, resistance index between the middle cerebral artery and uterine artery

**TABLE 2.** The demographic and clinical data of the participants

| | Gestational hypertension (n = 78) | Preeclampsia (n = 19) | 95% CI | $R^2$ | p value |
|---|---|---|---|---|---|
| aPTT (25–43 s) | 30.49 ± 0.46 | 31.90 ± 1.31 | –3.67 to 0.84 | 0.016 | 0.214 |
| PTs (10–15 sec) | 12.89 ± 0.15 | 12.95 ± 0.19 | –0.69 to 0.57 | 0 | 0.849 |
| INR (0.8–1.3) | 1.05 ± 0.01 | 0.97 ± 0.02 | 0.01 to 0.13 | 0.057 | 0.019 |
| PTp (70–120%) | 95.07 ± 2.16 | 106.60 ± 3.45 | –20.87 to –2.12 | 0.059 | 0.017 |
| Fibrinogen (200–400 mg/dL) | 344.50 ± 5.99 | 314.20 ± 11.01 | 3.90 to 56.83 | 0.052 | 0.025 |
| PLT (150–400 × $10^4$/μL) | 280.90 ± 8.63 | 234.20 ± 19.59 | 7.00 to 86.39 | 0.054 | 0.021 |
| MPV (7–11 fL) | 8.60 ± 0.12 | 8.72 ± 0.35 | –0.72 to 0.48 | 0.002 | 0.692 |
| PDW (10–18%) | 16.20 ± 0.30 | 17.35 ± 1.04 | –2.71 to 0.42 | 0.022 | 0.150 |

p = 0.003, respectively). We found no statistically significant differences between the two groups regarding BMI, obesity, gestational diabetes, vaginal bleeding, vertigo, fetal morphology scan, nulliparity, miscarriage and multiple pregnancy. However, headache and severe hypertension were significantly more frequent in patients with preeclampsia (p = 0.011 and p = 0.010, respectively). The resistance index between the middle cerebral artery and uterine artery was found to be significantly lower in patients with preeclampsia (p = 0.0192).

### Blood coagulation parameters and platelet indices

Serum levels of aPTT, PTs, and PTp were elevated in patients with preeclampsia compared to those with gestational hypertension. PTp was significantly higher in patients with preeclampsia compared to patients with gestational hypertension (106.6 vs. 95.07, p = 0.0166). However, patients with preeclampsia had significantly lower levels of INR (0.975 vs. 1.048, p = 0.019), fibrinogen (314.2 mg/dL vs. 344.5 mg/dL, p = 0.0247), and PLT (234.20 ± 19.59 × $10^4$/μL vs. 280.90 ± 8.63 × $10^4$/μL, p = 0.0214) than women with gestational hypertension. We found no statistically significant differences between the groups regarding MPV and PDW.

## DISCUSSION

In this study, we found significant differencies in blood coagulation parameters and platelet indices between the two study groups, including PTp, INR, fibrinogen, and PLT, which may be indicative of altered coagulation status in patients with preeclampsia compared to those with gestational hypertension.

Mean levels of aPTT, PTs and PTp were higher in patients with preeclampsia compared to those with gestational hypertension, in the case of PTp the difference being statistically significant. Preeclampsia involves the dysfunction of the endogenous coagulation pathways, leading to impaired coagulation. However, fibrinogen levels were lower in patients with preeclampsia, which is somewhat contradictory, as lower fibrinogen levels would

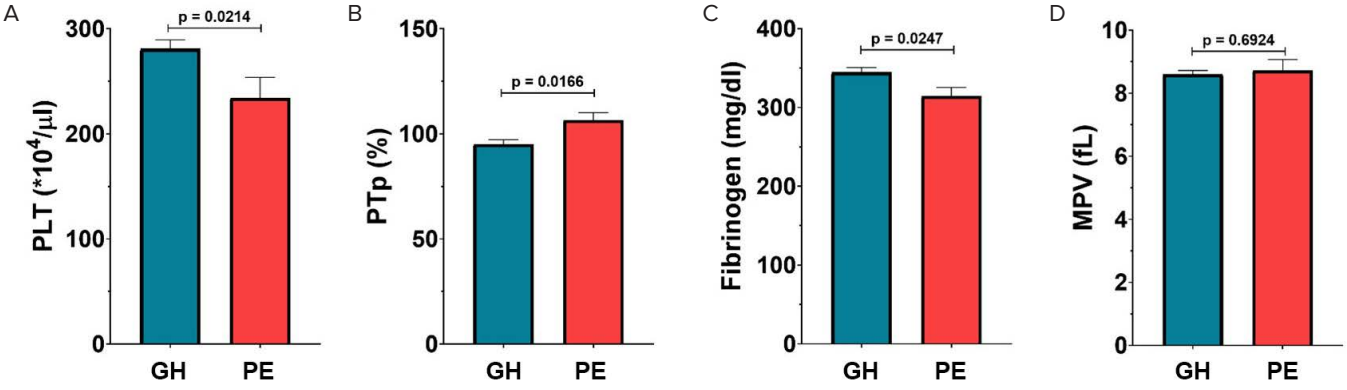


**FIGURE 1.** Comparison of the two groups in terms of PLT (**A**), PTp (**B**), fibrinogen (**C**), and MPV (**D**). GH, gestational hypertension; PE, preeclampsia

typically be associated with diminished coagulation. In preeclampsia, fibrinogen synthesis in the liver may be insufficient to compensate for increased consumption that occurs due to the decompensation of coagulation, meaning that the body's ability to produce enough fibrinogen to maintain normal coagulation may be compromised in preeclampsia. PTp could potentially be an ideal parameter in predicting preeclampsia.

In their study, Han *et al*. observed some changes during late pregnancy in the group of patients with normal pregnancy, including a reduction in aPTT, PLT, thrombin time, and PTs, and an increase in fibrinogen levels and MPV. On the other hand, they found an increase in aPTT, thrombin time, MPV, and D-dimer levels in the third trimester in patients with preeclampsia.[5]

The research carried out by Altınbas *et al*. concluded that neither the MPV-to-PLT ratio, nor MPV alone can be considered reliable indicators for predicting the severity or the risk of developing preeclampsia.[12] In a recent study by Doğan *et al*., it was observed that women with preeclampsia had significantly lower PLT and PLT-to-MPV ratio compared to the control group. In addition, there was a noticeable increase in MPV in women with preeclampsia.[13]

The study conducted by AlSheeha *et al*. found no significant variations in PDW and MPV between women with preeclampsia and the control group.[14] Yavuzcan *et al*. did not find any significant differences in MPV between women with severe preeclampsia, healthy pregnant women and healthy non-pregnant women.[15] In the study conducted by Temur *et al*. it was reported that there were no significant differences observed in plateletcrit, mean PLT and PDW between the preeclampsia group and the control group. However, they did find that MPV values were significantly higher in patients with preeclampsia.[16] Yang *et al*. found that PDW was considerably elevated in women suffering from severe preeclampsia compared to those with mild preeclampsia.[17] Dundar *et al*. proposed that the MPV could serve as an indicator for predicting the development of preeclampsia.[18]

Awodu hypothesized that the prolonged PT observed in patients with preeclampsia could be attributed to abnormalities, either quantitative or qualitative, of factors within the extrinsic pathway of coagulation. Additionally, prolonged aPTT was suggested to be linked to the presence of anti-phospholipid antibodies or lupus anticoagulant.[19] In their study, Jaremo *et al*. discovered that increased MPV was linked to the presence of hypertension rather than overall platelet changes. They attributed this observation to disrupted platelet density distributions.[20]

It is important to note that the discrepancy between studies regarding MPV might be attributed to the method of measurement. It is known that measurements conducted in EDTA can be relatively unreliable, and MPV tends to increase over time in this type of measurement.[18]

## CONCLUSIONS

Platelet count is a promising method for diagnosing preeclampsia due to its simplicity, cost-effectiveness and accessibility. However, more research is needed to understand the significance of platelet-related parameters in the progression and intensity of preeclampsia. The study also found that MPV along with the prolongation of APTT and PTs increases but not significantly between the two groups during pregnancy, indicating a hypercoagulable state in third-trimester in preeclampsia patients. PTp increased significatly statistic and could be a potentially parameter in predicting preeclampsia. It is worth mentioning that the restricted number of participants and the inclusion of women in the later stages of pregnancy hinder the ability to reach definitive conclusions. Further studies evaluating sequential blood coagulation parameters and platelet indices throughout pregnancy are necessary to provide a clearer understanding of the relationship between platelet parameters, blood coagulation parameters and preeclampsia.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## REFERENCES

1. Mtali YS, Lyimo MA, Luzzatto L, Massawe SN. Hypertensive disorders of pregnancy are associated with an inflammatory state: evidence from hematological findings and cytokine levels. *BMC Pregnancy Childbirth*. 2019;19:237.
2. Tanjung MT, Siddik HD, Hariman H, Koh SC. Coagulation and fibrinolysis in preeclampsia and neonates. *Clin Appl Thromb Hemost*. 2005;11:467–473.
3. Deng Y, She L, Li X, et al. Monitoring hypertensive disorders in pregnancy to prevent preeclampsia in pregnant women of advanced maternal age: trial mimicking with retrospective data. *Open Med (Wars)*. 2022;17:1840–1848.
4. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol*. 2019;133:1.
5. Han L, Liu X, Li H, et al. Blood coagulation parameters and platelet indices: changes in normal and preeclamptic pregnancies and predictive values for preeclampsia. *PLoS One*. 2014;9:e114488.
6. Brown MA, Magee LA, Kenny LC, et al. International Society for the Study of Hypertension in Pregnancy (ISSHP). The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2018;13:291–310.
7. Heilmann L, Rath W, Pollow K. Hemostatic abnormalities in patients with severe preeclampsia. *Clin Appl Thromb Hemost*. 2007;13:285–291.
8. Jung E, Romero R, Yeo L et al. The etiology of preeclampsia. *Am J Obstet Gynecol*. 2022;226:S844–S866.
9. Hale SA, Sobel B, Benvenuto A, et al. Coagulation and Fibrinolytic System Protein Profiles in Women with Normal Pregnancies and Pregnancies Complicated by Hypertension. *Pregnancy Hypertens*. 2012;2:152–157.
10. Manchanda J, Malik A. Study of platelet indices in pregnancy-induced hypertension. *Med J Armed Forces India*. 2020;76:161–165.
11. Freitas LG, Alpoim PN, Komatsuzaki F, Carvalho Md, Dusse LM.

Preeclampsia: are platelet count and indices useful for its prognostic? *Hematology*. 2013;18:360–364.
12. Altınbas S, Toğrul C, Orhan A, Yücel M, Danısman N. Increased MPV is not a significant predictor for preeclampsia during pregnancy. *J Clin Lab Anal*. 2012;26:403–406.
13. Doğan K, Guraslan H, Senturk MB, et al. Can platelet count and platelet indices predict the risk and the prognosis of preeclampsia? *Hypertens Pregnancy*. 2015;34:434–442.
14. AlSheeha MA, Alaboudi RS, Alghasham MA, Iqbal J, Adam I. Platelet count and platelet indices in women with preeclampsia. *Vasc Health Risk Manag*. 2016;12:477–480.
15. Yavuzcan A, Cağlar M, Ustün Y, et al. Mean platelet volume, neutrophillymphocyte ratio and platelet-lymphocyte ratio in severe preeclampsia. *Ginekol Pol*. 2014;85:197–203.
16. Temur M, Taşgöz FN, Çift T, Serpim G, Üstünyurt E. Role of platelet indices in prediction of preeclampsia. *Ginekol Pol*. 2021;92:792–796.
17. Yang SW, Cho SH, Kwon HS, Sohn IS, Hwang HS. Significance of the platelet distribution width as a severity marker for the development of preeclampsia. *Eur J Obstet Gynecol Reprod Biol*. 2014;175:107–111.
18. Dundar O, Yoruk P, Tutuncu L, et al. Longitudinal study of platelet size changes in gestation and predictive power of elevated MPV in development of pre-eclampsia. *Prenat Diagn*. 2008;28:1052–1056.
19. Awodu OA, Shokunbi WA, Ejele OA. Lupus anticoagulant in Nigerian women with Pre-eclampsia. *West Afr J Med*. 2003;22:240–242.
20. Järemo P, Lindahl TL, Lennmarken C, Forsgren H. The use of platelet density and volume measurements to estimate the severity of pre-eclampsia. *Eur J Clin Invest*. 2000;30:1113–1118.