International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 15, Issue 6, 2023

Original Article

UNLOCKING THE FUTURE OF MATERNAL HEALTH: PLATELET INDICES AS PREDICTORS OF PRE-ECLAMPSIA

SONAKSHI SHARMA*, ANOOP SHARMA, GEETIKA GUPTA SYAL

Kamla Nehru State Hospital Mother and Child, Shimla, (H. P.) India
***Corresponding author: Sonakshi Sharma; *Email: sharmasonakshi584@gmail.com**

Received: 15 Aug 2023, Revised and Accepted: 02 Oct 2023

ABSTRACT

Objective: Pre-eclampsia is a serious complication of pregnancy, posing significant risks to maternal and fetal health. Predictive indicators for this condition are essential for early diagnosis and management. Platelet indices, including platelet count (PC), platelet distribution width (PDW), mean platelet volume (MPV), and platelet crit (PCT), are potential biomarkers for pre-eclampsia due to their association with coagulation abnormalities. This study aims to investigate the utility of platelet indices in predicting pre-eclampsia.

Methods: The study was conducted at Kamla Nehru State Hospital for Mother and Child, Shimla, Himachal Pradesh, from March 1, 2021, to February 28, 2022. Normotensive pregnant women with singleton pregnancies after 20 w of gestation were included, and those with pre-existing conditions were excluded. Platelet indices were measured throughout pregnancy, and patients were categorized based on the development and severity of pre-eclampsia. Data were analyzed using SPSS-PC-25, and statistical tests were performed to determine the significance of platelet index variations.

Results: The study reveals significant differences in platelet indices between normotensive and preeclampsia (PE) patients. PE patients exhibited elevated mean platelet volume (MPV), decreased platelet count, and increased platelet distribution width (PDW) compared to normotensive individuals. Notably, MPV increased significantly in PE, preceding blood pressure elevation. Platelet count decreased significantly in severe PE cases. Receiver Operating Characteristic (ROC) curve analysis demonstrated the potential of platelet count and MPV as predictors for PE. These findings underscore the relevance of platelet indices in PE diagnosis and highlight their potential utility as early markers of this hypertensive disorder during pregnancy.

Conclusion: Platelet indices, particularly platelet count, MPV, and PDW, hold promise as early markers for predicting and monitoring pre-eclampsia. Monitoring platelet indices alongside blood pressure could aid in assessing the severity and progression of the condition, contributing to improved maternal and fetal outcomes. Further research in this area is warranted to refine predictive models and enhance clinical utility.

Keywords: Pre-eclampsia, Platelet count, Mean platelet volume, Platelet distribution width, Plateletcrit, Predictive markers, Pregnancy complications, Maternal health, Fetal outcomes

DOI: https://dx.doi.org/10.22159/ijcpr.2023v15i6.4005. Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

INTRODUCTION

Pre-eclampsia, a difficult and sometimes fatal illness, complicates around 5% of pregnancies and poses a serious threat to maternal health [1]. This illness not only causes maternal morbidity and mortality, but it also increases the risk of fetal growth restriction, premature delivery, and perinatal death. Pre-eclampsia is defined by the abrupt development of hypertension and proteinuria in previously normotensive women after 20 w of pregnancy or postpartum or by the start of hypertension with substantial end-organ failure. According to how severe it is, it is further divided into other categories [2]. Severe characteristics include elevated blood pressure, proteinuria, thrombocytopenia, renal insufficiency, decreased liver function, pulmonary edema, and neurological symptoms.

It's interesting to note that 7% of patients with pre-eclampsia in one pregnancy run the risk of suffering it again in subsequent pregnancies, underscoring the need to comprehend its underlying processes and prognostic indicators [3]. Addressing the problems associated with pre-eclampsia is crucial for improving maternal healthcare in India, where the prevalence of the illness is estimated to be between 8 and 10% among pregnant women [4].

Pre-eclampsia has a complex etiology, with aberrant placentation identified as a major contributing cause. The etiology of pre-eclampsia is heavily influenced by the defective invasion of spiral arteries by cytotrophoblast cells, which causes changes in the coagulation and fibrinolysis processes [5]. The change of maternal spiral arteries that results from trophoblastic invasion into myometrial blood vessels during a healthy pregnancy ensures appropriate placental perfusion. Failure to carry out this process results in the persistence of high-resistance spiral arterioles, which then causes maternal endothelial cell dysfunction and relative hypoxemia [6].

Placental hypoxia and ischemia continue the chain of events, increasing angiogenic indicators, including soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) [7]. These indicators influence the maternal vasculature's endothelial dysfunction, which leads to a vasoconstrictive state, oxidative stress, and microemboli that damage several organ systems. Endothelial injury increases the coagulation system's activity, leading to increased platelet consumption and hematologic abnormalities, the most prevalent of which is thrombocytopenia. It's significant that variations in platelet indices show promise as predictors and early diagnostic tools for pre-eclampsia [8].

Several metrics are included in platelet indices, such as platelet count (PC), platelet distribution width (PDW), mean platelet volume (MPV), and platelet crit (PCT) [9]. While PDW depicts the variability in platelet morphology caused by the presence of bigger platelets with normal-sized ones, MPV displays the average size of platelets [10]. Contrarily, PCT provides information on platelet activity and represents the entire platelet mass while being impacted by both platelet count and MPV. These parameters are useful for predicting pre-eclampsia even before changes in conventional coagulation parameters like prothrombin time (PT), activated partial thrombin time (aPTT), and thrombin time become apparent because a low PCT may indicate reduced platelet activity in the blood.

We explore the important connection between platelet indices and the onset of pre-eclampsia in the sections that follow, offering insight on their potential as diagnostic indicators for this illness. We intend to determine the predictive usefulness of platelet indices in the early identification of pre-eclampsia through a prospective study, which would eventually enhance the results for maternal healthcare [12].

MATERIALS AND METHODS

Study setting

The study, was conducted at the Department of Obstetrics and Gynecology, Kamla Nehru State Hospital for Mother and Child, Shimla, Himachal Pradesh. Ethical approval for the study was obtained from the Institutional Ethics Committee at IGMC Shimla. The study took place from March 1, 2021, to February 28, 2022.

Patient selection

Inclusion criteria

1. Normotensive pregnant women with singleton pregnancies after 20 w of gestation.

2. Patients willing to participate in the study and able to provide valid informed consent.

Exclusion criteria

1. Pre-existing hypertension.

2. Known chronic renal disease.

3. Known connective tissue disorder.

4. Use of anticoagulants.

5. Hematologic disorders.

6. Acquired or congenital hematologic disorder.

7. Use of any medication that can interfere with platelet function or number.

8. Asthmatic patients requiring steroids.

Sample size

The calculated sample size was approximately 270, ensuring a 95% confidence interval.

Methodology

A total of 270 pregnant women between 20-24 w of gestation with singleton pregnancies and normal blood pressure were recruited for the study after obtaining written informed consent. Baseline characteristics, including age, parity, gestational age, and socioeconomic status, were collected, along with obstetric and menstrual history. Physical examinations and systemic assessments were performed. Blood pressure was measured using the auscultatory method in a seated position during every visit. Diagnosis of pre-eclampsia was established if diastolic blood pressure was≥9 0 mmHg on two occasions 4 h apart or a single reading of≥11 0 mmHg with systolic blood pressure≥14 0 mmHg or a single reading of≥16 0 mmHg. Patients were categorized into pre-eclampsia with non-severe features and pre-eclampsia with severe features based on defined criteria. Blood samples were collected under aseptic conditions and analyzed within one hour using a hemat analyzer. Patients were followed until delivery, with data collected on mode of delivery, baby conditions, and changes in platelet indices.

Ethical consideration

The study adhered to ethical guidelines outlined by the Indian Council of Medical Research (ICMR, 1994) and the Helsinki Declaration (modified 2000). Informed consent was obtained from all participants, and their privacy, confidentiality, and physical and mental well-being were protected throughout the study.

Statistical analysis

Data was analyzed using SPSS-PC-25. Normality of data was tested, and quantitative data was expressed as mean±standard deviation or median with interquartile range, depending on normality. Differences between groups were analyzed using appropriate statistical tests. Qualitative data was expressed in frequency and percentage. ROC curves were created, and cut-off values were determined for platelet-related parameters to predict pre-eclampsia. Correlation between parameters was assessed using Spearman correlation coefficient, with p-values<0.05 considered statistically significant.

RESULTS

Table 1 compares mean platelet volume (MPV) changes between normotensive pregnant patients and those with pre-eclampsia (PE). MPV significantly increased in PE, with a 26.8% change in PE without severe features and 57.5% in PE with severe features, peaking between 32-36 and 36-40 w. This MPV increase preceded a significant blood pressure rise by 4 to 6 w. Conversely, MPV in normotensive pregnant women increased non-significantly. When comparing all three groups every 4 w, PE with severe features had the highest MPV, followed by PE without severe features and normotensive pregnant patients, with a significant statistical difference (P<0.001).

Table 2 compares platelet count changes between normotensive pregnant patients and those with pre-eclampsia (PE). In PE, there was a significant platelet count decrease, notably between 32-36 w (37.1%) in severe cases and 18.2% in non-severe cases. This drop occurred before a significant blood pressure rise and was more pronounced as pregnancy advanced. Comparatively, normotensive patients had higher platelet counts throughout, with a statistically significant difference (P<0.001) among the groups.

Table 3 compares platelet distribution width (PDW) changes in normotensive pregnant patients and those with pre-eclampsia (PE). PDW increased insignificantly in normal pregnancy until 32 w. In PE patients, PDW values were higher and significantly increased with hypertension severity, even before blood pressure rise. PE with severe features had the highest PDW increase (37.1%), followed by PE without severe features (29.3%), and normotensive patients (20%). These differences were statistically significant (P<0.001).

Table 4 shows comparison of changes in Plateletcrit between normotensive pregnant patients and pre-eclampsia patients. This table shows that plateletcrit reduced in all three groups at every 4 w till 36-40 w. The Plateletcrit reduced in normotensive patients to around 16.7% but the difference was insignificant. Plateletcrit also reduced in PE without severe feature group to 18.2%. On comparison, platelet crit reduced significantly in PE with severe feature group to around 20% from 32-40 w of gestation with a significant P-value of 0.03.

Table 1: Comparison of changes in mean platelet volume (fl) between normotensive pregnant patients and preeclampsia patients

POG (weeks)	Normotensive	PE without severe feature	PE with severe feature	P value
≥20 to ≤24(a_1)	9.04±0.87	10.27±0.84	11.21±0.66	<0.001
≥24 to≤28(a2)	9.20±0.91	10.54±1.06	12.23±0.81	<0.001
≥28 to≤32(a3)	9.72±0.89	11.30±0.98	14.97±0.60	<0.001
≥32 to≤36(a4)	10.29±1.02	12.37±0.81	15.77±1.58	<0.001
≥36 to≤40(a5)	10.51±0.98	12.93±1.29	17.6±1.020	<0.001
% Change between a1 to a5	16.7%	26.8%	57.5%	

Table 2: Comparison of changes in platelet count (10^3/µl) normotensive pregnant patients and preeclampsia patients

POG (weeks)	Normotensive	PE without severe feature	PE with severe feature	P value
≥20 to ≤24(a_1)	248.10±62.25	217.17±63.71	184.38±48.95	<0.001
≥24 to ≤28(a2)	244.19±61.77	207.17±63.67	176.88±57.75	<0.001
≥28 to ≤32(a3)	240.14±60.70	199.17±59.64	175.63±30.32	<0.001
≥32 to ≤36(a4)	236.52±61.10	189.17±58.51	146.25±30.79	<0.001
≥36 to ≤40(a5)	235.33±61.13	181.17±62.82	124.13±22.72	<0.001
% Change between a1 to a5	6.1%	18.2%	37.1%	

Table 3: Comparison of changes in platelet distribution width (fl) between normotensive pregnant patients and preeclampsia patients

POG (weeks)	Normotensive	PE without severe feature	PE with severe feature	P value
≥20 to ≤24(a_1)	13.18±1.13	14.90±0.58	16.11±0.75	<0.001
≥24 to ≤28(a2)	13.47±0.97	15.07±0.60	17.02±0.69	<0.001
≥28 to ≤32(a3)	14.35±0.94	15.33±0.71	18.47±0.33	<0.001
≥32 to ≤36(a4)	15.52±1.16	16.3±1.07	19.9±1.11	<0.001
≥36 to ≤40(a5)	15.74±1.19	19.07±1.68	21.98±1.47	<0.001
% Change between a1 to a5	20%	29.3%	37.1%	

Table 4: Comparison of changes in plateletcrit (%) between normotensive pregnant patients and preeclampsia patients

POG (weeks)	Normotensive	PE without severe feature	PE with severe feature	P value
≥20 to ≤24(a_1)	0.24±0.04	0.22±0.10	0.21±0.14	0.05
≥24 to ≤28(a2)	0.23±0.04	0.21±0.05	0.19±0.05	0.10
≥28 to ≤32(a3)	0.22±0.04	0.20±0.05	0.18±0.04	0.04
≥32 to ≤36(a4)	0.21±0.04	0.19±0.05	0.18±0.05	0.03
≥36 to ≤40(a5)	0.20±0.04	0.18±0.06	0.17±0.05	0.03
% Change between a1 to a5	16.7%	18.2%	20%	

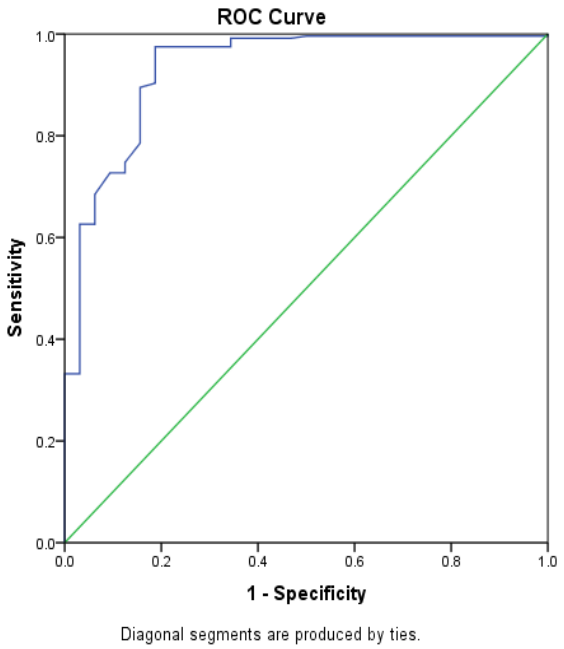

Fig. 1: Receiver operating characteristic curve for platelet count in prediction of preeclampsia cases

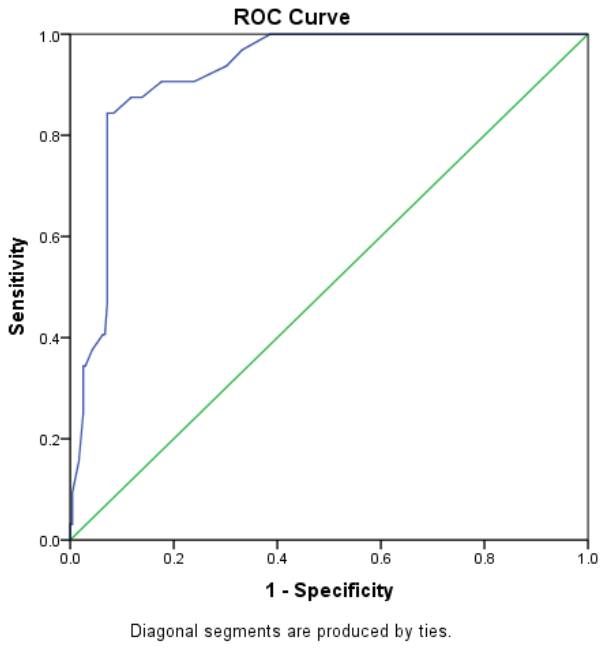

Fig. 2: Receiver operating characteristic curve for MPV in the prediction of preeclampsia cases

Fig. 1 depicts the results of the ROC curve analysis, where the area under the curve (AUC) for predicting Hypertensive Disorder of Pregnancy using platelet count was determined to be 0.93 (with a 95% confidence interval ranging from 0.88 to 0.98). At a defined cut-off value of≤184 (103/ µl), it effectively differentiated between the control group and the Hypertensive Disorder of Pregnancy group, achieving an 81.85% sensitivity and an impressive 94.12% specificity. Additionally, it exhibited a positive predictive value of 65% and a high negative predictive value of 97.39%.

In fig. 2, the area under the curve (AUC) for predicting Hypertensive Disorder of Pregnancy using MPV was found to be the highest, measuring 0.92 (with a 95% confidence interval ranging from 0.85 to 0.96). At a defined cut-off value of≥10.1fl, it effectively differentiated between the control group and the Hypertensive Disorder of Pregnancy group, achieving an impressive 84.38% sensitivity and a strong 92.86% specificity. Additionally, it exhibited a positive predictive value of 61.36% and a notably high negative predictive value of 97.79%.

Table 5: Comparison of mean platelet volume, platelet count, PDW and plateletcrit between normotensive pregnant patients and preeclampsia patients

Platelet indices	Normotensive	Preeclampsia	P value
MPV (fl)	9.04±0.87	10.51±0.89	<0.001
Platelet count (10^3/µl)	248.10±62.25	193.97±59.86	<0.001
PDW (fl)	13.18±1.13	15.2±0.81	<0.001
Plateletcrit (%)	0.24±0.04	0.22±0.11	<0.001

In table 5, preeclampsia patients exhibited significant differences in various platelet indices compared to normotensive individuals. Mean platelet volume (MPV) was higher in preeclampsia (10.51±0.89 fl) compared to normotensive patients (9.04±0.87 fl), with a significant p-value<0.001. Platelet distribution width (PDW) was also elevated in preeclampsia (15.2±0.81 fl) compared to normotensive women (13.18±1.13 fl). Platelet count was lower in preeclampsia (193.97±59.86 x 10^3/µl) than in healthy pregnant females (248.10±62.25 x 10^3/µl), with a significant p-value<0.001. Similarly, Plateletcrit was significantly lower in the preeclampsia group (0.22±0.11%) compared to normal controls (0.24±0.04%).

Table 6: Correlation index between mean arterial blood pressure and platelet count, mean platelet volume and platelet distribution width in patients with preeclampsia

POG (weeks)	Platelet count (10^3/µl)		Mean platelet volume (fl)		Platelet distribution width(fl)	
	r value	p value	r value	p value	r value	p value
≥20 to ≤24(a_1)	-0.51	<0.001	+0.74	<0.001	+0.57	<0.001
≥24 to ≤28(a2)	-0.60	<0.001	+0.79	<0.001	+0.65	<0.001
≥28 to ≤32(a3)	-0.81	<0.001	+0.80	<0.001	+0.59	<0.001
≥32 to ≤36(a3)	-0.87	<0.001	+0.84	<0.001	+0.67	<0.001
≥36 to ≤40(a5)	-0.85	<0.001	+0.87	<0.001	+0.76	<0.001

Table 6 demonstrates strong positive correlations between mean arterial blood pressure and platelet indices. Mean platelet volume (MPV) exhibited a significant positive correlation with increasing blood pressure, peaking at 36-40 w of gestation (r=+0.87, p<0.001). Platelet distribution width also showed a high positive correlation across all gestational ages, with the maximum value at 36-40 w (r=+0.76, p<0.001). Conversely, a negative correlation was observed between blood pressure and platelet count, reaching its peak at 32-36 w (r=-0.87, p<0.001) in the pre-eclampsia group.

DISCUSSION

Specifically in the context of normotensive pregnancies and those affected by pre-eclampsia (PE), our work has shown that the measurement of platelet indices in pregnant patients has provided insightful information about the dynamics of platelet-related alterations throughout gestation. Understanding the pathogenesis of the complex multisystem illness pre-eclampsia and treating its effects for the mother and fetus continue to be very difficult tasks [13].

270 pregnant women with singleton pregnancies and normal blood pressure participated in our study at the gestational ages of 20 to 24 w. Until birth, these patients were seen every four weeks, and at each visit, complete blood counts (CBCs) and blood pressure were checked routinely. Our study's conclusions provided important new information on numerous crucial elements of platelet dynamics in normotensive and pre-eclamptic pregnancies [14].

The incidence of pre-eclampsia, which was found to be 13%, somewhat higher than the global norm of 5–10%, is one of the study's significant results. This difference can be related to the fact that our hospital is a tertiary care referral facility, where a greater percentage of pre-eclampsia cases may be seen due to the complicated and high-risk nature of referrals [15].

The average age at which pre-eclampsia developed in our sample was 29.81 5.65 y, which is consistent with findings from other studies carried out in comparable circumstances. This finding emphasizes the impact of delayed pregnancies brought on by later marriages, which increases the risk of hypertensive disorders of pregnancy in women aged 25 to 29 [16].

Our study found that primigravida women were more prone to pre-eclampsia than multigravida women, with 59.4% of cases falling into this category compared to 40.6% of instances in the latter group. This is consistent with earlier studies showing that primigravida women are more likely to experience pre-eclampsia. Importantly, our study examined platelet indices at several gestational stages, including platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and platelet crit. Between normotensive and pre-eclamptic individuals, we found these platelet indices to be significantly different [17].

With gestational age, platelet count showed a significant decline, with severe pre-eclampsia patients showing the most dramatic decline. This decline in platelet count was a sign of thrombocytopenia, a frequent and early complication of pre-eclampsia associated with endothelium injury and activation of the coagulation system. Furthermore, in individuals with pre-eclampsia, we discovered a negative connection between mean artery pressure (MAP) and platelet count [18]. A predictive technique for determining the severity and progression of pre-eclampsia may be found in the monitoring of platelet count coupled with blood pressure. This negative link became stronger as gestational age increased, notably between 32 and 36 w [19].

Our research also looked at MPV, which significantly rose in pre-eclamptic patients relative to normotensive people as gestational age grew. In cases of severe pre-eclampsia, this spike was more prominent, possibly due to increased platelet synthesis and the release of bigger platelets in response to thrombocytopenia [20]. Similar to PDW, platelet heterogeneity was shown to increase with increasing gestational age, especially in cases of severe pre-eclampsia. PDW is a marker for platelet activation, and in this situation, it may draw attention to the active turnover of platelet synthesis in response to peripheral platelet consumption [21].

In pre-eclampsia patients, correlation study between mean arterial pressure and MPV or PDW revealed positive correlations, indicating that these indices may be useful in predicting the development and severity of hypertension during pregnancy. Finally, our study assessed the diagnostic value of these platelet indices in predicting hypertensive disorders of pregnancy. We found that a platelet count of ≤184×10^3/µl, a PDW of≧14.15 fl, and an MPV of ≥10.1 fl were associated with an increased risk of developing hypertensive disorders in pregnancy [22].

CONCLUSION

In conclusion, this study has shed light on the potential of platelet indices as valuable predictors and monitoring tools for pre-eclampsia, a serious and potentially life-threatening pregnancy complication. We observed significant differences in platelet indices,

including mean platelet volume (MPV), platelet count, and platelet distribution width (PDW), between normotensive and pre-eclamptic patients. Importantly, these differences often preceded the onset of clinically significant blood pressure elevation, emphasizing their potential utility as early markers of pre-eclampsia.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

REFERENCES

1. American College of Obstetricians and Gynecologists. Hypertension in pregnancy: report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2020;135(3):e237-60.
2. American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia. Obstetrics and Gynecology. 2019;133(1):e1-e25.
3. Poon LCY, Kametas NA, Maiz N, Akolekar R, Nicolaides KH. First-trimester prediction of hypertensive disorders in pregnancy. Hypertension. 2009;53(5):812-8. doi: 10.1161/hypertensionaha.108.127977.
4. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33(3):130-7. doi: 10.1053/j.semperi.2009.02.010.
5. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science. 2005;308(5728):1592-4. doi: 10.1126/science.1111726.
6. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005;365(9461):785-99.
7. Roberts JM, Gammill HS. Preeclampsia: recent insights. Hypertension. 2005;46(6):1243-9. doi: 10.1161/01.HYP.0000188408.49896.c5.
8. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376(9741):631-44. doi: 10.1016/S0140-6736(10)60279-6.
9. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol. 2002;102(1):181-92.
10. Karumanchi SA, Granger JP. Preeclampsia and pregnancy-related hypertensive disorders. Hypertension. 2016;67(2):238-42. doi: 10.1161/hypertensionaha.115.05024.
11. Amaral LM, Palei AC. Platelets: emerging contributors of preeclampsia. World J Obstet Gynecol. 2017;6(1):24-31.
12. Erez O, Romero R, Espinoza J, Fu W, Todem D, Kusanovic JP. The change in concentrations of angiogenic and anti-angiogenic factors in maternal plasma between the first and second trimesters in risk assessment for the subsequent development of preeclampsia and small-for-gestational-age. J Matern Fetal Neonatal Med. 2008;21(5):279-87. doi: 10.1080/14767050802034545.
13. Harsem NK, Staff AC, He L. Platelet activation in pre-eclampsia. Hypertens Pregnancy. 2003;22(2):121-31.
14. Braekke K, Holthe MR, Harsem NK, Staff AC. Calibrated automated thrombin generation in normal pregnancy and pregnancy complicated by preeclampsia. Thromb Res. 2004;113(5):371-6.
15. Ozdemir R, Yildirim E, Yilmaz S, Yildirim A, Korkmaz M, Oltulu F. The role of platelet parameters in the diagnosis of preeclampsia. Pregnancy Hypertens. 2017;9:9-13.
16. Goto S, Kojima Y, Nishikawa T, Koyamada R. Platelet size reflects disease severity in patients with myelodysplastic syndromes. Leuk Res. 2000;24(12):1043-8.
17. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003;111(5):649-58. doi: 10.1172/JCI17189.
18. Salahuddin S, Lee Y, Vadnais ML, Sachs BP. Karpatkin S. Elevation of platelet activation and aggregation in pregnancy: quantitation by flow cytometry. Thromb Haemost. 1997;78(04):991-6.
19. Svensson J, Siegbahn A, Bergqvist D, Bergqvist A. Tissue factor pathway inhibitor and other endothelium-dependent haemostatic factors in healthy men and women: relation to gender. Blood Coagul Fibrinolysis. 1999;10(7):389-94.
20. Yoneyama Y, Sawa R, Suzuki S, Otsubo Y, Takeishi Y, Atarashi H. Usefulness of mean platelet volume as a biomarker for long-term outcomes after acute myocardial infarction. Am J Cardiol. 2016;118(3):338-44.
21. Shen F, Li M. The relationship between platelet indices and preeclampsia. Pak J Med Sci. 2018;34(1):136-40.
22. Gonzalez Quintero VH, Kathiresan AS. The role of platelet-to-lymphocyte ratio as a predictor of maternal and fetal morbidity in preeclampsia. J Clin Ultrasound. 2008;36(3):159-64.