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The Role of Platelet Indices in Prediction of Pre-eclampsia

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objective: The aim of this work is to investigate the diagnostic value of platelet count (PC), mean platelet volume (MPV), the PC to MPV ratio and platelet distribution width (PDW) for prediction of pre-eclampsia (PE).

Subjects and Methods: This prospective cohort study included 100 pregnant women, in the first trimester of pregnancy attending to University Hospital, Obstetric Outpatient Clinic, for routine obstetric care from January 2019 to December 2019. Routine obstetric follow-up consists of monthly visits until 32nd gestational week, bimonthly visits between 32nd and 36th gestational week, and weekly thereafter. Patients were classified into two groups: group I: 9 pre-eclamptic patients and group II: non pre-eclamptic 91 patients. CBC indices were measured at each planned visit

Results: PC, PC/MPV were significantly decreased, MPV and PDW were significantly increased in group I than group II at the 2nd part of pregnancy. To predict pre-eclampsia, PC at cut-off ≤214, sensitivity was 77.78, specificity was 76.92. MPV at cut-off >9.7, sensitivity was 77.78, specificity was 100.00, PC-MPV at cut-off ≤26.89, sensitivity was 88.89, specificity was 78.02. PDW at cut-off >10.4, sensitivity was 88.89, specificity was 54.95.

Conclusion: The increase in the MPV and PDW and the decrease in PC and PC/MPV were observed in preeclampsia. Thus, the platelet indices which are easily available, as well as economical, can also be used in the prediction and early diagnosis of preeclampsia.

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Keywords: Platelet Indices; prediction, pre-eclampsia; mean platelet volume; PC/MPV ratio; platelet distribution width.

1. INTRODUCTION

Preeclampsia (PE) is an intractable obstetric disorder that affects 6 –8% of pregnancies worldwide. PE is characterized by hypertension (blood pressure ≧140/90 mmHg), proteinuria (≧0.3 g/d), and other symptoms and may begin as early as the 20th gestational week and last for 6 weeks after delivery. Furthermore, PE has high morbidity and mortality rates [1].

Although the exact pathophysiology of PE is not completely understood, certain factors have been attributed to it, which include deficient trophoblastic invasion of the maternal vascular bed with subsequent reduction of placental blood flow [2]. Placental under perfusion initiates widespread systemic, maternal endothelial dysfunction, and increased vascular permeability. Coagulation system is activated by the contact of platelets with the injured endothelium leading to increase in consumption as well as bone marrow production of platelets [3].

Alterations in hemostatic system, including endothelial cell damage, platelet activation and enhanced intravascular thrombin generation, are the major pathophysiologic events in PE [4]. Various indices are used to measure platelet functions, for example, the platelet count (PC), mean platelet volume (MPV), the PC to MPV ratio, and platelet distribution width (PDW); PDW measures platelet size distribution [5].

To date, there is no effective treatment for PE in addition to the termination of pregnancy. Therefore, a reliable predictor for PE would play an important role in early prevention and intervention [6].

The aim of this work is to investigate the diagnostic value of PC, MPV, the PC to MPV ratio and PDW for prediction of pre-eclampsia.

2. SUBJECTS AND METHODS

This prospective cohort study included 100 pregnant women, in the first trimester of pregnancy, attending to Tanta University Hospital, Obstetric Outpatient Clinic, for routine obstetric care.

2.1 Inclusion Criteria

i. Singleton living pregnancy.
ii. Pregnancy in the first trimester calculated from the 1st day of last menstrual period or ultrasonographic estimation.

2.2 Exclusion Criteria

1. Women with systemic diseases (Hypertension, diabetes mellitus, collagen tissue disease, heart disease, renal disease, hepatic disease, ITP, any hematological disease).
2. Poor obstetric history requiring medication during gestation (recurrent pregnancy loss, previous occurrence of pre-eclampsia, preterm labor, intrauterine growth retardation or intrauterine demise).
3. History of use of anticoagulant drugs.
4. History of use of oral contraceptive drug.
5. Smokers; active or passive

The gestational age was calculated from the first day of the last menstrual period and confirmed by ultrasound scan.

Only pregnant women who have received all their antenatal examinations and delivered in our hospital were included in this study. Cases were termed pre-eclampsia when there was high blood pressure (systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg, repeated two times four hours apart), proteinuria (≥0.3 g/dl), and other major symptoms (head ache, blurred vision, right upper quadrant pain) as early as the 20th gestational week.

According to the study protocol, complete blood count (CBC) was taken from women at each visit and recorded to measure complete blood count parameters, PC, MPV, the PC to MPV ratio and PDW: PDW measures platelet size distribution at monthly visits until 32nd gestational week, bimonthly visits between 32nd and 36th gestational week, and weekly thereafter.

Under aseptic conditions, the sample (2 ml) was collected in ethylene diamine tetra acetic acid (EDTA) vials. CBC was done by full automatic blood cell counter (ERMA® INC. PCE-210N).

Platelet indices at 24th week were used for prediction of pre-eclampsia.

2.3 Sample Size Calculation

Sample size calculation was done by G*Power 3.1.9.2 (Universitat Kiel, Germany). With 80% power, 5% confidence limit, AUC of ROC curve of prediction of PE is 0.85 according to with Tesfay et al. [7] and null hypothesis AUC of ROC curve is 0.5. Therefore, we recruited 100 patients in the study.

2.4 Statistical Analysis

The collected data were statistically analyzed by SPSS version 20 (IBM, Chicago, Illinois, USA). Normality of data was checked with Shapiro-Wilks test and histograms and all variables were normally distributed. Quantitative data were presented as mean and standard deviation (SD) and compared by unpaired student t test. Categorical data were presented as number and percentage and were compared by Chi-square test. The level of significance was adopted at $p<0.05$.

3. RESULTS

Patients were classified into two groups: Group I: included 9 pre-eclamptic patients and Group II: included non pre-eclamptic 91 patients. All patients in group I were mild pre-eclampsia.

The comparison between both groups showed insignificant difference as regard to the age but there was significant decrease in gestational age in group I than group II (P = 0.012). (Table 1)

Hemoglobin and total leucocytic count was insignificantly different between both groups at all times of measurements.

PC was significantly decreased in group I than group II at 24, 28, 32, 36 and 37 weeks (P = 0.017, 0.006, 0.028, 0.009, 0.001, 0.015 respectively). (Table 2).

Table 1. Patients characteristics of both groups

		Group I (n = 9)	Group II (n = 91)	P value
Age (years)	Mean ± SD	27.11 ± 6.13	28.89 ± 6.39	0.426
	Range	20-38	20-40	
Gestational age (weeks)	Mean ± SD	32.67 ± 3.43	35.29 ± 2.88	0.012*
	Range	28-37	31-40	

**significant as P value <0.05*

Table 2. Platelet count (*10^3/dL) of both groups

	Group I (n = 9)		Group II (n = 91)		P value
	Mean	± SD	Mean	± SD	
4w	277.78	69.87	284.18	72.50	0.801
8w	268.56	70.43	282.38	72.84	0.587
12w	261.44	72.15	281.00	72.61	0.442
16w	253.00	71.91	279.40	72.48	0.300
20w	246.56	71.09	278.74	72.74	0.208
24w	215.78	61.61	276.97	72.83	0.017*
28w	206.00	50.22	276.10	73.51	0.006*
32w	202.20	68.78	279.16	74.77	0.028*
34w	168.00	59.06	273.22	75.95	0.009*
36w	115.00	54.37	275.10	72.40	0.001*
37w	133.00	49.50	267.50	72.54	0.015*
38w	---	---	257.80	78.91	---
39w	---	---	256.06	75.13	---
40w	---	---	262.14	86.94	---

**significant as P value <0.05*

At cut-off ≤214 of PC to predict PE, sensitivity was 77.78, specificity was 76.92, PPV was 25.0, NPV was 97.2, AUC was 0.748 and P value was 0.003. (Fig. 1)

MPV was significantly increased in group I than group II at 20, 24, 28, 32, 36 and 37 weeks (P < 0.001). (Table 3)

At cut-off >9.7 of MPV to predict PE, sensitivity was 77.78, specificity was 100.00, PPV was 100.0, NPV was 97.8, AUC was 0.936 and P value was <0.001. (Fig. 1)

PC/MPV was significantly decreased in group I than group II at 20, 24, 28, 32, 36 and 37 weeks (P = 0.003, <0.001, <0.001, 0.001, 0.001, <0.001, 0.007 respectively). (Table 4)

At cut-off ≤26.89 of PC-MPV to predict PE, sensitivity was 88.89, specificity was 78.02, PPV was 28.6, NPV was 98.6, AUC was 0.894 and P value was <0.001. (Fig. 1)

PDW was significantly increased in group I than group II at 20, 24, 28, 32, 36 and 37 weeks (P = 0.023, 0.007, 0.001, <0.001, 0.001, 0.001, <0.001 respectively). (Table 5)

Table 3. MPV (fL) of both groups

	Group I (n = 9)		Group II (n = 91)		P value
	Mean	± SD	Mean	± SD	
4w	8.01	0.98	7.51	0.76	0.067
8w	7.40	1.09	7.50	0.83	0.731
12w	7.90	1.01	7.47	0.87	0.168
16w	8.29	1.14	7.45	0.99	0.019
20w	9.48	1.00	7.52	1.01	<0.001*
24w	9.92	1.06	7.56	1.02	<0.001*
28w	10.41	0.96	7.54	1.08	<0.001*
32w	10.28	0.96	7.51	1.18	<0.001*
34w	10.95	0.70	7.49	1.20	<0.001*
36w	12.43	0.81	7.51	1.14	<0.001*
37w	12.50	1.56	7.39	0.97	<0.001*
38w	---	---	7.70	0.99	---
39w	---	---	7.99	0.91	---
40w	---	---	8.06	0.91	---

**significant as P value <0.05*

Table 4. PC/MPV of both groups

	Group I (n = 9)		Group II (n = 91)		P value
	Mean	± SD	Mean	± SD	
4w	35.53	11.14	38.23	10.42	0.462
8w	37.34	12.00	38.04	10.40	0.849
12w	33.81	10.67	38.16	10.79	0.251
16w	31.31	10.22	38.12	10.94	0.077
20w	26.37	8.12	37.75	11.05	0.003*
24w	21.77	5.55	37.31	10.99	<0.001*
28w	19.93	5.34	37.39	11.20	<0.001*
32w	19.78	6.77	37.88	11.92	0.001*
34w	15.19	4.52	37.46	12.07	0.001*
36w	9.25	4.20	37.76	12.31	<0.001*
37w	10.47	2.66	37.39	13.10	0.007*
38w	---	---	34.51	12.66	---
39w	---	---	32.74	11.40	---
40w	---	---	33.57	13.78	---

**significant as P value <0.05*

Table 5. PDW (%) of both groups

	Group I (n = 9)		Group II (n = 91)		P value
	Mean	± SD	Mean	± SD	
4w	9.82	0.95	10.05	1.14	0.557
8w	9.97	0.72	10.08	1.19	0.780
12w	10.41	0.78	10.06	1.20	0.388
16w	10.51	1.00	10.04	1.23	0.273
20w	11.07	0.82	10.10	1.22	0.023*
24w	11.38	0.99	10.14	1.30	0.007*
28w	11.74	1.11	10.16	1.31	0.001*
32w	12.58	1.38	10.22	1.38	<0.001*
34w	12.95	1.66	10.37	1.37	0.001*
36w	12.90	0.96	10.37	1.23	0.001*
37w	14.20	0.00	10.22	1.24	<0.001*
38w	---	---	10.25	1.25	---
39w	---	---	10.18	1.21	---
40w	---	---	10.53	1.27	---

**significant as P value <0.05*

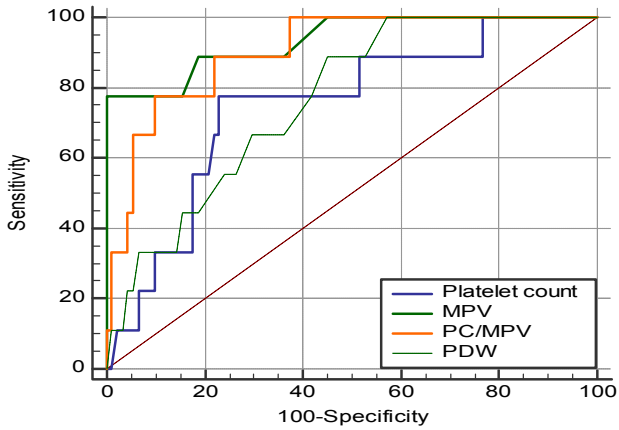

Fig. 1. ROC curves of platelet count (PC), MPV, PC/MPV and PDW to predict preeclampsia

At cut-off >10.4 of PDW to predict PE, sensitivity was 88.89, specificity was 54.95, PPV was 16.3, NPV was 98.0, AUC was 0.764 and P value was 0.002. (Fig. 1)

4. DISCUSSION

It has also been suggested that the alterations in coagulation and fibrinolysis play a role in the pathogenesis of preeclampsia [8]. The markers of platelet activation include platelet count (PC), PDW, MPV and PCT [9]. These indices are cost-effective and easily available as they are derived from routine blood investigations. Platelet indices may be used as an early markers for the diagnosis of thromboembolic diseases [10]. These parameters can be used for prediction of PE before the derangement in prothrombin time (PT), activated partial thrombin time (ApTT) and thrombin time (TT) values are observed [11].

Thrombocytopenia is the most common hematological abnormality observed in preeclampsia and it may be due to consumption of platelets during abnormal activation of the coagulation system. A number of studies have shown that D-dimer, soluble vascular endothelial growth factor receptor and platelet distribution width may be used as preeclampsia, however due to varied effects on the coagulation-fibrinolytic system in preeclampsia in late pregnancy, no conclusive evidence can be drawn [3].

The aim of this work is to investigate the diagnostic value of PC, MPV, the PC to MPV ratio and PDW for prediction of pre-eclampsia (preceding development of pre-eclampsia).

PC was significant decreased in group I than group II at 24, 28, 32, 36 and 37 weeks. This was in agreement with Han et al. (2014) who have also reported decreased platelet counts as the disease progressed, but normal counts in the initial stages [12]. Also, this was in agreement with AlSheeha et al [3] who showed that PC was significantly lower in the cases compared with the controls. This was in line with Tesfay et al. [7] who found that PC was lower in the pre-eclamptic patients compared with the controls. This was in agreement with Mannaerts et al [13] who found that PC was significantly lower in the PE group. This was in contrast to Thalor et al (2019) [14] who found that the PC was on the lower side in the patients with PE, (median was 217 × 10^6), as compared to the healthy pregnant females (median was 241 × 10^6), however none of the patients had severe thrombocytopenia with no statistically significant difference between both groups. The contrast to our results may due to their smaller number of patients (60 cases).

Also, Karateke et al. [9] showed that there were no significant differences between the PE group and the control group in terms of PC.

At cut-off ≤214 of PC to predict PE, sensitivity was 77.78, specificity was 76.92, PPV was 25.0, NPV was 97.2, AUC was 0.748 and P value was 0.003.

This was in line with Tesfay et al. [7] who found that PC can differentiate controls from preeclamptic pregnant women at a cut off value <233x10^9/L with sensitivity of 70.9%, specificity of 83.9%, PPV of 70.9%, NPV of 83.6% and AUC (0.77).

This was in agreement with AlSheeha et al [3] who showed that the PC cutoff was 248.0×103/μL for diagnosis of PE (P=0.19). The area under the ROC curve was 62.4% (standard error =5.1%), which suggest poor predictability.

MPV was significantly increased in group I than group II at 20, 24, 28, 32, 36 and 37 weeks.

This was in line with Mahmoud et al. [15] who showed that the MPV was higher in pre-eclampsia patients.

This was in agreement with Thalor et al [14] who found that the MPV in PE and healthy females was elevated, with median values of 11.8 and 10.5 and interquartile ranges of 1.7 and 2.8, respectively. The difference between pre-eclamptic patients and controls was statistically significant.

This was in agreement with Mannaerts et al [13] who found that MPV was significantly elevated in the PE group compared to the controls (p =.006).

Also, Mayer-Pickel et al [16] showed that MPV was significantly higher in women who developed PE compared to women with normal pregnancies at 24 (p = .011), 28 (p = .037), 32 (p = .002), and 36 weeks of gestation, respectively (p = .015).

Moreover, Abdel Razik et al (2019) [17] found that patients who developed PE had significant increase of PDW than normotensive women (p < 0.001). The study included 270 normal pregnancy primigravida <20 years at 20–24-week gestation. The PC, MPV, PDW and platelet large cell ratio (Plcr) was measured by automated blood picture.

This agreed with Bellos et al. [18] meta-analysis was based on outcomes reported from 50 studies that included 14,614 women. MPV was significantly higher in preeclamptic than healthy pregnant women (7905 women, MD: 1.04 fl, 95% CI [0.76, 1.32]). The mean difference was less evident among women with mild PE (6604 women, MD: 0.65 fl, 95% CI [0.19, 1.11]), compared to the severe ones (6119 women, MD: 1.28 fl, 95% CI [0.75, 1.80]). The results of the univariate meta-regression analysis showed that region, sample size, time to analysis, anticoagulant, PC and NOS score did not affect the outcomes of the meta-analysis.

Also, Dadhich et al. showed that the MPV values increased with the duration of gestation, as well as the severity of the disease [8].

This was in line with Tesfay et al. [7] who found that MPV was higher in the pre-eclamptic patients compared with the controls.

This was in disagreement with AlSheeha et al [3] who showed that there was no significant difference in MPV between the two groups.

Also, Karateke et al. [9] showed that there were no significant differences between the PE group and the control group in terms of MPV.

At cut-off >9.7 of MPV to predict PE, sensitivity was 77.78, specificity was 100.00, PPV was 100.0, NPV was 97.8, AUC was 0.936 and P value was <0.001.

This was in line with Mahmoud et al. (2020) [15] who showed that the cut-off value of MPV was >9.2 fl and it showed a high specificity of 86.7% and a sensitivity of 100% with a $p < 0.001$.

This was in line with Tesfay et al. (2019) [7] who found that MPV can differentiate NT pregnant women from preeclamptic pregnant women at a cut off value >9.45fl with sensitivity of 83.5%, specificity of 86.4%, PPV of 77.6%, NPV of 90.3% and AUC (0.85).

This was in agreement with Mannaerts et al (2019) [13] who found that MPV at cut-off point of 8.15 (sensitivity 66.7%, specificity 56.3%) for predicting PE.

Also, Mayer-Pickel et al (2019) [16] showed that MPV at cut-off point of 10.85 fl (sensitivity 65.6%, specificity 26.2%) for the prediction of PE.

PC/MPV was significantly decreased in group I than group II at 20, 24, 28, 32, 36 and 37 weeks.

This was in agreement with AlSheeha et al (2016) [3] who showed that PC/MPV was significantly lower in the cases compared with the controls.

At cut-off ≤26.89 of PC-MPV to predict PE, sensitivity was 88.89, specificity was 78.02, PPV was 28.6, NPV was 98.6, AUC was 0.894 and P value was <0.001.

This was in agreement with AlSheeha et al (2016) [3] who showed that PC/MPV cutoff was 31.2 for diagnosis of PE (P=0.035). The AUC was 62.2%.

PDW was significantly increased in group I than group II at 20, 24, 28, 32, 36 and 37 weeks.This was in line with Mahmoud et al. (2020) [15] who showed that the PDW was higher in pre-eclampsia patients.

This was in agreement with Thalor et al (2019) [14] who found that the PDW increased in both the PE group and the normotensive pregnant females, but the values were significantly higher in PE. The median value of the PDW was 16.1fl in PE and 13.3 in normotensive patients, respectively.

This was in line with Tesfay et al. (2019) [7] who found that PDW was higher in the pre-eclamptic patients compared with the controls.

Moreover, Abdel Razik et al (2019) [17] found that patients who developed PE had significant increase of PDW than normotensive women ($p < 0.001$).

This was in disagreement with AlSheeha et al (2016) [3] who showed that there was no significant difference in PDW between the two groups.

Also, Karateke et al. (2015) [9] showed that there were no significant differences between the PE group and the control group in terms of PDW.

At cut-off >10.4 of PDW to predict PE, sensitivity was 88.89, specificity was 54.95, PPV was 16.3, NPV was 98.0, AUC was 0.764 and P value was 0.002.

This was in line with Tesfay et al. (2019) [7] who found that PDW can differentiate NT pregnant women from preeclamptic pregnant women at a cut off value >10.85fl with sensitivity of 72.2%, specificity of 52.1%, PPV of 46.0 %, NPV of 76.8% and AUC (0.625).This wasn't in line with Mahmoud et al. (2020) [15] who showed that the PDW was higher in pre-eclampsia patients and the cut-off value of PDW was above 17.7, it showed a high specificity of 93.3% and a sensitivity of 96% with a $p < 0.0001$.

The increase in both the MPV and PDW, which are the markers of platelet activation, suggests an active turnover of platelet production in the bone marrow due to peripheral consumption. The increase in values of both the MPV and PDW, along with increased BP, further suggests that they are also elevated in severe PE with higher elevations of BP [14].

5. CONCLUSION

PE is a serious condition which leads to maternal morbidity and mortality. The increase in the MPV and PDW and the decrease in PC and PC/MPV were observed in PE. Thus, the platelet indices which are easily available, as well as economical, can also be used in the prediction and early diagnosis of PE.

6. LIMITATIONS

Our small sample size is one of the limitations. Therefore, further studies in a larger sample size and different countries are needed. All patients in group I were mild pre-eclampsia only.

CONSENT AND ETHICAL APPROVAL

The study was conducted in one year from January 2019 to December 2019 after approval from ethical committee of Faculty of Medicine, Tanta University. All women were informed prior to enrollment and their written consent was obtained. In our study, 100 cases of pregnant women from the first trimester until delivery.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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