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Original Research Article

Predicting risk and prognosis of preeclampsia by evaluating platelet indices

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ABSTRACT

Background: Preeclampsia is an obstetric disorder affecting 2-8% pregnancies globally and 8-10% pregnancies in India. The study was conducted to evaluate platelet count, mean platelet volume and platelet distribution width as potential predictor of preeclampsia. It also aimed to see if these platelet indices have a prognostic significance in determining the preeclampsia severity.
Methods: A prospective study was conducted on 120 pregnant women at 20 to 24 weeks of gestation with singleton pregnancy. At monthly intervals CBC (complete blood count) was done from 20 to 24 weeks till delivery and 7 days after delivery. Data with increasing gestation were collected, analysed and expressed as mean, standard deviations and correlation coefficients.
Results: We observed significant decrease in PC and increase in MPV and PDW in patients with preeclampsia compared to normotensive patients. We also observed that it was more significant in severe preeclampsia than non-severe preeclampsia. The r value of PC for normotensive, non-severe and severe preeclampsia was -0.58, -0.59 and -0.94 respectively. The r value of MPV for normotensive, non-severe and severe preeclampsia was 0.89, 0.97 and 0.98 respectively. The r value of PDW for normotensive, non-severe and severe preeclampsia was 0.98, 0.98 and 0.99 respectively.
Conclusions: Patients with preeclampsia are more likely to have changes in PC, MPV and PDW, which can be observed in early pregnancy. Thus, estimation of PC, MPV and PDW can be considered as an early, simple and cost-effective procedure in the estimating the severity of preeclampsia

Keywords: Pregnancy, Preeclampsia, Platelet count, Mean platelet volume, Platelet distribution width

INTRODUCTION

Preeclampsia is an intractable obstetric disorder affecting 2-8% pregnancies globally and 8-10% pregnancies in India. Preeclampsia has high perinatal, maternal morbidity and mortality rates.[1,2] One possible pathophysiological mechanism is the deficient trophoblastic invasion of the maternal vascular bed, reducing the flow of maternal blood to the placenta, thus creating a degree of ischemia. Placental under perfusion triggers angiogenic responses causing endothelial dysfunction, increase vascular permeability and vasoconstriction. The coagulation system activates upon the contact of platelets with the injured endothelium, thereby increasing both the bone marrow production and the consumption of platelets.[3,4] The measurement of platelet function can be indirectly done by assessing its various indices, such as platelet count (PC), platelet

distribution width (PDW) and mean platelet volume (MPV).[4] MPV and PDW describe the average size and variation in platelet size. MPV provides information regarding the activation of platelets and can be scrutinised with a complete blood test. Depending on the inflammatory response severity, it may either increase or decrease. PDW represents platelet morphology heterogeneity due to the presence of large platelets along with normal-sized platelets. Platelet volume indices (PVIs), viz, MPV, PC and PDW, are a set of parameters that are derived from regular blood counts. They are economical to measure. MPV and PDW are the best validated and prominent of platelet indices and are thus, attraction of research on indices in clinical settings as their availability to clinicians is widespread.[5,6] In the present study, an attempt was made to assess the relationship between platelet indices and preeclampsia and to verify if these parameters can be used as prognostic markers.

METHODS

Study design

Current study was prospective study conducted to predict and evaluate the role of the platelet indices in preeclampsia in outpatient department of upper India sugar exchange maternity hospital, GSVM Medical College, Kanpur, India during a period of 20 months.

Inclusion criteria

Healthy normotensive pregnant women aged 18-45 years at 20-24 weeks of gestation period were included in the study.

Exclusion criteria

Women with pre-existing renal disease, women with insulin-dependent diabetes, women with asthma requiring steroidal treatment, women with chronic hepatitis (with or without hepatic dysfunction), women with severe trauma history, women with oral contraceptive use history, women with smoking history, women with ITP, women with HELLP syndrome, women with gestational thrombocytopenia or any haematological diseases were excluded from the study.

Procedure

Informed consent was taken from the patients fulfilling inclusion criteria and they were enrolled in the study. The demographic data, such as age, weight, parity, residence, socioeconomic status was observed. Blood pressure was measured by auscultatory method in the sitting position after making patient comfortable. Patients was regarded hypertensive if systolic BP is greater than or equal to 140 mmHg and diastolic blood pressure is greater than or equal to 90 mm Hg on two occasions 4 hours apart. It was further divided into non-severe and severe preeclampsia. Patients with systolic BP between 140 and 160 mmHg and diastolic BP between 90 and 110mm Hg was considered as non-severe and those with systolic BP greater than 160 mm Hg was considered as severe preeclampsia. A 2-mL blood sample from each patient was collected into vacuum tube (purple cap) containing 2.0 mg/mL EDTA-2K and preserved at 37˚C for platelet analysis. The blood sample was measured using the LH 755 quantitative hematology analyser. BP was recorded at 1st visit and each monthly visit. 1st sample of CBC was performed between 20 to 24 weeks and then sample was taken at monthly interval till 40 weeks and 7 days after delivery. The patient was followed till delivery to study the maternal and foetal outcome in non-severe and severe preeclampsia. The aim, risk and benefit of the study as well as their right to withdrawal from the study at any time were verbally explained for the study participants using local language in the study area and their informed verbal consent was obtained prior to data and sample collection. Samples were coded and confidentiality of patient data was maintained throughout the study

Statistical analysis

The results were obtained as mean±standard deviation (SD). The statistical significance was calculated using one-way analysis of variance (ANOVA) was used to compare the difference in mean platelet parameter amongst the three groups (normotensive, non-severe preeclampsia, severe preeclampsia). Pearson correlation test was used to investigate relationship amongst the three groups and inferences were made accordingly, $p<0.05$ was considered as statistically significant.

RESULTS

Total number of patients analysed were 120, out of which 26 were loss to follow up, amongst remaining 94 patients, 16 patients developed preeclampsia giving incidence of 17%. Out of 16 preeclamptic patients, 13 were non-severe preeclamptic and 3 were severe preeclamptic. Incidence of non-severe pre-eclampsia in the study was 13.8% and severe preeclampsia was 3.19%, excluding lost to follow up cases (Figure 1).

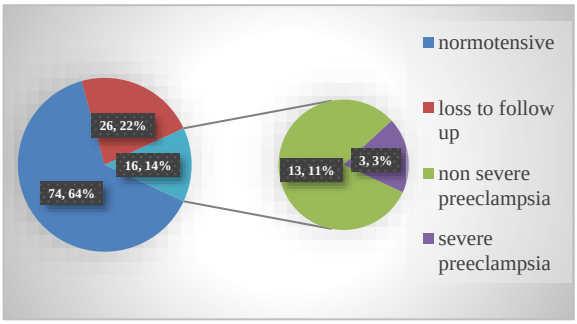

Figure 1: Incidence of preeclampsia.

There was a decrease in PC in normotensive pregnant female with gestational age when sequential PC was

compared every month from 20 weeks to 40 weeks, which was 0.18. The decrease in PC was also observed in non-severe and severe preeclampsia, which was 0.31 for non-severe preeclampsia and 0.62 for severe preeclampsia ($p<0.001$). There was also an increase in MPV with gestational age when sequential counts were compared every month from 20 weeks to 40 weeks, which was 0.89 in normotensive pregnant patients. Increase in MPV was also observed in both non-severe and severe preeclampsia, this increase was 3.67 for non-severe preeclampsia and 4.7 for severe preeclampsia ($p<0.001$). There was also increase in PDW in normotensive pregnant patients with gestational age when sequential counts were compared every month from 20 weeks to 40 weeks, which were 3.55. The increase in PDW was also observed in non-severe preeclampsia and severe preeclampsia. The increase in PDW observed was 5.09 for non-severe preecalmpsia and 7.93 for severe preeclampsia ($p<0.001$) (Table 1). Correlation coefficient between PC for normotensive patient was -0.58, for non-severe preeclampsia was -0.59 and for severe preeclampsia is -0.94. As observed in our study, correlation coefficient of PC was decreasing as BP is increasing. So, it was found that PC was significantly negatively correlated with BP ($p<0.001$) (Figure 2).

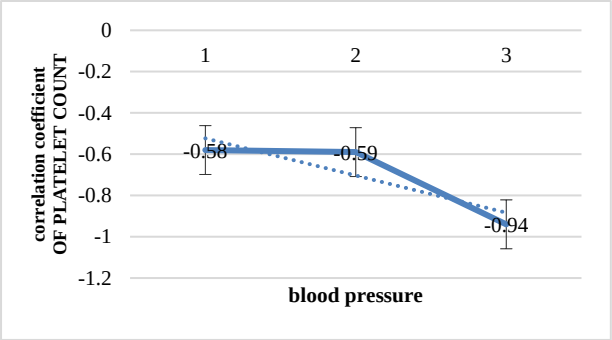

Figure 2: Platelet count.

Correlation coefficient between MPV of normotensive, non-severe preeclampsia and severe preeclampsia is depicted in (Table 2). Correlation coefficient for normotensive patient 0.89 while for non-severe preeclampsia is 0.97 and for severe preeclampsia is 0.98. Correlation coefficient was increasing as BP was increasing. So, MPV showed positive correlation with BP ($p<0.001$) (Figure 3). Correlation coefficient between PDW of normotensive, non-severe preeclampsia and severe preeclampsia is depicted in (Table 2). Correlation coefficient for normotensive patient 0.9, for non-severe preeclampsia was 0.98 and for severe preeclampsia was 0.99. Correlation coefficient was increasing as BP was increasing. Hence, PDW also showed significant ($p<0.001$) positive correlation with BP (Figure 4, Table 2). It was found that PC has sensitivity of 75%, specificity of 82%, PPV of 46.15%, NPV of 94.12% while MPV showed sensitivity of 81.25%, specificity of 85.8%, PPV of 54.17%, NPV of 95.71% and PDW showed sensitivity of 93.75%, specificity of 92.31%, PPV of 71.43%, NPV of 48.63% (Table 3). Severe preeclampsia groups manifest lower PC and higher MPV, PDW as opposed to non-severe preeclampsia and control groups ($p<0.001$).

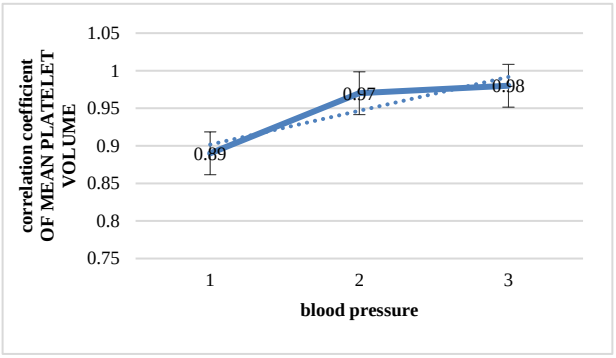

Figure 3: Mean platelet volume.

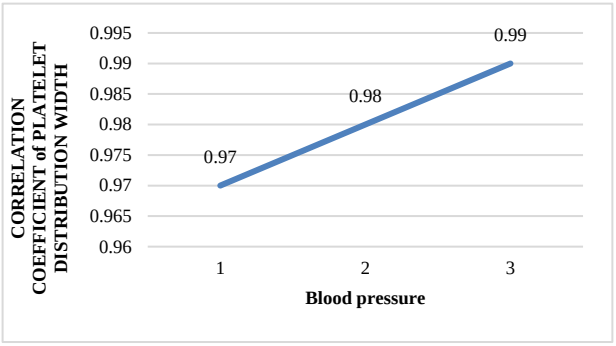

Figure 4: Platelet distribution width.

DISCUSSION

Pregnancy is often allied with complex and some partly understood changes concerning blood coagulation. Varying trends have been observed with respect to the information regarding the platelet behaviour in normal pregnancy. In the present study, sequential changes in PC, MPV and PDW in normotensive and preeclamptic patient were assessed with gestational age. A correlation coefficient between BP and PC, MPV and PDW was also established. In our study group, the incidence of pre-eclampsia was found to be 17%, which was comparable to the incidence of pre-eclampsia in developing countries which is 8-10% [2]. Dadhich et al showed comparable rate of pre-eclampsia, where the incidence of pre-eclampsia 13% in a sample size of 200, while Mayrink et al showed incidence of 7.5%.[7,8] The reduction in PC in normotensive patients, non-severe preeclampsia patient and severe pre-eclampsia patient with gestational age when sequentially counted at monthly maternal from 20 to 40 weeks was 0.18, 0.31 and 0.62 respectively (Table 1). Therefore, it was evident that maternal thrombocytopenia was more in severe PE than non-severe PE. Hence, upon monthly estimations of PC, it was found that decline in PC was proportional to preeclampsia severity.

Table 1: Comparison of changes in platelet indices (platelet count, mean platelet volume and platelet distribution width) amongst normotensive, non-severe preeclampsia and severe preeclampsia.

POG (weeks)	Platelet count (lac cells/mm³)					Mean platelet volume (fl)					Platelet distribution width (%)				
	NT (mean ±SD)	NSP (mean ±SD)	SP (mean ±SD)	F test	P value	NT (mean ±SD)	NSP (mean ±SD)	SP (mean ±SD)	F test	P value	NT (mean ±SD)	NSP (mean ±SD)	SP (mean ±SD)	F test	P value
≥20 to ≤24 (a1)	2.5 ±0.21	2.23 ±0.34	1.7 ±0.34	22.65	<0.001	9.62 ±0.3	10.9 ±0.69	13.8 ±1.15	192.4	<0.001	12.8 ±0.47	14.96 ±0.53	17.9 ±0.62	255.294	<0.001
≥24 to ≤28 (a2)	2.37 ±0.35	2.0 ±0.37	1.65 ±0.3	11.39	<0.001	9.83 ±0.72	11.50 ±0.73	15.08 ±0.72	99.95	<0.001	13.6 ±0.64	15.89 ±0.68	18.4 ±0.61	140.158	<0.001
≥28 to ≤32 (a3)	2.42 ±0.19	2.07 ±0.28	1.55 ±0.21	39.63	<0.001	10.11 ±0.47	12.12 ±0.78	15.66 ±0.5	230.08	<0.001	14.2 ±0.52	16.62 ±0.9	18.8 ±0.75	169.295	<0.001
≥32 to ≤36 (a4)	2.4 ±0.21	1.97 ±0.27	1.4 ±0.005	49.21	<0.001	10.34 ±0.35	12.91 ±0.98	17.56 ±0.35	450.629	<0.001	15.17 ±0.66	17.92 ±0.62	22.9 ±1.1	269.829	<0.001
≥36 to ≤40 (a5)	2.32 ±0.14	1.92 ±0.30	1.08 ±0.14	22.65	<0.001	10.51 ±0.34	14.57 ±0.64	18.51 ±0.6	1075.40	<0.001	16.35 ± 0.73	20.05 ± 0.62	25.83 ±0.51	379.698	<0.001
Mean Difference between a1 and a5	0.18	0.31	0.62	-	-	0.89	3.67	4.7	-	-	3.55	5.09	7.93		
Puerperium (a6)	2.74 ±0.16	2.48 ±0.28	1.83 ±0.76	33.18	<0.001	9.43 ± 0.61	9.08 ±0.55	11.4 ±0.52	1.95	<0.001	13 ±1.13	11.87 ±0.91	13.9 ±0.3	7.34	<0.001

NT=Normotensive, NSP= Non severe preeclampsia, SP=Severe preeclampsia.

Table 2: Correlation coefficient (r) in platelet indices (platelet count, mean platelet volume, platelet distribution width) amongst normotensive, non-severe preeclampsia and severe preeclampsia.

Variables	Platelet count			Mean platelet count			Platelet distribution width		
	Normotensive	Non severe preeclampsia	Severe preeclampsia	Normotensive	Non severe preeclampsia	Severe preeclampsia	Normotensive	Non severe preeclampsia	Severe preeclampsia
Mean Difference between a1 and a5	0.18	0.31	0.62	0.89	3.67	4.7	3.55	5.09	7.93
Correlation coefficient (r)	-0.58	-0.59	-0.94	0.89	0.97	0.98	0.97	0.98	0.99
T value	6.29	2.46	2.92	17.08	14.06	6.27	36.11	22.49	17.1
P value	<0.001	<0.05	<0.05	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

This can be correlated with PE pathophysiology as endothelial activation would have induced increase in the platelet aggregation and consumption resulting in decrease PC. Similar findings were found when Dadhich et al, Tesfay et al, Mohapatra et al, Dhakre et al and Han et al investigated.[8-12] However, a study by Thalor et al showed no correlation of BP and PC.[13]

Table 3: comparison between the diagnostic values of platelet parameters of the study.

Platelet indices	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)	Cut-off
PC (lac/mm³)	82	75	46.15	94.12	<2.45
MPV (fl)	85.80	81.25	54.17	95.71	>9.62
PDW (fl)	92.31	93.75	71.43	48.63	>12.8

Increase in MPV was observed in normotensive pregnant patients, non-severe and severe PE patients with gestational age when sequentially counted monthly from 20 to 40 weeks, which was 0.89, 3.67 and 4.7 respectively ($p<0.001$). MPV was more in severe PE than in non-severe PE and normotensive individuals (Table 1). This indicated the direct proportionality between an increase in MPV and preeclampsia severity. It can be clearly correlated to pathophysiology, as due to increased consumption and destruction of platelets, bone marrow would have produced and released large platelets, thus leading to an increase of MPV in PE. However, on reviewing literature, contradicting results regarding the relation between MPV and PE were also found. Similar findings were reported by Astuti et al , Thalor et al, Dhakre et al, Nooh et al, Alkholy et al and Dadhich et al, where there was an increase in MPV as pregnancy advanced.[8,11,13-16] However, similar study by Al Sheeha et al showed no significant difference in MPV and PDW amongst women with mild PE, severe PE, and healthy control.[17] Increase in PDW in normotensive, non-severe PE and severe pregnant patients with gestational age when sequentially counted monthly from 20 to 40 weeks were compared was 3.55, 5.09 and 7.93 respectively ($p<0.001$). An inter-relationship was found between severity of preeclampsia and PDW. The increase in PDW was more in severe PE than non-severe PE and normotensive individuals (Table 1). The increased PDW could be explained by an increase in platelet production following decrease in platelets survival time as a result of increase in platelets destruction. Increase in bone marrow activity also contributes to the observed high PDW. Similarly rise in PDW also serves as an important indicator of disease severity.

Similar finding was reported by Alkholy et al, Nooh et al, Astuti et al, Thalor et al, Dhakre al, Dadhich et al where PDW increased at 32-36 weeks as pregnancy PDW.[8,11,13-16] However, AlSheesha et al showed no significant difference in PDW amongst woman with severe PE, mild PE and healthy control.[17] There has been a clash for better prognostic factors to predict severity of disease. To achieve this correlation coefficient, sensitivity, specificity, PPV, NPV was calculated for each parameter and relationship between BP and each of these three parameters, i.e. PC, MPV and PDW was observed.

There was a negative correlation between BP and PC. As BP increased significantly, the correlation indexes of PC decreased from -0.58 to -0.94. In present study, correlation index r=-0.58 for normotensive, r=-0.59 for non-severe PE and for severe PE was -0.94 (Table 2). A similar finding was seen in Nooh et al study with r = -0.474, Dadhich et al also showed negative correlation with r = -0.868.[8,15] There was a positive correlation with BP, MPV and PDW as correlation index increased from 0.89 to 0.98 (r=0.89 for normotensive, and 0.97 to 0.99 in patients of healthy control and severe preeclampsia respectively). A similar finding was seen in Nooh et al where correlation coefficient for MPV (r=0.475) and PDW (r=0.902).[15] The same results was seen by Dadhich et al who demonstrated a month wise increase in PDW in preeclampsia group as compared to those in normal pregnant group.[8] Similar finding was reported by Annam et al and Mohamed et al As r=0.99 for PDW shows that highly positive correlation in comparison to other platelet indices.[18,19] To support this sensitivity specificity PPV and NPV of different parameter was also calculated (Table 3) and it is evident that PDW showed highest sensitivity (93.75%), specificity (92.31%), PPV (71.43%) and lowest NPV (48.63%). Thus, PDW being highly correlated ($p<0.001$) serves as the best indicator of severity of preeclampsia. Hence, these parameters can be used as useful sensitive and specific markers for prognosis prediction of severity of preeclampsia and foreseeing likelihood of development of hypertension do that early management can be done.

Strengths and limitations

The strengths of this study are worthy of note. All blood samples for CBC were sent within two hours after drawing blood. Assessments were carried out using the same anticoagulant and the same automated counter. Limitation of the study was sample size. More accurate results would be seen on a larger sample size. However, the study had adequate sample size to get statistically significant results.

CONCLUSION

The platelet indices estimation method is a promising tool to predict pre-eclampsia. It can be used as adjunct for diagnosing preeclampsia with other clinical parameters. It consumes less time and is economical. It is a rapid

procedure for assessing the severity of preeclampsia. It can also detect whether the patients are likely to develop progressive hypertension and requiring an early intervention. Also, platelet indices can assess the prognosis of preeclampsia in pregnant women and can have significant impact on maternal and perinatal outcome. Further research should be directed at confirming these findings, and if confirmed, at developing strategies to diagnose preeclampsia at earlier gestational age and hence decrease incidence of maternal and fetal morbidity and mortality in non-severe and severe preeclampsia. Research on large scale with large sample size can prove platelet indices as predictive indicator for risk and prognosis of preeclampsia at much earlier gestational age.

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