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ORIGINAL ARTICLE

Prediction of Preeclampsia by Measuring of Mean Platelet Volume and Platelet Distribution Width

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ABSTRACT

Background: Preeclampsia (PE) is a significant cause of pregnancy mortality and maternal and fetal morbidity. The aim of this work was to assess whether mean platelet volume and platelet distribution width during pregnancy could be used as markers for prediction of development of preeclampsia.

Methods: A prospective cohort study was carried out to assess the probability of development of preeclampsia ≥13week with changes in platelet volume and distribution width in pregnant women, at maternity unit of obstetric and gynecology department, Zagazig University hospitals during the period from May 2017 till February 2018. 40 Pregnant women ≥13 week of gestation were invited to participate; 40 women accepted. At their 1st antenatal care visit, complete blood count test was taken for measurement of platelet volume (MPV), platelet distribution width (PDW), blood pressure was measured as well as urine albumin test by urinary dipstick was taken.

Results: The correlation between high MPV and development of preeclampsia was highly significant; it showed a high specificity of 86.7% and a sensitivity of 100% with a $p < 0.0001$, the correlation between high PDW and development of preeclampsia was highly significant and the cut-off value of MPV was 9.2fl and above and PDW was above 17.7, it showed a high specificity of 93.3% and a sensitivity of 96% with a $p < 0.0001$.

Conclusions: Among platelet indices, the PDW are higher in pregnant women who developed later preeclampsia. Therefore, MPV& PDW measurement may contribute significantly in the identification of at-risk women.

Key words: platelet volume (MPV), platelet distribution width (PDW), preeclampsia (PE).

INTRODUCTION

Preeclampsia (PE) is a pregnancy-specific multisystem disorder characterized by an irregular placental vascular response associated with increased systemic vascular resistance, increased platelet aggregation, coagulation system activation and endothelial cell dysfunction resulting in decreased organ perfusion **[1]**.

Despite thorough inquiries, the origin of PE remains elusive **[2].**

Current PE diagnostic requirements include de novo hypertension (blood pressure of a range of 140/90 mmHg), proteinuria or any other multisystem anomalies that occur after the 20th week of gestation **[3]**.

Identification of pregnant women with an elevated risk of PE is a key goal of modern obstetrics. Recognition of sensitive, specific, cost-effective and easy-to-perform biomarkers would not only allow women at risk of PE to be detected, but would also allow close monitoring, accurate PE diagnosis and timely intervention. Since PE may progress rapidly, prompt intervention can require evaluation in tertiary treatment and termination of pregnancy, either by inducing labor or by Cesarean section, the only known cure for this condition **[4].** Since this affects multiple organs, no single, accurate and cost-effective marker has yet been proposed to predict PE **[5]**.

Many models were proposed but found not to be clinically significant **[6]**.

Measurement of blood pressure is a screening test which is routinely used in antenatal care to detect or predict hypertensive disease **[7]**. Precise prediction of women at risk for preeclampsia is crucial for proper allocation of monitoring resources and the use of preventive treatment, **Duley. [8]** And a view to boost maternal and neonatal outcomes. Studies examining the predictive accuracy of reporting contradictory findings for the blood pressure calculation. Given these contradictory studies, it is unclear if the measurement of blood pressure should be regularly used as a predictive test or used only to diagnose hypertensive disorders during pregnancy once they are suspected **[9]**.

Platelet indexes [platelet count (PC), mean platelet volume (MPV), and platelet distribution width (PDW)] are part of the blood count (CBC) test observable results. The applicability of these indices has been investigated for the clinical and pathophysiological understanding of vascular diseases, including PE, but their importance has still not been fully substantiated**[10]**.

Mean Platelet Volume (MPV) is an average size number of platelets present in blood and usually used in blood testing. Since the average platelet size is greater when the body produces increased platelet amounts, the findings of the MPV test can be used to draw inferences regarding platelet development in bone marrow. Anomalously high MPV values mainly correlate with thrombocytopenia **[11]**.

we aimed to assess whether mean platelet volume and platelet distribution width during pregnancy could be used as markers for prediction of development of preeclampsia.

METHODS:

After obtaining approval of the ethics committee, a prospective cohort study was carried out to assess the probability of development of preeclampsia ≥13week with changes in platelet volume and distribution width in pregnant women, at maternity unit of obstetric and gynecology department, Zagazig University hospitals during the period from May 2017 till February 2018. Included 40 Pregnant women ≥13 week of gestation were invited to participate; the mean gestational age of diagnosis was 24.5 ± 1.6 weeks. Using ROC curve analysis of the MPV value at 20-28 weeks, we identified an MPV >9.2 fL as optimal cut-off for the prediction of preeclampsia. We followed-up them weekly until labor. During that period of antenatal care, we monitored the medical condition of those patients if they developed or not Preeclampsia CBC was taking every two weeks for mean platelet volume and platelet distribution width detection.

Inclusion criteria: Age the selected women are between 20 and 35 years old, Primigravida, Gestational age ≥13 week weeks gestation and Non proteinuric (by urinary dipsticks). **Exclusion criteria:** Women with diabetes history, renal disease, hypertension, cardiovascular disease, pregnancy instability, multiple pregnancy, multiparity, severe obesity [body mass index (BMI) 40 kg / m2], ntra-uterine fetal death (IUFD). Written informed consent was obtained from all participants, and the study was accepted by the Faculty of Medicine Research Ethical Committee, Zagazig University.

The work was carried out for studies involving humans in accordance with the World Medical Association's Code of Ethics (Helsinki Declaration).

Method Protocol

All pregnant women who met the selected criteria were subjected to vital signs blood pressure, heart rate, temperature, respiratory rate and systemic examination of heart, lungs, abdomen, lower limbs and neurological examination. Determination of gestational age by ultrasonography.

At their 1st antenatal care visit, complete blood count test was taken for measurement of MPV, PDW, blood pressure was measured as well as urine albumin test by urinary dipstick was taken. Since then, we followed-up them weekly until labor. During that period of antenatal care, We tracked the medical condition of those patients if Preeclampsia CBC was established or not taking median platelet volume and platelet width detection every two weeks.

Blood sampling and analysis

Blood and urine samples were collected upon admission of the patient at delivery time. Samples of blood were obtained in EDTA-containing tubes and in tubes without an anticoagulant.2 milliliters of unclotted blood are obtained from the antecubital vein and mean platelet volume is measured by automated cell counter Cell- Dyn, 4000 with quality control valdation using sodium citrate high concentration (1:4: v/v with blood) as the anticoagulant; Reference range : 6.5 – 9.5 fl. **[12]** .

Statistical Analysis:

Based on Microsoft Excel software, data collected throughout history, basic clinical evaluation, laboratory tests, and outcome measures were marked, entered, and analysed. The data were then imported into the Social Sciences Statistical Package (SPSS version 20.0) (Social Sciences Statistical Package) for analysis tools. According

to the form of qualitative data defined as number and percentage, quantitative continuous category defined by mean ± SD, the following tests were used to assess meaning differences; discrepancy and correlation of qualitative variable by Chi square assess (X^2). Differences were performed between quantitative independent groups by t check, correlation by Pearson's correlation, study of the receiver operating characteristics (ROC). For small results P value was set at < 0.05 and for high significant results < 0.001.

RESULTS:

In the study, 8 patients develop preeclampsia and all of them had an MPV higher than 9.2, and only 2 of 32 patients who did not develop preeclampsia presented an MPV higher than 9.2. **Figure 1**

This study showed that there was no significant difference between groups as age distributed between developed and non-developed preeclampsia as 25.2±3.34 and 25.66±2.52 respectively. That systolic blood pressure distribution between groups was not significantly different but diastolic blood pressure (DBP) was significantly higher in preeclampsia group 26W **Figure 2**. There was sig difference between groups regard BMI at 32w. **Table 1**

There was a significant area under curve with cutoff >9.2 for platelet volume (MPV) and >17.7 for platelet distribution width (PDW). **Table 2**

This study showed that platelet volume (MPV) sig positive correlated with platelet distribution width (PDW) and diastolic blood pressure (DBP), PDW sig positive correlation with systolic (SBP) and diastolic blood pressure (DBP). **Table 3**

This table shows that MPV (10.08±0.607 and 8.53±0.79 respectively) and PDW (21.9±2.02 and 13.86±2.47 respectively) B were significantly higher in developed Preeclampsia than non-developed Preeclampsia at 20w. **Table 4**

The receiver operating characteristic (ROC) curve of platelet indices in the preeclampsia group (PE) to identify the optimum cut-off level for PE severity prediction. The MPV > 9.2fL was defined as an ideal cut-off for preeclampsia prediction. An MPV > 9.2fL had 100 per cent sensitivity and 86.7 percent specificity for pre-eclampsia prediction. **Figure 3**.

Table 1: Relation between age, developed and non-developed preeclampsia

	developed Preeclampsia N=8	non developed preeclampsia N=32	t	P
Age	**25.2±3.34**	**25.66±2.52**	**-0.466**	**0.644**
SBP	**121.2±8.32**	**116.0±8.28**	**1.916**	**0.063**
DBP	**78.8±4.39**	**70.0±9.25**	**4.072**	**0.00****
BMI	**25.28±2.2**	**27.98±2.19**	**3.12**	**0.001****

Systolic (SBP)**,** diastolic blood pressure (DBP)**,** Body mass index (BMI)

Table 2: Area under curve and cutoff

Test Variable(s) Result	Area	Cutoff	P	95% Confidence Interval	
				Lower Bound	Upper Bound
MPV at 20w	**0.945**	**>9.2**	**0.00****	**0.867**	**1.000**
PDW at 20w	**0.979**	**>17.7**	**0.00****	**0.939**	**1.000**

Table 3: Correlation of MPV and PDW with other parameters.

		MPV	PDW
PDW	Pearson Correlation	**.756****	**1**
	Sig. (2-tailed)	**.000**	
	N	**40**	**40**
Age	Pearson Correlation	**.023**	**-.163-**
	Sig. (2-tailed)	**.886**	**.316**
	N	**40**	**40**
SBP	Pearson Correlation	**.294**	**.343***
	Sig. (2-tailed)	**.066**	**.030**
	N	**40**	**40**
DBP	Pearson Correlation	**.415****	**.509****
	Sig. (2-tailed)	**.008**	**.001**
	N	**40**	**40**

platelet distribution width (PDW), Systolic (SBP)**,** diastolic blood pressure (DBP)

Table 4: Platelet volume (MPV) and distribution width (PDW) distribution between groups.

	developed Preeclampsia N=8	Non developed Preeclampsia N=32	t	p
MPV at 14w	8.09±0.702	7.23±0.85	5.658	0.456
PDW at 14w	15.9±2.28	10.86±2.47	9.788	0.468
MPV at 16w	8.23±0.809	7.43±0.65	5.627	0.651
PDW at 16w	15.9±2.02	11.86±1.74	9.886	0.496
MPV at 18w	9.505±1.017	7.12±0.54	5.368	0.650
PDW at 18w	18.88±4.499	11.54±2.22	10.568	0.644
MPV at 20w	10.08±0.607	8.53±0.79	6.967	0.00**
PDW at 20w	21.9±2.02	13.86±2.47	11.159	0.00**

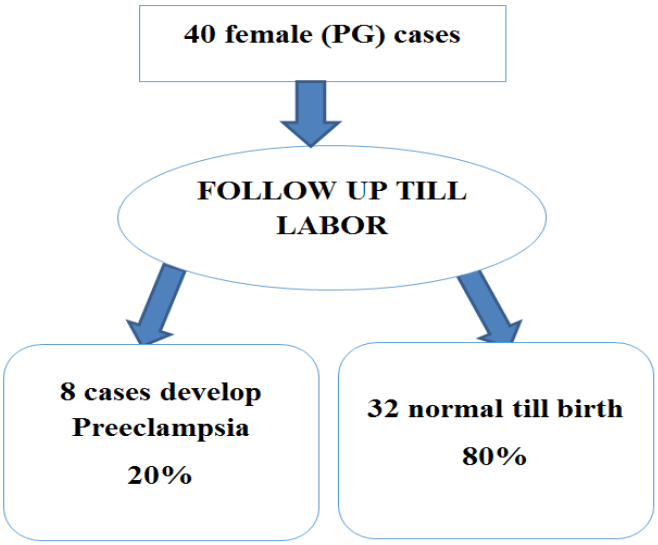

Figure (1)

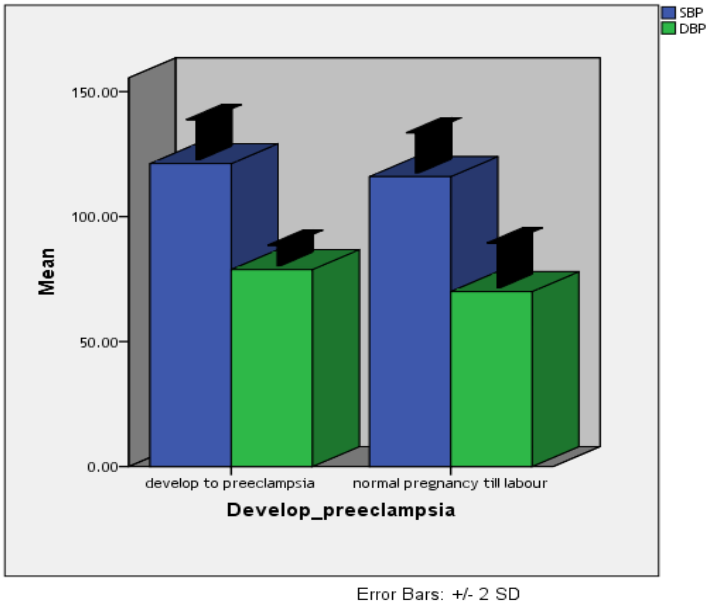

Figure (2): Blood pressure distribution

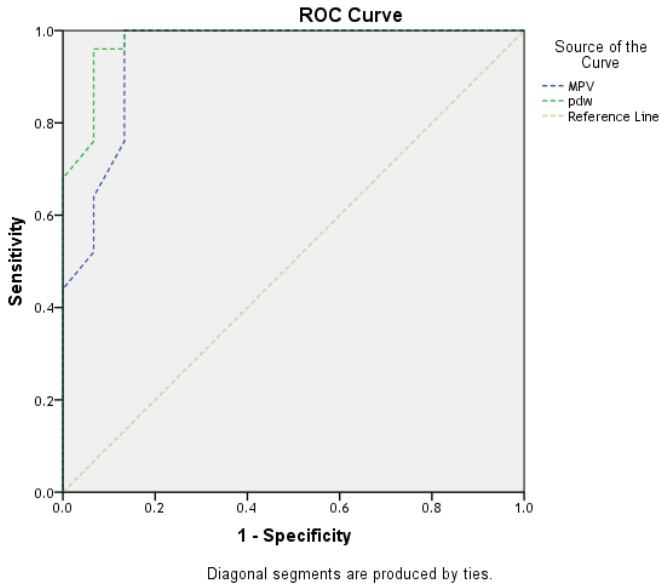

Figure (3): ROC curve for detection of cutoff of MPV and PDW regard Preeclampsia

DISCUSSION

In the past, the difference in platelet size has been observed on peripheral smear or wet preparation, but an accurate platelet volume could not be obtained tried to represent platelet volume by the density gradient centrifugation method, but this method has not been utilized in clinical medicine because of the technical difficulties involved **[13]**.

An automated blood analyzer, the Coulter counter has been introduced. It has made it possible to determine platelet size from a routine specimen of blood collected for a cell count. Platelet size, as measured by this counter, is expressed as mean platelet volume (MPV) **[14]**.

In normal pregnancies a small increase in platelet aggregation was observed, which is compensated for by increased synthesis and consequently increased mean platelet volume (MPV) **[15].**

It has long been known that platelet volumes are direct indicator of increased platelet synthesis, moreover it was suggested that in normal pregnancy, changes in platelet volumes may be more sensitive than platelet numbers as a measure of altered platelet function **[14].**

Alterations in hemostatic system, including endothelial cell damage, platelet activation and enhanced intravascular thrombin generation, are the major pathophysiologic events in pre-eclampsia. Several reports investigating changes in platelet number, volume and function indicate increased platelet turnover following activation within the maternal vasculature in pre-eclampsia **[10].**

Conflicting results have been published regarding platelet number and size changes during normal and preeclampsia pregnancies. Some researchers **Ceyhan et al., [16]** found no difference in platelets count and MPV values between pre-eclamptics and controls, whereas others demonstrated lower platelet and higher MPV in pre-eclamptics **Jaremo et al., [17],** referring these changes to the increased platelet consumption in pre-eclampsia.

It should be noted that the principal explanation for the difference between these studies is possibly the MPV measurement process. Measurements performed in EDTA are considered to be relatively inaccurate and MPV increases in this type of measurement in a time-dependent manner **[18].**

Additionally, it is recognized that up to 40% of different systems used in MPV calculation can produce different results **[19]**. It may explain the variations between the studies but the findings of this research are still strong because all the tests were performed with the same anticoagulant and the same method.

Dundar et al., [10] found that there was a decrease in platelet count throughout pregnancy reaching a nadir around 30 weeks and suggested that the decrease was due to plasma dilution and increased consumption. The mean platelet volume (MPV) is increased during pregnancy indicating a younger platelet population. In preeclampsia there is a true decrease in the platelet count, a decreased life span and the cutoff point for MPV elevation was (10.5) but our cut off point was (9.5).

Davis [20] found that the platelet count decreased in the early evolution of preeclampsia, and suggested that it could be a predictor of preeclampsia. Beta thromboglobuin (BTG) is found in the alpha granules of platelets. An increase BTG in the plasma indicates platelet stimulation and release of alpha granules. An

increase in BTG has been reported to precede the clinical development of preeclampsia by four weeks.

Our results agree with **Dundar, et al., [10]** Longitudinal research showing that pregnant women with elevated MPV are at risk of preeclampsia in the second quarter of a single random blood sample.

A relatively broad cross-sectional study presented proof of 90% sensitivity and 83.3 percent accuracy in predicting preeclampsia in reduced PLT and elevated MPV**.** In gestational weeks between 8th and 42nd week one blood sample was taken from 349 participants. However, this study suggested that serial monitoring of MPV is more beneficial in prediction of preeclampsia than a single measurement. These results correlate significally with our results **[10]**.

Our results agree with **Jaremo et al., [21]** regarding the elevation of MPV in preeclamptic women but they demonstrated normal PLTs count with preeclampsia and attributed that the disturbed platelet density distributions secondary to the activation of platelets as high-density platelets have a large number. In our study, we investigated only the MPV in the prediction of preeclampsia.

Our results agree also with **Missfelder-lobos et al., [22].** They reported a significant elevation of MPV in preeclamptic women and also a strong correlation to the severity of pregnancy hypertensive disorders.

Levy JH., recently it was confirmed that the early stages of preeclampsia are followed by excessive accumulation of whole blood platelets. He noticed that in early pregnancy eclampsia, an rise in the entire blood platelet aggregation response to collagen had a 100 per cent positive predictive value of subsequent preeclampsia growth. Late pregnancy was of no predictive interest **[23]**.

This study has strong correlations with **Gioia et al., [24]** longitudinal cross-study proposing the addition of a cut-value of average 10 fL as part of the significant parameters capable of predicting unfavorable neonatal outcomes in women with altered uterine artery doppler velocimetry and providing evidence that reduced PLT and elevated MPV are 90 percent sensitive and 83% sensitive.

This study significantly correlates with **Dundar, et al., [10],** in their study on 1361 pregnant women, serial assessment of mpv beginning at 20 weeks gestation revealed good correlation of MPV in prediction of preeclampsia with 90% sensitivity and 83% specificity. However, they showed a positive correlation of MPV level with gestational age, our study revealed negative correlation of MPV with gestational age which does not agree with **Dundar** study and this may be due to the narrow interval range for gestational age in our study.

The results of this study revealed an increase in MPV in pregnants who developed later preeclampsia and the cut-off value of MPV was above 9.2 fl. However, there was no increase in MPV in pregnants who did not develop later preeclampsia.

In This tudy results, the correlation between high MPV and development of preeclampsia was highly significant; it showed a high specificity of 93.7% and a sensitivity of 100% with a $p < 0.0001$.

In this study, the onset of diagnosis using changes in PDW started at 20-28 weeks gestation, and substantial increases in PDW were noted to precede PE development by around 2-8 weeks. Our findings comply with those from previous studies **[5] .**

ROC curve analysis of changes in PDW values at 20-28 weeks gestation in this study provided a PDW > 17.7 as the optimal cut-off for predicting PE production. This cut-off point had an 87.5 percent sensitivity and a 96.8 percent specificity for PE growth prediction. Women with PDW > 17.7 at 20-28 weeks of gestation have been at risk of developing PE more than 13 times. PDW was also noted to have a positive association with MAP in women with PE, and the increase in PDW was proportional to the increase in MAP ($r= -0.902$; $p= 0.000$); making PDW the best possible predictor for predicting hypertension severity. Yang et al. however defined a PDW value of > 13.5 as the optimum cut-off point for PE severity prediction **[5].**

They noticed that this value had a 0.74 AUC, a 72 per cent sensitivity and a 71 per cent specificity. They also stated that only PDW had a statistically significant association with MAP ($r= 0.231$, $p= 0.011$), and thus concluded that PDW was the best marker for PE.

They noticed that this value had a 0.77 AUC (95 percent CI: 0.66-0.85), a 55.17 percent sensitivity and 86.21 percent specificity. They also stated that only PDW had a statistically significant correlation ($r= 0.231$, $p= 0.011$) to MAP. Conflicting results concerning changes in platelet indices in normotensive pregnancies and PE have been published.

CONCLUSIONS

This study evidence that MPV & PDW are higher in pregnant women who developed later preeclampsia. The sensitivity and specificity of MPV at 20-28th gestational weeks with a cut-off value of 9.2 fL for predicting preeclampsia were 100% and 93.7%, respectively, the sensitivity and specificity of PDW at 20-28th gestational weeks with a cut-off value of 17.7 for predicting

preeclampsia were 87.5% and 96.8%, respectively. Therefore, MPV& PDW measurement may contribute significantly in the identification of at-risk women.

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