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Case-Control Study

Platelet Parameters in Nonthrombocytopenic Preeclampsia: A Case-Control Study

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Background: Preeclampsia is a pregnancy-specific, multisystem condition characterized by the onset of de novo hypertension and proteinuria occurring in a previously normotensive woman after the twentieth week of pregnancy. Pregnancy is associated with physiological adaptation led to change in hematological system including platelet parameters.

Objectives: Is to compare platelet count, platelet indices, namely mean platelet volume platelet distribution width and platelet count to mean platelet volume MPV ratio in preeclamptic patients with normal pregnant women.

Methods: A case-control study was carried out in department of obstetrics and gynecology at Al-Khansaa Maternity and Children Teaching Hospital, Mosul, Iraq over a period extending from February 2020 to the end of December 2020. A sample of 120 pregnant women participated in the study fulfilling inclusion criteria. Sixty of them diagnosed with preeclampsia PE (30 pregnant women with mild PE and 30 pregnant women with severe PE) and sixty healthy pregnant women as control group. Platelet count, mean platelet volume and platelet distribution width (PDW) were measured and statistical analysis by mini tab program was done for all collected data.

Results: A significant linear correlation between mean platelet volume (MPV) and platelet distribution width (PDW) with mean arterial pressure in Preeclampsia group with p value of (0.025 and 0.001) respectively and a significant inverse correlation between the platelet count and mean arterial pressure with p value of (<0.001) was observed.

Conclusion: Platelet parameters are cost-effective, easily measurable, and practical markers which can be used for monitoring of preeclampsia. Mean platelet volume (MPV) and platelet distribution width (PDW) has a significant linear correlation with mean arterial pressure in severe preeclampsia and can be used as biomarker for severity of preeclampsia in high-risk pregnant women.

Keywords: Mean platelet volume; Platelet Count; Platelet distribution width; Platelet Parameters; Preeclampsia thrombocytopenia.

Introduction:

Preeclampsia is an idiopathic disorder of pregnancy characterized by proteinuria and hypertension (1), the disorder is specific to pregnancy characterized by new onset of hypertension and proteinuria after 20 weeks of gestation. Preeclampsia usually presents during pregnancy; however, it may sometimes manifest in the postpartum period in a previously normotensive woman. Preeclampsia is defined as blood pressure of greater than 140 mmHg systolic and/or 90 mmHg diastolic, measured on at least two occasions, not less than four hours apart in the presence of at least 300mg protein in a 24-hour collection of urine or urinary protein / creatinine ratio of greater than 30mg/mmol (2,3). Hypertension complicates 6–12% of all pregnancies and includes two relatively benign conditions (chronic and gestational hypertension) and the more severe conditions of preeclampsia or eclampsia (4). Preeclampsia complicates 5% of all pregnancies worldwide (5). Platelets count (PC) and mean platelet volume (MPV) are largely unchanged in most pregnant women, even though platelets survival is reduced. Platelet reactivity is increased in the second and third trimesters and does not return to normal until about 12 weeks after the delivery (4). Platelets play an important role in the pathogenesis of preeclampsia. The platelets are normally present in the blood stream in an inactive state, but they can be activated instantly when they come in contact with the damaged or activated endothelial wall (6). Increased consumption of platelets as well as decreased life span in the uteroplacental circulation has been suggested to be the explanation of the reduction in the number of circulating platelets during pregnancy. Platelet counts as well as other hemostatic factors return to normal after 6 weeks of delivery (7). The platelets count decreases by an average of 10% during the third trimester of uncomplicated pregnancy due to hemodilution (8,9). Platelets count is always included in the reporting of complete blood count results. Automated blood cell analyzers have

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measured mean platelet volume (MPV) and platelet distribution width, and as a result the PC to MPV ratio can be calculated. The MPV is a measure of the average volume of platelets in a sample. Large platelets are often biochemically more active than smaller platelets; high mean platelet volume is associated with less bleeding in patients with severe thrombocytopenia (10). In healthy people, there is an inverse relationship between platelet count and size. Because of this inverse relationship, the MPV and the platelet count must be considered together. The increased MPV and increased platelet aggregation have been defined as precursors to the onset of preeclampsia and intrauterine growth restriction (11,12). The MPV is elevated proportionally with the severity of preeclampsia (13). When platelets are activated, there will be an increase in production and they become larger in size which causes increased platelet indices such as mean platelet volume (MPV). So, platelet indices can give an idea of platelet activation (14). Platelet distribution width (PDW) is a measurement of platelet anisocytosis (12,15). PDW can act as an indicator of platelet volume variability and increases in the presence of platelet anisocytosis. In addition, PDW can be affected by the morphology change of platelet when the platelet is activated during inflammation and thrombosis process (16). Platelet distribution width is considered a marker of platelet function and activation (17). On the other hand, lowered platelet count and increased platelet indices in pregnant women during antenatal check may be considered as a risk factor for development of preeclampsia and eclampsia. This group of pregnant women may be considered for special attention to prevent the development of preeclampsia (18,19).

Patients and method

A case-control study was carried out in obstetrics and gynecology department at Al-Khansaa maternity and childhood Teaching hospital, Mosul, Iraq over a period extending from February 2020 to the end of December 2020.

Inclusion criteria for cases and controls:

- Viable singleton pregnancy.
- Third trimester of pregnancy.

Exclusion criteria for cases and controls:

- Chronic hypertension.
- Anemia
- Cardiovascular disease.
- Diabetes mellitus type 1 and 2.
- Multiple gestations.
- Smoking.
- Chronic renal disease.
- Intrauterine fetal death.
- Fetal anomalies.
- Autoimmune disease.
- Eclampsia, HELLP syndrome (hemolysis, elevated liver enzyme and low platelet).
- Thrombocytopenia (platelets count less than 150 × 109/L).
- Maternal age not less than 16 years and not more than 35 years.

A sample of 120 pregnant women participated in the study fulfilling inclusion criteria, who presented at antenatal care out-patient clinic and/or admitted in maternity wards. Sixty of them diagnosed with preeclampsia PE (30 pregnant women with mild PE and 30 pregnant women with severe PE) and sixty healthy pregnant women as control group. Cases with severe PE were using aspirin from early pregnancy and stopped uses at 36 weeks of pregnancy. The diagnosis of preeclampsia was made by NICE guideline criteria (20); Include clinical features, blood pressure measurement and laboratory investigation which included a complete blood count, renal function test, liver function test and detection of protein in urine done by clean–catch midstream or catheter specimens of collected urine > 4 hours apart with 2+ on reagent strip, urine dipstick testing 1+ = 0.3 g/L, 2+ = 1 g/L and 3+ = 3 g/L.

Platelet count, mean platelet volume and platelet distribution width were measured and statistical analysis was done for all the data collected.

Blood pressure was measured by auscultatory method with a properly calibrated standard mercury sphygmomanometer, the woman should be rested and sitting at a 45-degree angle or in left lateral position with the cuff on the left arm at the level of the heart. Pulse pressure (PP) was calculated as the difference between SBP and DBP. Mean arterial pressure (MAP) was calculated as DBP plus 1/3 of PP. hematological analyzer Abbott Diagnostic Division (Max - Plank –Ring 2) used for determination of the hemoglobin, platelet count (PC), platelet indices, which includes mean platelet volume and platelet distribution width as a part of full blood count. MPV was recorded as femtoliter (fL). The range of normal values for platelet count in our laboratory was (150-400×109 /L), for mean platelet volume 7.6-10.6 fL and for platelet distribution width 14-19 fL.

Statistical Analysis:

A comparison between the above-mentioned platelet parameters was performed on the data presented by mini tab program version 17, minimum, maximum, arithmetic mean and standard deviation, The significance of difference of different means (quantitative data) was tested using students t-test for difference between two independent means or one-way analysis of variance (ANOVA) test for difference among more than two independent means with Tukey's Pair wise comparisons were used. Means that do not share a letter are significantly different. The significance of difference of different percentages (qualitative data) was tested using Pearson Chi-square test (x2-test). Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. To know the correlation between MAP and platelet (PLT) indices, pearson's correlation coefficient "r" was used which is a measure of strength and direction of linear dependence between two variables. The correlation coefficient value (r) either positive (direct correlation) or negative (inverse correlation), a

statistical significance was considered whenever the P value was equal or less than 0.05.

Results

The results presented in this study were based on the analysis for a total data of 120 pregnant women in their third trimester. Sixty of them have preeclampsia (cases) in which 30 of them were with severe preeclampsia and 30 with mild preeclampsia and other 60 women were control group. The demographic and obstetric characteristics of all groups are shown in table (1).

The mean maternal age ± SD was 24± 5.4 years in the preeclampsia and 26.5± 5.05 years in the control group, with very high significant (P = 0.009) difference between them. 41.67 % of cases had positive history of previous preeclampsia with very high significant (P= 0.000) difference between preeclampsia and control group. There was no significant difference in the parity and gestational age with (P = 0.217 and P = 0.306), respectively, between cases and control group.

Table (1): Demographic and obstetric characteristics of preeclampsia and control groups

Parameter (Range)	Cases "Preeclampsia" [n = 60] Mean ± SD	Control "Normotensive" [n = 60] Mean ± SD	*p*-value*
Maternal age (years)	24± 5.4	26.5± 5.05	0.009
Parity	1.767 ±1.798	2.217 ±2.156	0.217
Gestational age (weeks)	38.1 ± 2.07	38.5 ± 2.06	0.306
History of previous preeclampsia, no. (%)	25 (41.67)	0 (0.00)	<0.001

** Independent T-test of two means was used for comparison in measurable variables whereas, chi-square test applied for categorical data.*

Table (2) Compared Platelet count PC (×109/L), Mean platelet volume MPV (fL), platelet distribution width PDW (fL), PC/MPV distribution for the preeclampsia patients with control group. The present study found out the mean PC ± SD was 178.50 ± 41.80×109/L in severe preeclampsia, 232.2 ± 63.6×109/L for the mild preeclampsia group and 254.25 ± 41.08×109/L in the control group. The mean ± SD for MPV was 11.807± 1.368 fl in severe preeclampsia, 10.663± 1.439 fL for the mild preeclampsia group and 9.472 ±0.945 fl in the control group. While mean ± SD for PDW was 20.390 ±2.415 fl in severe preeclampsia, 17.360 ±2.404 fL for the mild preeclampsia group and 14.443± 4.683 fl in the control group. Whereas mean PC/MPV ± SD was 16.81 ±5.69 in severe preeclampsia group, 23.00 ±8.63 for the mild preeclampsia group and 27.308 ±6.474 in the control group. The difference was statistically significant for all (P = <0.001).

Table (2): Comparison of platelet count and platelet indices among severe preeclampsia, mild preeclampsia, and control groups

Parameters	Groups (Mean ± SD)			P-value*
	Severe preeclampsia	Mild preeclampsia	Normotensive	
No. of women	30	30	60	
Platelet count (×109/L)	178.50 ± 41.80	232.2 ± 63.6	254.25 ± 41.08	<0.001
Mean platelet volume (fl)	11.807± 1.368	10.663± 1.439	9.472 ±0.945	<0.001
Platelet dist. W(fl)	20.390 ±2.415	17.360 ±2.404	14.443± 4.683	<0.001
PC/MPV	16.81 ±5.69	23.00 ±8.63	27.308 ±6.474	<0.001

** One-way ANOVA-test with Tukey's Pair wise comparisons was used.*

Table (3) demonstrated the platelet count distribution for the preeclampsia and control groups. Twenty-one patients (70%) of severe Preeclampsia group with 8 patients (26.6%) in mild preeclampsia group and zero in control group had a platelet count between (150-199) ×109/L. While 6 patients (20%) of severe Preeclampsia group with 11 patients (36.6%) in mild group and 28 patients (46.6%) in control group had a platelet count between (200-249) ×109/L. This was compared with 3 patients (10%) in severe preeclampsia group, 11 patients (36.6%) in mild preeclampsia group and 32 women (53.33%) in the control group had a platelet count of ≥ 250 × 109/L. This difference between proportions for platelet count in the studied groups was statistically significant (P= <0.001).

Table (3): Distribution of platelets count distribution among the study groups

	Severe preeclampsia [n = 30]				Normotensive [n = 60]		P-value*
	No.	%	No.	%	No.	%	
150 - 199	21	70	8	26.6	0	0	<0.001
200 - 249	6	20	11	36.6	28	46.6	
≥ 250	3	10	11	36.6	32	53.33	

** Chi-square test was used, d.f = 4.*

Table (4) demonstrates the mean platelet volume MPV (fL) distribution for the preeclampsia and control groups. None in the severe preeclampsia group and mild preeclampsia group had MPV below 8fL. This compared with 4 women (6.67%) in the control group who had MPV below 8 fL. While one the patient in severe preeclampsia group (3.33%), 17 patients (56.67%) in mild preeclampsia group and 48 women (80%) in control group had MPV between 8 – 10.5 fL. However, 29 patients (96.67%) in severe preeclampsia group, 13 patients (43.33%) in the mild

preeclampsia gr,oup, and 8 women (13.33%) in the control group had MPV equal or above 10.6 fL.
This difference between proportions for MPV in the studied groups was statistically significant (p = <0.001).

Table (4): Statistical difference of MPV among the study groups

MPV (FL)	Severe preeclampsia [n = 30]		Mild preeclampsia [n = 30]		Normotensive [n = 60]		*p*-value *
	No.	%	No.	%	No.	%	
< 8	0	0	0	0.00	4	6.67	<0.001
8 – 10.5	1	3.33	17	56.67	48	80	
≥ 10.6	29	96.67	13	43.33	8	13.33	

** Chi-squared test was used, d.f = 4.*

Table (5) listed the distribution of platelet width PDW (fL) for Preeclampsia and control groups. 6 patients (20%) in the severe preeclampsia group, 20 patients (66.67%) in the mild preeclampsia group,
and 40 women (66.67%) in the control group had PDW < 19.0 fL. This was compared with 24 patients (80%) in severe preeclampsia group, 10 patients (33.33%) in mild preeclampsia group and 20 women (33.33%) in control group had PDW ≥ 19.0 fL.
This difference between proportions for PDW in the presented study sample groups was statistically significant (p = <0.001).

Table (5): Distribution of platelet width (PDW) distribution between preeclampsia cases and control groups

PDW (fl)	Severe preeclampsia [n = 30]		Mild preeclampsia [n = 30]		Normotensive [n = 60]		*p*-value *
	No.	%	No.	%	No.	%	
< 19.0	6	20	20	66.67	40	66.67	<0.001
≥ 19.0	24	80	10	33.33	20	33.33	

** Chi-square test was used, d.f = 2.*

To know the correlation between MAP and platelet (PLT) indices, Pearson's correlation coefficient "*r*" was used which is a measure of strength and direction of linear dependence between two variables.
It ranges from + 1 to −1, where 1 indicates total positive correlation, 0 indicates no association, and −1 indicate total negative correlation. Table (6) showed the correlation analysis between platelet counts (PC), Mean platelet volume (MPV) and platelet distribution width (PDW) parameters in preeclampsia groups with mean arterial pressure (MAP) there was a statistically significant inverse correlation between platelet count and the mean arterial pressure with r value of -0.517 and (p= <0.001). Also, compared the direct correlation between MPV, PDW and MAP with r values of 0.390, 0.411 and P values of (0.025, 0.001), respectively.

Table (6): Correlation between MAP, Platelet count and platelet indices in preeclampsia women, [n = 60]

Platelet indices MPA (mmHg)	Pearson`s correlation coefficient "r"	*p*-value
Platelet count ($\times 10^9$/L)	-0.517	<0.001
MPV (fl)	0.390	0.025
PDW (fl)	0.411	0.001

Discussion

In fact, there is a proof that in hypertension during pregnancy, the thrombocyte production time is noticeably reduced in comparison with normal pregnancy. Young platelets shown in a circulation are larger and represent a higher tendency to coagulation (18,21). It is obvious that endothelial injury led to increased platelet activation and thrombocyte consumption by creating micro thrombosis. In this condition, megakaryocytes in the bone marrow release platelets, which have a larger volume and more activity to compensate the thrombocyte consumption (22). Mean platelet volume MPV and platelet distribution width PDW are simply measured platelet parameters, which increase during thrombocyte activation. In order to get a larger surface platelet, change in shape during activation. Their shape changes from discoid to the spherical (12,23). The current study demonstrated significantly lower PC and PC to MPV ratio in patients with severe preeclampsia compared with the mild preeclampsia and control groups This is agreed with Doğan et al. and AlSheeha et al.(24,25) who observed significantly lower PC and PC/MPV in preeclamptic women compared with the controls. The same studies found no significant difference in PDW in the preeclamptic women than healthy control groups. While in the current study, there was significant difference in MPV. AlSheeha et al.(25) study stated that there was no significant difference in MPV in the preeclamptic women compared with the controls but Doğan et al.(24) who documented a higher level of MPV in the preeclamptic women compared with the controls. The difference may probably be due to the different sample size included in their studies, different in equipment and/or method of the automatic blood count devices used to obtain hemogram. Current study showed that, platelet count decreased significantly with severe preeclampsia which is similar to the findings reported by Dogru et al.(13), Ustün et al.(26), Vijaya et al.(27), and Annam et al.(28) studies. In this study, in spite of the platelet count being normal in all the cases included, it was observed that platelet count decreased as the severity of the disease increased and was statistically significant when severe preeclampsia cases were compared with mild preeclampsia cases and control group. Dhakre et al.(29) study revealed that, PDW and MPV increase as pregnancy progresses and these changes were more marked in the preeclampsia group complicated pregnancy than normotensive pregnancy while, the Platelet count decreases. Furthermore, Nooh et al.(30) and Dundar et al.(31) noted a

significant increase MPV. Both of them also reported that, the increase MPV preceded onset of development of preeclampsia and started from 24 week of gestation. In both types of preeclampsia cases, platelet (PLT) count was statistically correlated with MAP in a negative manner, whereas MPV and PDW values were positively correlated with MAP with significant P value this was resembled the study done by Reddy et al.(32), While Unlü et al.(33) and Ceyhan et al.(34) observed no significant change between preeclamptic groups and controls in respect to relation between MAP and platelet count. It was suggested that the main cause for the inconsistency between these studies is probably due to the method of measurement of these platelet parameters, measurements performed in EDTA and change in a time-dependent manner. Also, different systems used in measurement can give different results, and this difference may extend up to 40% (29). Yang et al.(35) study showed that among three groups mild, severe PE and normotensive women the platelet count lowered in the preeclamptic group. However, PDW and the MPV increased. When compared with the levels of other platelet indices, the PDW showed significant elevation in the severe PE group. In the severe and mild preeclampsia groups, the PDW was statistically correlated with the mean arterial pressure (MAP) ($r = 0.231$; $P< 0.05$), this was corresponding with the results of the present study which was shown among platelet parameters, the PDW and MPV is significantly higher in women with severe preeclampsia than in women with mild preeclampsia and control group and is positively correlated with the MAP this was similarly reported by Vijaya et al.(27).

Conclusion:

Platelet parameters are cost effective, easily measurable, and practical markers can be used for monitoring of preeclampsia. Mean platelet volume (MPV) and platelet distribution width (PDW) has a significant linear correlation with mean arterial pressure in severe Preeclampsia and can be used as biomarker for severity of preeclampsia in high-risk pregnant women.

Recommendations

Ascertain the use of platelet parameters as an aid in the detection and management of a patient with preeclampsia.

Availability and accessibility of platelet parameters in the antenatal care health center will serve in discovering preeclampsia earlier especially the pregnant women who were at high risk for preeclampsia.

Authors Declaration:

Conflicts of interest: None.

We hereby confirm that all the Figures and Tables in the manuscript are ours. The project was approved by the Iraqi Board for Medical Specializations.2019

Authors Contributions:

The concept and study design, and the critical revision were done by Ahmed J. Alhusaynei, acquisition of data analysis, and the drafting of the manuscript was done by Hanan Dh. Nayyef.

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معلمات الصفائح الدموية لدى النساء الحوامل المصابات بمقدمات الارجاج وبدون نقص في عدد الصفيحات الدموية: دراسة مقارنة

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الخلاصة

الخلفية: مقدمات الارجاج هو اضطراب خاص بالحمل متعدد الأجهزة، يتميز بتطور ارتفاع ضغط الدم والبيلة البروتينية التي تنشأ بعد الأسبوع العشرين من الحمل في امرأة كانت ذات ضغط طبيعي سابقًا ويرتبط الحمل بالتكيف الفسيولوجي الذي يؤدي الى تغيير في نظام الدم ومن ضمنها معلمات الصفائح الدموية.

هدف الدراسة: دراسة لمقارنة العلاقة بين عدد الصفائح الدموية (pc) ومؤشرات الصفائح الدموية وهي متوسط حجم الصفائح الدموية (MPV) وتوزيع الصفائح الدموية (PDW) ونسبة عدد الصفائح الى حجمها في النساء المصابات بمقدمات الارجاج مع النساء ذوات الحمل الطبيعي.

المرضى والطريقة: تم إجراء دراسة الحالة والشاهد في قسم النسائية والتوليد في مستشفى الخنساء التعليمي للأطفال والولادة ، الموصل، العراق على مدى فترة تمتد من الاول من شباط ٢٠٢٠ إلى نهاية كانون الأول٢٠٢٠. شاركت عينة من ١٢٠ امرأة حامل في الدراسة ممن استوفين معايير الاشتمال. ٦٠ منهن تم تشخيص إصابتهن بمقدمات الارجاج (٣٠ امرأة حامل مع مقدمة الارجاج الخفيف و ٣٠ امرأة حامل مع مقدمة الارجاج الشديد و٦٠ امرأة حامل حملا طبيعيا كمجموعة شاهد. تم قياس عدد الصفائح الدموية ومتوسط حجم الصفائح الدموية كجزء من تعداد الدم الكامل.

النتائج: علاقة خطية معنوية بين متوسط حجم الصفائح الدموية (MPV) وعرض توزيع الصفائح الدموية (PDW) بمتوسط ضغط شرياني في مجموعة تسمم الحمل بقيمة p (0.025 و 0.001) على التوالي وعلاقة عكسية معنوية بين عدد الصفائح الدموية ومتوسط الضغط الشرياني مع p تمت ملاحظة قيمة (<0.001).

الخلاصة: تعتبر مؤشرات الصفائح الدموية فعالة من حيث التكلفة، وسهلة القياس، وعلامات عملية لرصد مقدمة الارجاج ، وان متوسط حجم الصفائح الدموية وعرض توزيعها له علاقة طردية كبيرة مع متوسط الضغط الشرياني في حالة مقدمة الارجاج الشديد.

الكلمات المفتاحية: مقدمة الاتعاج، معلمات الصفائح الدمويه، عدد الصفائح الدمويه، حجم الصفائح الدمويه، توزيع الصفائح الدمويه.