INT. J. BIOL. BIOTECH., 16 (3): 655-660, 2019.

A COMPARISON OF PLATELET INDICES OF NORMOTENSIVE, HYPERTENSIVE, AND PREECLAMPTIC PREGNANT WOMEN IN PAKISTAN

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ABSTRACT

This study aimed to assess and compare the platelet profiles of normotensive, hypertensive, and preeclamptic pregnant women. Further, to find out if mean platelet volume (MPV) and/or platelet distribution width (PDW) could serve as an indicator of the severity of hypertension and the diagnostic marker of preeclampsia. This is a case-control study, in which we included 300 hypertensive and preeclamptic pregnant females aged between 20 to 40 years. Blood samples were analyzed using the Roche® model at Dow Diagnostic Research and Reference laboratory (DDRRL). Data were analyzed using Statistical Package for Social Sciences 23 (SPSS Inc., Chicago, IL). A p-value of less than 0.05 was considered statistically significant. High MPV were observed as 9.57 $\pm$ 2.6, 10.9 $\pm$ 5.4 and 12.3 $\pm$ 34 among control, hypertensive and preeclamptic females. Statistically significant differences were observed between control vs. hypertensive with a p-value of 0.005, and 0.0001 between control vs. preeclampsia. Moreover, PDW mean values were observed as 13.5 $\pm$ 8.9, 14.2 $\pm$ 5.6 and 19.2 $\pm$ 6.4 in control, hypertensive and preeclamptic females and the result was statistically significant (p-value = 0.004). Calculation of plateletcrit (PCT) showed, mean PCT of 0.29 $\pm$ 3.9, 0.19 $\pm$ 4.8 in control and hypertensive and 0.12 $\pm$ 6.7 in preeclamptic group respectively. The study observed no significant difference in between hypertensive and normotensive pregnant females (p-value = 0.05), whereas, there was a significant reduction (p-value = 0.004) in the mean values of PCT in control and preeclamptic females.

Key-words: Platelets, Hypertension, Preeclampsia, Mean Platelet Volume, Platelet Distribution Width.

LIST OF ABBREVIATIONS

PIH	Pregnancy Induced Hypertension
ACOG	American College of Obstetrics and Gynaecology
vLDL	Very Low density lipoprotein
MPV	Mean Platelet Volume
sFlt	Soluble fms-like tyrosine kinase 1
CBC	Complete blood count
PDW	Platelet distribution width
PCT	Plateletcrit
DUHS	Dow University of Health Sciences
BASR	Board of advance studies and research department
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
ACC	American College of Cardiology
DDDRRL	Dow Diagnostic Reference and Research Laboratory

INTRODUCTION

Pregnancy is associated with significant cardiovascular and hemodynamic changes. To accommodate the developing embryo, maternal plasma volume and cardiac output increases, which lead to an increase in blood pressure. This elevation is counteracted by compensatory vasodilator synthesis and release, maintaining blood pressure readings within the normal range. In a normal pregnancy, blood pressure decreases throughout the second trimester and then slightly increases in the third trimester (Pillay *et al*., 2016). This variation in blood pressure could be complicated by hypertension in around 10% of pregnancies worldwide, and it might exacerbate underlying hypertension. Pregnancy-induced hypertension (PIH) is defined as a systolic blood pressure reading of at least 140 mmHg and/or a diastolic blood pressure reading of at least 90 mmHg. According to the American College of

Obstetrics and Gynaecology (ACOG), PIH is attributed to four main conditions, pre-existing chronic essential hypertension; gestational hypertension; preeclampsia; and chronic hypertension exacerbated by preeclampsia or gestational hypertension (ACOG Practice Bulletin., 2019).

New-onset hypertension that appears after 20 weeks of gestation in 2 episodes at least 4 hours apart is mainly due to gestational hypertension or preeclampsia. If this elevation in blood pressure is coupled with evidence of systemic involvement, such as proteinuria, the patient is said to be preeclamptic (Upadya and Rao, 2018). Pre-eclampsia affects 2-8% of pregnancies globally, and it ranks third after infection and hemorrhage as a cause of feto-maternal morbidity and mortality. Since the only treatment of preeclampsia is delivery, it is important to detect preeclamptic changes early, which is challenging due to its unclear pathophysiology. It is believed that initially, higher concentrations of circulating antiangiogenic factors resulting from uteroplacental ischemia explain the angiogenic imbalances in preeclampsia. Other proposed mechanisms include immune maladaptation, Very Low-density lipoprotein (v-LDL) toxicity, increased necrosis or apoptosis of trophoblasts, and an exaggerated maternal inflammatory response to the protruding trophoblasts. All preceding mechanisms would ultimately lead to hypertension, platelet activation, and systemic endothelial dysfunction, eventually leading to vasoconstriction and end-organ ischemia (Tannetta and Sargent, 2013).

Important players in the pathogenesis of pre-eclampsia have been identified, such as soluble forms like tyrosine kinase 1 (sFlt 1); endothelial microparticles; and platelets (Kohley *et al*., 2016). These have been studied as potential predictive markers of pre-eclampsia. Platelet profile has shown promising results in the anticipation, and hence, the prevention of pre-eclampsia. It is inexpensive, available, and routinely ordered with complete blood count (CBC). Several studies are conducted to observe platelet count and other indices in hypertensive and preeclamptic pregnant females but the results were inconsistent. Some studies observed no significant differences in mean values of platelet profile, however, the other found significant thrombocytopenia, more prominent in preeclampsia due to platelet consumption. Multiple studies have shown that elevated mean platelet volume (MPV) as an early marker for the development of preeclampsia, in contrast, other studies suggested platelet distribution width (PDW) as an indicator of preeclampsia, reflecting megakaryocyte production as a result of long-standing thrombocytopenia (Vilchez *et al*., 2017). In a few studies, plateletcrit (PCT) was found significantly lower (Karateke *et al*., 2013) however, in other studies difference was non-significant (Chen *et al*., 2017) in preeclamptic pregnancies in comparison to healthy ones. Therefore, more research is needed to estimate the optimal cut-off values and a more appropriate marker for the prediction of preeclampsia. This study aims to observe and compare the platelet profiles of normotensive, hypertensive, and preeclamptic pregnant women in Pakistan. In addition, to find out if MPV and/or PDW could serve as an indicator of the severity of hypertension and diagnosis of preeclampsia.

MATERIAL AND METHODS

This is a case-control study on hypertensive and preeclamptic pregnant females attending OPD and Gynecology ward of Civil Hospital and Dow University Medical Institute (DUHS) in Karachi, Pakistan. The sample consists of 300 pregnant females aged between 20 to 40 years, who were selected by purposive random sampling. All subjects were informed verbally about potential risks and benefits associated with their participation in the study besides taking their written consent on a detailed form. Study was approved by the board of advance studies and research department (BASR), University of Karachi. Subjects were then divided into three groups, normotensive, hypertensive, and pre-eclamptic. Pregnant women with a history of diabetes mellitus, dyslipidemia, hepatic/renal disease, congestive heart failure, or a recent myocardial infarction were excluded from the study. Detailed personal and medical history was recorded on a pre-designed Performa, and a complete physical examination was performed to exclude the presence of any medical condition. Blood pressure was measured three times on separate occasions, and the average reading was considered. Pregnant women who had systolic blood pressure (SBP) readings below 140 mmHg and diastolic blood pressure (DBP) readings below 90 mmHg were considered normotensive. Out of these normotensive pregnancies, the control group (Group I) had healthy females who were not on hormone-replacement therapy during the time of the study nor were receiving medications for cardiac disease. Hypertensive women (Group II) were diagnosed according to the American College of Cardiology (ACC) criteria, with SBP of at least 140 mmHg and/or DBP of at least 90 mmHg (ACC criteria, 2018). Group III included preeclamptic pregnancies that had been already diagnosed according to the American College of Obstetrics and Gynecology (ACOG) criteria. Five microliters of blood was drawn from the cubital vein of each subject and transferred to a previously-mixed EDTA tube. Blood samples were analyzed using the auto analyzer (Roche, Germany) in Dow Diagnostic Research and Reference laboratory (DDRRL), Dow University of Health Sciences. Statistical Package for Social Sciences 23 (SPSS Inc., Chicago, IL) was used for data analysis and interpretation. ANOVA/t- test was utilized to compare the mean values of continuous variables. Pearson correlation was further used to find out the

relationship between mean arterial pressure and platelet indices. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Among all subject 76 normotensive, 90 hypertensive and 74 preeclamptic females agreed to participate voluntarily as shown in Table 1. Study observed a mean age of (24.41± 3.29), (28.23 ± 4.8) and (32.31 ± 5.4) in normal pregnant, hypertensive and in preeclamptic females, respectively and found to be statistically significantly different ($p < 0.000$). A significant ($p<0.000$) pre-pregnancy body mass index (PreBMI) of (23.61 ± 2.9) (25.4 ± 3.9) and (30.44 ± 5.3) was recorded among control, hypertensive and preeclamptic patients as illustrated in Table 2.

Table 1. Distribution of Subjects in Study Population.

Subjects	Frequency (n=240)	Percentage (%)
Normotensive	76	31.6
Hypertensive	90	37.6
Preeclamptic Females	74	30.8
Total	240	100

Highly significant mean systolic blood pressures (SBP) among the three groups (control, hypertensive and preeclamptic) were measured in sitting position and found as (127.73 ± 4.7), (148.59 ± 15.1) and (158.87 ± 16.3) respectively and mean diastolic blood pressure (DBP) was observed as (89.75 ± 2.66), (96.66 ± 10.6) and (101.92 ± 11.05) respectively. Analysis showed significant differences ($p <0.000$) in both SBP and DBP among the three groups (Table 2).

The observed mean and standard deviation of platelets level was found 365.72 ± 56.2 in control patients, however, 296.7 ± 68.2 and 277 ± 63.4 were found in hypertensive and preeclamptic group respectively. This clearly shows the decline in platelets count in hypertensive and preeclamptic groups. The observations on the study samples with respect to pregnancy weeks revealed that most of the women were in their 3rd trimester. As mean gestational weeks in control and hypertensive groups were 33.97 ± 1.9 and 32.93 ± 3.4, and 35.4 ± 3.8 in the preeclamptic group. High mean platelets volume was observed as 9.57 ± 2.6, 10.9 ± 5.4 and 12.3 ± 3.4 among control, hypertensive and preeclamptic females. Significant differences were observed between control vs hypertensive with a p-value of 0.005, and 0.000 between control vs. preeclampsia. Furthermore, PDW mean values were observed as 13.5 ± 8.9, 14.2 ± 5.6 and 19.2 ± 6.4 in control , hypertensive and preeclamptic females and evident as significantly raised (p-value = 0.004) between control and preeclamptic females, though non-significant (p-value= 0.05) in hypertensive pregnant subjects. Calculation of plateletcrit showed, mean PCT of 0.29 ± 3.9, 0.19 ± 4.8 and 0.12 ± 6.7 in control and hypertensive and in preeclamptic group respectively. Study recorded no significant difference in between hypertensive and normotensive pregnant females (p-value = 0.05), whereas, there was a significant reduction (p-value = 0.004) in the mean values of PCT in control and preeclamptic females (Table 3).

Table 2. Clinical Characteristics of Control, Hypertensive and Preeclamptic females.

Characteristics	Control (n=74)	Hypertensive females (n=90)	Preeclamptic females (n=76)	P-value
Age(years)	24.41 ± 3.29	28.23 ± 4.8	32.31 ± 5.4	0.000***
Pre BMI (kg/m^2)	23.61 ± 2.93	25.4 ± 3.9	30.44 ± 5.3	0.000***
SBP (mm of Hg)	127.73 ± 4.7	148.59 ± 15.1	158.87 ± 16.3	0.000***
DBP (mm of Hg)	89.75 ± 2.66	96.66 ± 10.6	101.92 ± 11.05	0.000***
Gestational age (weeks)	33.97 ± 1.90	32.93 ± 3.4	35.4 ± 3.8	0.000***

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, *** highly significant at $p <0.001$

Table 3. Hematological and biochemical measures of Control, Hypertensive and peeclamptic females.

Indices	Control	Hypertensive	Preeclamptic	P-value Control vs. Hypertensive	P- value Control vs. Preeclampsia
Mean Platelets	365.72± 56.2	296.7 ± 68.2	277 ± 63.4	0.005**	0.000***
MPV	9.57 ± 2.6	10.9 ± 5.4	12.3 ± 3.4	0.044*	0.001*
PCT	0.29 ± 3.9	0.19 ± 4.8	0.12 ± 6.7	0.05	0.004*
PDW	13.5 ± 8.9	14.2 + 5.6	19.2 ± 6.4	0.2	0.001*

PC: Platelet count; MPV: Mean platelet volume; PDW: Platelet distribution width

Table 4. Correlation between mean arterial pressure and platelet indices in hypertensive and preeclamptic pregnant females.

Parameters	Hypertensive r (p-value)	Preeclampsia r (p-value)
Platelet Count	-0.41 (0.02*)	-0.49 (0.002*)
MPV	0.42 (0.05)	0.465 (0.000*)
PDW	0.81 (0.04*)	0.90 (0.001*)
PCT	-0.39 (0.1)	-0.41 (0.001*)

r = Correlation Coefficient, * significantly different at p-value <0.05

Pearson correlation of mean arterial pressures and platelet indices showed significant positive correlation of MPV (r=0.465; p=0.000), PDW (r=0.90; 0.001) and significant negative correlation of mean platelet count (r=-0.49; p=0.002) and PCT (-0.41; p=0.001) in control and preeclamptic females. However, study observed significant strong positive correlation with PDW (r=0.81; p=0.04), non-significant positive correlation with MPV(r=0.42; p=0.05), significant negative correlation with platelet count (r=-0.41; p=0.02) and non-significant with PCT (r=-0.39; p=0.1) as illustrated in Table 4.

DISCUSSION

Pregnancy is one of the physiological phenomena linked with a lot of hemodynamic changes, including coagulation of blood and deficiency of platelets, probably due to increase consumption (Missfelderlobos *et al*., 2002). Hypertension during pregnancy is quite a common problem in pregnancy and affects about 6 to 8% of pregnancy. Uncontrolled hypertension leads to preeclampsia, which significantly increases morbidity and mortality rate among pregnant women and found to be associated with thrombocytopenia. Hypertension and preeclampsia during pregnancy cause serious complication to fetus like intrauterine growth restriction (IUGR), premature delivery, less Apgar score, and still birth.

Clinician nowadays depends more on labs test for the early diagnosis and management of the diseases rather than physical examination. During pregnancy, platelet and other related parameters play a significant role in the indicating severity of hypertension, which then consequently lead to preeclampsia. Increased platelet activation and aberration in coagulation has been associated with hypertension and preeclampsia in many studies. In 2014, Vijay *et al*., pointed out the platelet profile as a reliable source for the indicator of disease. So, this study aims to investigate platelet indices in normotensive, hypertensive and preeclamptic pregnant females and significant parameters were further correlated with blood pressure (Vijay *et al*., 2014).

Present study observed significant thrombocytopenia in hypertensive (p-value = 0.005) and preeclamptic females (p-value = 000) as compared to normotensive females. Several other studies observed the similar findings like Bhavana and his colleagues also noticed significantly reduced (p-value =0.0001) platelets count in preeclamptic

(1.55.500 ± 31.300) and eclamptic females in comparison to normotensive (2.18.400 ± 28.250) females (Bhavana *et al*., 2016). In another study, Amit Gupta and his colleagues (Gupta *et al*., 2018) also reported significantly lower ($p < 0.05$) mean platelets count in mild (197.29 ± 73.65) and severe preeclampsia (145.23 ± 66.91 109 /L) than in normal pregnant females (229.61 ± 73.27). Moreover, Eledo and his other researchers also reported decreased platelet count, elevated prothrombin and activated partial thromboplastin time in hypertensive patients and explained that decline in platelets is associated with endothelial dysfunction as a result of atherosclerosis (Eledo *et al*., 2018).

Brien *et al* also explained the similar mechanism of thrombocytopenia in preeclamptic females, that adherence of platelets to damaged vascular endothelium results in the destruction of platelets (Brien *et al*., 1986). Removal of aggregated platelets is one of the cause for thrombocytopenia often observed in pregnancy-induced hypertension said by Damani in his study (Damani *et al*., 2016).

Present study also demonstrated significantly high mean MPV (p-value= 0.044; 0.001) in both hypertensive and preeclamptic females. However, PDW was significantly high in preeclamptic females (p-value=0.004) and there was no significant difference (p-value=0.05) in hypertensive females when compared with control females. Though MPV is the mode of the measured platelet volume. The platelet volume is noticed to be linked with multiple cytokines which control ploidy of megakaryocyte and platelet number, result in the production of larger platelets (Larsen *et al*., 2014). Usually MPV increase during platelet activation, which indicates an increase diameter of platelets due to change in shape from biconcave to spherical.

PDW is an indicator of volume variability in platelets size and is increased in the presence of platelet anisocytosis (Budak *et al*., 2016). The increase in MPV and PDW in hypertension and preeclampsia apparently indicates increased platelet utilization which would support the evidence that platelet survival time is reduced, which consequently result in enhanced PDW. These results were in agreement with study done by Annam *et al*. and Bhavana *et al*, who also found significantly increased MPV and PDW (p-value<0.05) in preeclamptic groups. Moreover, they also found high PDW (p-value> 0.05) in hypertensive patients as in this study but the result was insignificant in their study (Annam *et al*., 2011; Bhavana *et al*., 2016). This study also indicated the positive correlation of mean arterial pressure with MPV and PWD, and result were comparable with the study done by Ahmed Nooh, who found significant –ve correlation with platelet count ($r = -0.474^{**}$; $p = 0.001$); Mean platelet volume ($r = 0.475^{**}$, $p = 0.000$), and platelet distribution width ($r = 0.902^{**}$; $p = 0.000$) in preeclamptic females. However, none of the study indicated this relationship with hypertensive pregnant females.

Previous finding has already indicated that raised PDW and MPV levels are independent risk factors for myocardial infarction including coronary heart diseases (Alvitigala *et al*., 2018). Since, hypertension and preeclampsia are multifactorial diseases, cause increase platelet aggregation and activation either through systemic inflammation or pulmonary vascular endothelial dysfunction (Zheng *et al*., 2015). From findings of this study, it could be proposed that elevated MPV and PDW might be an indication to recognize the part of platelet activation in the interpretation of the cause of hypertension, and can be used as a prognostic marker of preeclampsia.

CONCLUSION

The present study concludes that platelet count significantly reduced in hypertensive and preeclamptic females, whereas MPV increases significantly in both the groups, however, PDW significantly increase in a preeclamptic female while non-significantly in the hypertensive female. There is a strong correlation of PDW with hypertension and preeclampsia, which not only be used as prognostic marker for preeclampsia but also to assess the severity of disease. Routine and regular testing of platelet indices should be part of the antenatal screening.

DECLARATION OF INTEREST: The study has no conflicts of interest.

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(*Accepted for publication April 2019*)