Platelet indices as predictors of fetal growth restriction in Pre-eclamptic Women

Índices plaquetarios como predictores de la restricción del crecimiento fetal en mujeres preeclámpticas

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Abstract

Background: Preeclampsia PE is one of the mysterious ailments implicating maternal and fetal well-being; fetal growth restriction is a well-known complication. This study links between platelet indices observed in PE deemed mothers and fetal growth restriction in involved fetuses in 34 weeks of pregnancy. **Methodology**: a cross-sectional study enrolled 33 patients randomly collected over 1 year, all with severe PE diagnoses based on the NICE 2019 guideline. Informed consent, history, and physical examination, including mean blood pressure, were gathered. For each participant, blood samples were obtained for platelet indices, including a platelet distribution width and mean platelet volume. An ultrasound and Doppler measurements evaluating the birth weight percentile and amniotic fluid index, Dopplers pulsatility, and resistance index [PI & RI]. **Result**: analysis showed a mean maternal BP of 93.3±9.8 ml/hg, mean platelet volume of 9.4±0.29 µm3, platelet distribution width of 17.7±1.1 percent. The ultrasound showed an amniotic fluid index of 6.34±264 cm and a mean fetal weight centile of 30.81±14.4 kg. As for Dopplers indices; the resistance index & pulsatility index of umbilical arteries UA showed 3.7288±15.9253 and 2.5216±0.3689 respectively. A correlation was found between the platelet distribution width and the pulsatility index by the coefficient of mallows. A platelet distribution width higher than 75% associate odds ratio of 16, and P-value=0.0131 for prediction of growth-retarded baby. In an amniotic fluid volume <5 cm, an odds ratio of 9 and a P-value =0.033 for prediction of growth-retarded baby. **Conclusion**: platelets indices PWD may serve as a good predictor of growth restriction in pre-eclamptic mothers along with amniotic fluid index & PI.

Keywords: Preeclampsia, fetal growth restriction, Platelet indices, platelet distribution width, mean platelet volume.

Resumen

Antecedentes: la preeclampsia PE es una de las misteriosas dolencias que implican el bienestar materno y fetal; la restricción del crecimiento fetal es una complicación bien conocida. Este estudio vincula los índices de plaquetas observados en las madres consideradas con EP y la restricción del crecimiento fetal en los fetos afectados en las 34 semanas de embarazo. **Metodología**: un estudio transversal reclutó a 33 pacientes recolectados aleatoriamente durante 1 año, todos con diagnósticos graves de EP según la guía NICE 2019. Se obtuvieron el consentimiento informado, la historia y el examen físico, incluida la presión arterial media. Para cada participante, se obtuvieron muestras de sangre para los índices de plaquetas, incluido un ancho de distribución de plaquetas y el volumen medio de plaquetas. Una ecografía y mediciones Doppler que evalúan el percentil del peso al nacer y el índice de líquido amniótico, la pulsatilidad Doppler y el índice de resistencia [PI & RI]. **Resultado**: el análisis mostró una PA materna media de 93,3±9,8 ml / hg, volumen medio de plaquetas de 9,4±0,29 µm3, ancho de distribución de plaquetas de 17,7±1,1 por ciento. La ecografía mostró un índice de líquido amniótico de 6,34 ± 264 cm y un percentil de peso fetal medio de 30,81±14,4 kg. En cuanto a los índices Dopplers; el índice de resistencia y el índice de pulsatilidad de las arterias umbilicales UA mostraron 3,7288±15,9253 y 2,5216±0,3689 respectivamente. Se encontró una correlación entre el ancho de distribución de las plaquetas y el índice de pulsatilidad por el coeficiente de malvas. Un ancho de distribución de plaquetas superior al 75% de la razón de posibilidades asociada de 16 y un valor de P=0,0131 para la predicción de un bebé con retraso del crecimiento. En un volumen de líquido amniótico <5 cm, una razón de posibilidades de 9 y un valor de P=0,033 para la predicción de un bebé con retraso del crecimiento. **Conclusión**: los índices de plaquetas PWD pueden servir como un buen predictor de la restricción del crecimiento en madres preeclámpticas junto con el índice de líquido amniótico y el IP.

Palabras clave: Preeclampsia, restricción del crecimiento fetal, índices plaquetarios, ancho de distribución plaquetario, volumen plaquetario medio.

Introduction

Preeclampsia (PE) is a pregnancy-specific syndrome known since the time of Hippocrates 400 BC, defined as new-onset hypertension in previously normotensive pregnant females, with the presence of proteinuria present after the 20th week of gestation. In the absence of proteinuria, new hypertension associated with end-organ dysfunction can be diagnosed[1]. PE encompassing 5 to 10% of all pregnancies[2]. The syndrome is characterized by vasospasm, hemoconcentration, and ischemic changes in the placenta, brain liver, and kidney; these changes are seen in severe PE. Theories have been proposed to unveil PE development. It is primarily a disease of the placenta, secreting a large amount of prostaglandin PG, plasma renin, erythropoietin, aldosterone, and even placental cortisol[1,3]. The affected placenta shows the failure of a secondary wave of trophoblast invasion. Consequently, spiral arteries will retain their muscular wall, continues to respond to vasoconstrictive hormones, and PG rendering placental perfusion leading to PE and endothelial damage[3,4].

Indeed, the severity of hypertension depends on placental renin secretion & PG secreted by diseased placentae like PGF2 alpha. The latter is a strong vasoconstrictor and inducer of platelet aggregation and coagulation cascade. The consumption of the platelet will stimulate the megakaryocytes in the bone marrow to produce more. Newly produced platelets will have a larger size and a wider range volume compared to those in normal pregnant women. Based on that observation, we hypothesized that the observed alteration in platelet parameters will predict fetal growth restriction in affected mothers with PE[4,5]. Fetal growth restriction FGR is defined as the statistical deviation of fetal size from a population-based reference, below the 10 centiles. Affected babies suffer an increased risk of adverse perinatal outcomes. Small-for-gestational-age (SGA) fetus is a majority of constitutionally small but healthy fetuses at lower risk of abnormal outcome[6,7]. There is no gold standard for diagnosing FGR. A recent consent to predict FGR in late pregnancy suggests an emphasis on amniotic fluid index AFI and Doppler indices, pulsatility index PI, and resistance index RI[6].

Materials and methods

A cross-sectional study was conducted at Al -Yarmouk gynecology and obstetrics division: a tertiary center that receives thousands of patients with multiple specialties. Cases were recruited in 1 year from March 2019–2020. With the approval of the ethical community of our department. All participants gave informed consent before embarking on the study. The target population was 33 Iraqi pregnant females in their 34 weeks of a singleton life pregnancy. Gestational age is estimated from the days of the last menstrual cycle and or confirmed by an early ultrasound report within the early pregnancy. We define the study group as pre-eclamptic pregnant ladies diagnosed with PE at the time of the initial visit with a growth-restricted baby.

Inclusion criteria: we invited 34 weeks pregnant women willing to participate in our study after we explain its purpose and procedure. Those were pregnant ladies with a single life growth-restricted babies with PE as a diagnosis upon recruitment into the study.

Exclusion criteria

Pregnant women with gestational age>than 34 weeks or those affected by medical disorders like liver, kidney, endocrine disease like thyroid, diabetes, whether personal or family history, cardiovascular or neuronal disorders, blood dyscrasias. Personal history of chronic hypertension, acute or chronic infections, or autoimmune disease. The history of smoking was also an exclusion.

Preeclampsia is defined based on NICE guidelines for PE; as blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic measured on 2 separate occasions at an interval of 4–6 h apart beyond 20 weeks of pregnancy in a previously normotensive woman and 1+proteinuria in dipstick screening[8,9]. In the absence of proteinuria, either thrombocytopenia (<100,000 /µl), renal impairment (creatinine serum concentrations > 1.1 mg/dL), liver failure (elevated concentrations of hepatic enzymes at the double normal concentrations), pulmonary edema, or cerebral or visual abnormalities have recently been reported in the presence of a diagnosis of PE is confirmed. Only severe cases were invited to our study.

The fetal growth restriction for more than 32 weeks [FGR] is defined by recently enacted expert consensus statement, including[1] ultrasonic estimated fetal weight (EFW) or abdominal circumference (AC) below the 3rd centile using current population charts or EFW or AC less than the 10th centile correlated with UA pulsatility index (PI) >95th centile or a cerebroplacental ratio (CPR) less than the 5th centile[6,10].

A detailed history was taken, vital signs recorded, general examination, and formal obstetrical exam. Out of 65

patients, only 33 participants fulfilled our criteria. Demographic parameters [including maternal systolic, diastolic, and mean blood pressure recording] were recorded for all. Platelets, total protein excreted along with ultrasound [amniotic fluid volume & estimated fetal weight centiles], and Doppler indices [PI & RI] were used for comparing.

Blood pressure was measured manually for all attendees, both systolic, diastolic, and mean arterial pressure. The MAP; was accurately calculated according to a formula; where the lower (diastolic) blood pressure is multiplied by 2 and added to the higher (systolic) blood pressure and the composite amount is then divided by 3[8].

The total protein excreted calculated from random urine samples by the estimation of albumin/creatinine ratio according to the formula PER=Protein Excretion Rate (U, mg/d) Prot = Protein (U, mg/dL) Cr=Creatinine (U, mg/dL)[8,9].

Five milliliters of venous blood were obtained from each participant and checked in EDTA tubes for counting platelet count (PC) and platelet Indices (mean platelet volume (MPV), Platelet Distribution Width (PDW). Using an automated hematology analyzer called DxH520 (Beckman Coulter SnBC010420. Germany)

The ultrasound and Doppler study conducted by B-mode ultrasound research at the labor ward. Color Doppler spectral exam was performed using transabdominal sonography (2.5 Mhz) sample fitted with the GE Voluson E6 system by the same 2D radiologist. For every participant, we recorded the most agreed signs for FGR based on Delphi's consent for diagnoses of late FGR>32 weeks an amniotic fluid index, estimated fetal weight, and centiles along with dopplers indices PI & RI[10].

Continuous variables were expressed as mean, standard deviations, linear regression, and coefficient of correlation was used to assess the correlation between the estimated variable. We used a 3-dimensional mesh figure to visualize the correlation between platelet indices with estimated fetal weight EFW indicating a strong positive correlation between EFW and AFI as an independent variable and PDW, as a dependent variable. The coefficient of mallows was generated to test the strength of the correlation with the least generated value as the most significantly correlated with the cross ponder. The Odd ratio was calculated to predict the risk FGR in mothers with PE based on their PWD and AFI. All correlations made by Minitab version 17, P-value was considered significant at <0.05.

Results

TO 33 pre-eclamptic mothers; we recorded demographic criteria including Mean Maternal BP ml/Hg, platelets MPV µm3, PDW %, Fetal AFI cm, Mean FW centile, Mean FW kg, Mean RI, and PI for umbilical arteries UA. Continuous data were expressed as mean and standard deviations, illustrated in Table 1.

Table 1: The demographic criteria and parameters collected for our study participants expressed as means, standard deviations. BP; blood pressure, MPV; mean platelets volume, PDW; platelets diameter width, AFI; amniotic fluid index, FW fetal weight, RI UA & PI UA resistance index and pulsatility index for umbilical arteries.

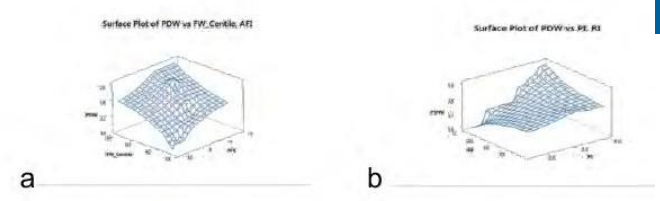
Variable	Mean ± Standard Deviation
Mean Maternal BP ml/Hg	93.3±9.8
Mean Maternal Sys BP ml/Hg	161.7±15.27
Mean Maternal Dias BP ml/Hg	101.5±10.9
MPV µm3	9.4±0.29
PDW %	177±1.1
Fetal AFI cm	6.34±264
Mean FW centile	30.81±14.4
Mean FW kg	1570.03±234.04
Mean RI UA Doppler	3.73±15.93
Mean PI UA Doppler	2.52±0.37

Table 2 illustrates the coefficient of correlation for estimated fetal variables on the Ultrasonic and Doppler exam challenged against platelet indices MPV and PDW. All correlations were statistically meaningful with a p-value of <0.0001, except for RI. The resistance index failed to score a meaningful correlation with an insignificant P-value of 0.69 and 0.80 for MPV and PDW respectively. PWD and MPV were positively correlated with PI and negatively correlated with EFW and AFI. To highlight these correlations; a 3-dimensional figure plot was constructed showing a strong positive correlation between EFW and AFI as an independent variable and PDW as a dependent variable; illustrated in Figure 1 a&b.

Table 2: The correlation between estimated fetal variables on ultrasound and dopplers; estimated fetal weight, amniotic fluid index, and platelet indices MPV, PDW

Variable	Coefficient of Correlation With PDW	*P-value*	Coefficient of Correlation With MPV	*P-value*
Estimated Fetal Weight kg	-0.96	P<0.0001 *	-0.95	P<0.0001*
Amniotic fluid index cm	-0.89	P<0.0001*	-0.90	P<0.0001*
PI Doppler	0.97	P<0.0001*	0.96	P<0.0001*
RI Doppler	0.04	P=0.81	-0.075	P=0.69

Figure 1. a) Illustration of the negative relationship between PDW as an independent variable versus EFW -centile and AFI as the dependent variable; b) Illustration of the positive relationship between platelets diameters width PDW as independent variable versus dopplers pulsitability index PI and resistance index RI as a dependent variable.



In Table 3; the coefficient of mallows CP is given for MPV and PDW versus PI and RI, showing the most significant correlation between PWD versus PI with a CP value of 1.4, as CP is significant for the lowest generated value.

Table 3: The estimated Coefficient of Mallows CP for Both Dopplers indices PI and RI versus platelet indices MPV, PDW.

Variables	Pulsatility Index PI	Resistance Index RI
MPV µm3	4.6	406.6
PDW % statistical significant value	1.4 *	456.4

Table 4; we calculated the Odd ratio for having growth-restricted infants; considering that the 75th centile of PDW is 19, and AFI<5 cm. A fetus whose mother has PDW higher than 75%, will have an Odd ratio of 16, confidence interval of (161.79) to (143.16), and P-value =0.01 for being growth-restricted.

As for mothers whose amniotic fluid index shows <5 cm, an Odd ratio of 9 with a confidence interval of (1.19 to 72.99 and a P-value of =0.03 to have growth-retarded fetus (Table 4).

Table 4: The Odd ratio for having a FGR baby based on maternal PDW and dopplers

Variable	Odds Ratio	95% Confidence interval	P-Value
75% PDW	16	1.79 to 143.16	P=0.0131
AFI< 5cm	9.33	1.19 to 72.99	P=0.033

Discussion

PE is a multiorgan syndrome and a major cause of FGR with hazardous maternal and neonatal morbidity and mortality[10-11]. FGR fetuses do not reach their biological growth potential as a result of a compromised placental activity opposite to small for gestational age fetuses. Besides the adverse long-term health outcomes, as impaired neurological and cognitive development, cardiovascular and endocrine diseases in adulthood 5. From that came to the necessity for predictive measures that assess placental activity at the time of evaluation[3].

One of the modules proposed was platelets PWD and MPV. We hypothesized that it is succinct in the pathophysiology of PE, so we set the objective of predicting FGR through biological and ultrasonic markers for patients with PE. Many researchers have tackled this topic with several promising results, yet others reported a contradictory and confusing result[7,12,13]. Our study was cross-sectional recruiting 33 patients with severe PE in 34 weeks diagnosed with FGR. We correlated platelets PWD, MPV changes measured against ultrasonic markers for FGR; EFW, AFI, PI, and RI.

Özdemirci et al. study enrolled 3 subgroups of severe pre-eclamptic women during pregnancy, depending on the gestational age as early and late preterm birth, <34 weeks, 34–37 weeks, and term (≥37) gestational weeks. At 24 h before birth, their MPV was collected aim to predict and usage (MPV) in evaluating severely pre-eclamptic women, and a comparison made with all subgroups according to the gestational age[7].

Ureyen et al.[9] study retrospectively followed 2 groups of pregnant ladies with and without FGR; it recruited fetuses with a birth weight less than the 10th percentile and subdivided into 3-groups according to the Doppler parameters. It correlated (MPV) with the severity of FGR and neonatal complications. Higher MPV correlated with respiratory distress syndrome in the FGR group[13]. Analyses showed that PWD and MPV are inversely correlated with EFW & AFI and positively correlated with Dopplers PI and RI in severely affected patients with PE; however, Özdemirci et al. reported an association of MPV in evaluating severely pre-eclamptic women these were in contrast to Ureyen et al.[9]. who describe no association between MPV and Doppler parameters in predicting the severity of FGR Nor with the perinatal complications[7,14].

The inverse correlation of PWD and MPV with PI is due to increased blood pressure damaging the endothelial blood vessel. The platelet will haste up to the site to repair. Consuming the latter will activate megacaryocyte in the bone marrow to generate younger but wider and larger platelets. This further added by the vasoconstriction induced by PE; will ultimately increase impudence in blood flow detected as an increase in PI by Doppler study[4,5,15]. The coefficient of mallows proved that MPV was the one intimately correlated to Dopplers PI and not the RI; a results in agreement with those obtained by Freitas et al.[13], Karateke et al[16], Yang et al.[17]. Our study was unable to dem-

onstrate a correlation between MPV and FGR markers; contrary to previous work by Özdemirci et al and Ureyen et al.[7,14]. This can be explained if we knew that MPV; is calculated by high power field microscopy where only a few platelets are examined in a small droplet of blood that will not reflect the true volume distribution in the whole blood that's why it fails to have a statistically meaningful value[18].

The coefficient of correlation revealed a positive association between PWD and PI and a negative correlation between PWD with EFW and AFI. These results corroborate the findings of Abdel et al.[19] who used Doppler and platelet indices to predict the onset and severity of PE, he reported that an increase in MPV and PDW along with a higher mean of PI, RI for the patient was affected by severe PE versus other study subgroups who did not show abnormalities in both ie Doppler and platelet indices.

What is unique for the current study, is the correlation of platelet indices; MPV & PWD with FGR markers in the affected fetus, a true validation of medical surveillance. An important point to address is the standardization of pre-eclampsia research study design. This will hasten our understanding of the etiology of FGR and the development of effective treatment strategies[16]. An interesting paper written by Delphi et al.[10] has set the most important variable to be taken during the sonographic exam of mothers with PE with late-onset FGR [>32 weeks]. The variables defining FGR according to the recently proposed expert consensus statement were Doppler PI, RI, EFW, and amniotic fluid index[20]. For diastolic blood flow, it was considered a marker for early rather than late FGR. Now an important question emerges: can we apply these conclusions into clinical practice? For that purpose, an Odd ratio was constructed. It invokes that mothers with PE with a 75% ratio increment of PDW have 16 times more risk of having an FGR baby. However, mothers with PE who suffer from a decrease of AFI<5 cm are 9 times more prone to have an FGR baby. From this, we reach into the quest of our study; platelet changes promote consequential FGR risk in the affected mother detected by platelet (PWD) and Doppler markers.

Some of the drawbacks of our research include that we did not consider the magnitude of PE, nor did it consider the onset, we were limited to an insignificant window to standardize our criteria, another issue that we were unable to mitigate our patients as our sample architecture is cross-sectional. Another relevant aspect is; we were curious to follow the fetuses in question to see their early and late neonatal outcome and have a glance at the changes we have witnessed, to unravel any complexity in the PE dilemma.

These findings will be of interest to primary health care to be conducted as part of their routine testing. Possibly using bigger study size and design, leading the way for better prediction and earlier interventions to halt the consequences of FGR.

Competing Interest

Theauthors declare that we have no conflict of interest.

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