Clinical research

Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, mean platelet volume and plateletcrit in isolated intrauterine growth restriction and prediction of being born small for gestational age

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Abstract

Introduction: Mean platelet volume (MPV), plateletcrit (PCT), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are accepted as inflammatory markers. In this study, we aimed to investigate the changes occurring in these parameters in pregnancies complicated with intrauterine growth restriction (IUGR) and the role of these parameters in the prediction of being born small for gestational age (SGA).
Material and methods: The study concerned a group of 200 patients with isolated IUGR and a control group of 200 patients without IUGR. Changes in MPV, PCT, NLR, and PLR were analyzed in patients with IUGR and prediction of SGA.
Results: Gravida, parity, gestational week at birth, and birth weight were significantly lower in the IUGR group. The PCT and MPV values were similar in both groups. Lymphocyte count was significantly higher and the PLR and NLR values were significantly lower in the IUGR group. In the ROC curve analysis, the area under the curve (AUC) values for NLR, PLR, and lymphocyte count were statistically significant (p = 0.005, 0.0001, 0.0001, respectively).
Conclusions: The NLR, PLR, and lymphocyte count appear to be useful markers for the prediction of SGA newborns. However, their low sensitivity and specificity values restrict their use in clinical practice.

Key words: small for gestational age, intrauterine growth restriction, mean platelet volume, plateletcrit.

Introduction

Intrauterine growth restriction (IUGR) is a major cause of perinatal morbidity and mortality, affecting approximately 4–7% of pregnancies [1]. The IUGR may result from maternal, fetal, and placental risk factors

that inhibit biologically determined growth potential of the fetus [2].

The primary function of platelets is to achieve hemostasis and prevent hemorrhage together with coagulation factors. In addition, platelets are considered to have a role in the pathophysiology of various diseases including severe infections, systemic inflammatory reaction syndrome, and thrombotic diseases [3, 4]. Platelet indices include plateletcrit (PCT), mean platelet volume (MPV), and platelet distribution width (PDW). These indices have been extensively used as diagnostic and prognostic markers in numerous clinical studies reporting on pre-eclampsia, risk of preterm delivery, gestational diabetes mellitus, abnormal placental invasion, and risk of recurrent miscarriage [5–9]. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inflammatory markers used to predict the diagnosis and severity of pre-eclampsia [5, 10]. To the best of our knowledge, there has been no study in the literature investigating the relationship between these inflammatory parameters (PCT, MPV, PLR, and NLR) and IUGR. Therefore, the aim of this study was to investigate the changes occurring in these parameters in pregnancies complicated with IUGR and the role of these parameters in the prediction of being born small for gestational age (SGA).

Material and methods

This cohort study was conducted in a tertiary hospital between January 2014 and January 2017. The study was approved by the Local Ethics Committee (approval no. 2016/21).

Intrauterine growth restriction (IUGR) was accepted as an estimated fetal weight (EFW) or abdominal circumference (AC) less than the 10th percentile for gestational age either with abnormal Doppler findings (increased umbilical artery pulsatility index above the 95th centile [11], absent/reverse diastolic flow or increased uterine artery resistance) or with an EFW/AC according to the Hadlock formula [12] less than the 3rd percentile despite having normal Doppler findings [13]. The SGA infants were accepted as infants with a birth weight less than the 10th percentile as per the birth weight standards defined for Turkey [14]. Patients with isolated IUGR referred to patients with no concomitant morbidity [15].

The retrospective study included 200 patients aged 18–45 years and at 24–37 weeks of gestation who were hospitalized and followed up at our maternal-fetal medicine unit due to the diagnosis of IUGR. All the patients were normotensive during the follow-up period and no proteinuria was detected in urine samples. Patients were excluded if their IUGR was caused by fetal chromosomal or congenital abnormalities or a maternal medical disease including hypertension, diabetes mellitus, pre-eclampsia or gestational hypertension, gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, pregnancy thrombocytopenia, maternal systemic infection, and multiple pregnancies. Patients using antiplatelet drugs and low-molecular-weight heparin, and patients detected with anemia on hemogram parameters were also excluded from the study. The control group included 200 gestational-age-matched patients with no chronic diseases and no history of drug use except for anti-anemic drugs who underwent routine antenatal follow-up and delivered appropriate gestational age babies in our clinic over the same period as the patient group. No IUGR was detected in the control group during the follow-up period.

The complete blood count parameters in the IUGR group including platelet count, PCT, MPV, lymphocyte count, NLR, and PLR were evaluated based on the initial parameters assessed at hospital admission. In the control group, these parameters were evaluated based on the routine hemogram parameters assessed during routine antenatal follow-ups.

Statistical analysis

Data were evaluated using SPSS 20.0 version for Windows (SPSS Inc., Chicago, IL, USA). The distributions of the continuous variables were tested using the Kolmogorov-Smirnov test. The variables with normal distributions were compared between groups using the independent samples *t*-test and were expressed as mean ± SD. The Mann-Whitney *U* test was used to analyze non-normally distributed variables and was expressed as the median (minimum-maximum or interquartile range).

A ROC curve analysis was performed for statistically significant parameters and the area under the curve (AUC) was calculated. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PLR, NLR and lymphocytes were calculated based on the cut-off point defined on the ROC curve. A p value of < 0.05 was considered significant.

Results

The study included a patient group of 200 women with IUGR and a control group of 200 women without IUGR. Table I presents the demographic and clinical characteristics of each group. Maternal age and gestational week at diagnosis were similar in both groups ($p > 0.05$). Gravida, parity, gestational week at birth, and birth weight were significantly lower in the IUGR group compared to the control group.

Table II presents the PCT, MPV, lymphocyte count, NLR, and PLR values for both groups. The

Table I. Comparison of demographic and clinical characteristics of IUGR and control group

Parameter	IUGR (n = 200)	Control (n = 200)	P-value
Maternal age	26.83 ±5.81	27.83 ±6.1	0.081
Gravidity	1 (1–7)	2 (1–11)	< 0.001
Parity	0 (0–5)	1 (0–8)	< 0.001
Gestational age at admission to hospital [weeks]	32.57 ±3.69	31.99 ±2.97	0.075
Gestational age at delivery [weeks]	34.65 ±3.21	38.23 ±1.30	< 0.001
Neonatal birth weight [g]	1728.33 ±633.72	3210.50 ±380.85	< 0.001

Data expressed as mean ± SD, median (interquartile range). P < 0.05 was considered statistically significant. IUGR – intrauterine growth restriction.

Table II. Comparison of some blood count parameters of IUGR and control group

Parameter	IUGR (n = 200)	Control (n = 200)	P-value
Neutrophil count [× 10^3/mm^3]	8.4 (3.3)	8.3 (3.5)	0.904
Lymphocyte count [× 10^3/mm^3]	2 (0.9)	1.90 (0.6)	< 0.001
NLR	3.92 (1.92)	4.36 (2.21)	0.006
Platelet count [× 10^3/mm^3]	220.78 ±56.46	228.36 ±59.72	0.177
PLR	106.82 (53.05)	122 (60.17)	< 0.001
PCT	0.20 (0.04)	0.20 (0.08)	0.096
MPV	9.18 ±1.77	9.38 ±1.73	0.223

Data expressed as mean ± SD, median (interquartile range). P < 0.05 was considered statistically significant. IUGR – intrauterine growth restriction, NLR – neutrophil-to-lymphocyte ratio, PLR – platelet-to-lymphocyte ratio, PCT – plateletcrit, MPV – mean platelet volume.

PCT and MPV values were similar in both groups. Lymphocyte count was significantly higher and PLR and NLR values were significantly lower in the IUGR group compared to the control group. In the ROC curve analysis, the AUC values for NLR, PLR, and lymphocyte count were 0.578, 0.611 and 0.604 and statistically significant (Figure 1) (p = 0.005, 0.0001, 0.0001, respectively). The best cut-off value for PLR was 135.8 with a sensitivity of 77.5 and a specificity of 38.7. The best cut-off value for NLR was 4.06 with a sensitivity of 54.5 and a specificity of 57.8. The best cut-off value for lymphocytes was 2.1 with a sensitivity of 42 and a specificity of 76.9 (Table III).

Discussion

To our knowledge, this is the first study in the literature to investigate the changes of inflammatory parameters in complete blood count in isolated IUGR cases and prediction of SGA newborns. We considered that these parameters could have a role in the prediction of SGA as in pre-eclampsia. However, unlike in pre-eclampsia, we found that the MPV and PCT values were similar in the patient and control groups but the NLR value was significantly lower and the PLR value was lower in the IUGR group compared to the control group.

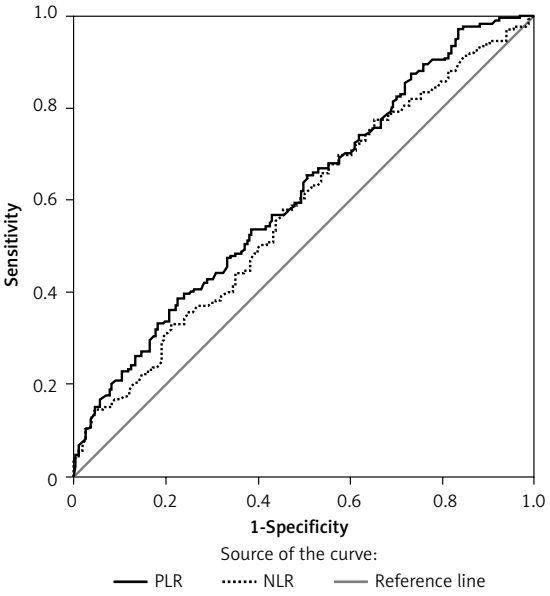

Figure 1. Receiver operating curve (ROC) for NLR and PLR in predicting IUGR

Also, lymphocyte count was significantly higher, but this increase was not clinically important.

Pre-eclampsia and IUGR are two disorders that share a common pathophysiology and are both characterized by placental insufficiency caused by insufficient trophoblastic invasion of the spiral ar-

Table III. ROC analysis of PLR, NLR and lymphocytes for predicting SGA

Parameter	AUC	Cut-off value	*P*-value	Sensitivity	Specificity	PPV	NPV
PLR	0.611	< 135.8	0.0001	77.5	38.7	59.5	59.7
NLR	0.578	< 4	0.005	54.5	57.8	60	52.3
Lymphocyte count [× 10^3/mm^3]	0.604	> 2.1	0.0001	42	76.9	67.8	53.3

AUC – area under curve, PLR – platelet-to-lymphocyte ratio, NLR – neutrophil-to-lymphocyte ratio, PPV – positive predictive value, NPV – negative predictive value.

teries in the placental bed [16]. In normal pregnancy, neutrophilia or mild neutrophil activation can be seen. However, in pre-eclampsia, marked neutrophil activation has been shown by both direct and indirect evidence as a result of placental ischemia [17–19]. Consequently, peripheral blood neutrophils play a key role in the development of endothelial cell dysfunction that characterizes the maternal syndrome of pre-eclampsia [20]. In their study on neutrophil activation, Sabatier *et al.* demonstrated that polymorphonuclear neutrophil activation was present in isolated IUGR and this activation was not different between IUGR and pre-eclampsia groups. The authors also suggested that neutrophil activation is a result of a local or systemic inflammatory response rather than being a primary marker consisting of pathological properties of these diseases [18]. In contrast, the marked neutrophilia seen in pre-eclampsia has not been reported in any patient with isolated IUGR [16]. Furthermore, in their animal study, Gelber *et al.* found that the complement activation at the maternal-fetal interface triggers recruitment of neutrophils and, ultimately, abnormal placentation and fetal death. The authors also suggested that the prevention of this initial inflammatory damage caused by neutrophils might have favorable effects on pregnancy outcomes [21]. The NLR has been shown in numerous studies to be a useful marker in the determination of the presence and severity of pre-eclampsia. These studies have also suggested that NLR is often increased in pre-eclamptic patients and can be a useful marker in clinical practice, particularly for prediction of the severity of pre-eclampsia [5, 10]. Although IUGR shares a common pathology with pre-eclampsia, we found that the neutrophil levels did not increase in the patients with isolated IUGR compared to the controls and the NLR value significantly decreased as a result of increasing lymphocyte count. Immunosuppression occurring in normal pregnancy is not observed in women with IUGR. It has been suggested that increased cellular immunity might play a role in the pathogenesis of IUGR [22]. Also, increase in B lymphocytes in women with IUGR might represent an immunological etiology [23]. The increased lymphocyte count in the present study might be related to fetal immunological rejection that is involved in pathogenesis of IUGR. The NLR values of 4.06 or less can predict SGA with 77.5% sensitivity and 38.7% specificity. Lymphocyte levels of 2.1 or more can predict SGA with 42% sensitivity and 76.9% specificity. In addition, we also found that the PLR value was significantly lower in the IUGR group compared to the control group. The PLR values of 135.8 or less can predict SGA newborns with 54.5% sensitivity and 57.8% specificity. We consider that no neutrophil elevation occurs in isolated IUGR since the physiopathological changes occurring in isolated IUGR are limited to the placenta, contrary to the systemic inflammatory response associated with neutrophil activation that occurs in pre-eclampsia.

In normal pregnancies, an increase in platelet synthesis and changes in platelet volumes are observed. Increase in the platelet indices including PCT and MPV are biomarkers of platelet activation [24]. In pre-eclampsia, uncontrolled intravascular platelet activation and increased platelet destruction occur in the maternal circulation as a result of endothelial damage [25, 26]. Similarly, in IUGR, endothelial damage and microthrombosis occur as a result of placental vascular dysfunction and vascular obstructions, leading to increased platelet destruction and increased platelet activity [27–29]. The literature presents controversial findings regarding the count and size of the platelets in IUGR and/or pre-eclamptic patients [21, 30–33]. Piazze *et al.* found that the MPV levels assessed in the third trimester were significantly higher in pregnancies complicated with pre-eclampsia compared to normal pregnancies [30]. Similarly, Kanat-Pektaş *et al.* reported that the MPV values assessed in the first trimester can predict pre-eclampsia with 66.7% sensitivity and 63.8% specificity and can predict IUGR with 82.4% sensitivity and 60.0% specificity at a cutoff point of 10.5 fl [34]. Conversely, Kashanian *et al.* reported that the MPV values assessed in the first and third trimester in pregnancies complicated with pre-eclampsia are relatively higher, have a lower predictive value, and are not a good predictor of pre-eclampsia [35]. In our study, we found no significant difference in the MPV values between the IUGR and the control group. The PCT refers to the volume occupied

by platelets in the blood as a percentage and is calculated according to the formula PCT = platelet count × MPV/10,000 [36–38]. Karateke *et al.* [39] reported that the PCT value was significantly lower in pregnancies complicated with severe pre-eclampsia compared to the control group, whereas Kirbas *et al.* [5] found no difference in the MPV and PCT values assessed in the first trimester between the pre-eclamptic patients and the controls. Similarly, we found no difference in the PCT values between the patient and control groups. Our findings may indicate that platelet activation does not occur in patients with isolated IUGR.

Our study was limited since it had a retrospective design. Further studies with a prospective design and larger patient series including IUGR patients with pre-eclampsia and evaluation of hemogram parameters assessed in the first trimester of pregnancy are needed.

In conclusion, NLR, PLR, and lymphocyte count appear to be useful markers for the prediction of SGA newborns. However, their low sensitivity and specificity values restrict their use in clinical practice.

Conflict of interest

The authors declare no conflict of interest.

References

1. Gardosi J, Chang A, Kalyan B, et al. Customized antenatal growth charts. Lancet 1992; 339: 283-7.
2. Lausman A, McCarthy FP, Walker M, et al. Screening, diagnosis and management of intrauterine growth restriction. J Obstet Gynaecol Can 2012; 34: 17-28.
3. Lopez E, Bermejo N, Berna Erro-A, et al. Relationship between calcium mobilization and platelet alpha- and delta-granule secretion. A role for TRPC6 in thrombin-evoked delta-granule exocytosis. Arch Biochem Biophys 2015; 585: 75-81.
4. Thachil J. Platelets in inflammatory disorders: a pathophysiological and clinical perspective. Semin Thromb Hemost 2015; 41: 572-581.
5. Kirbas A, Ersoy AO, Daglar K, et al. Prediction of preeclampsia by first trimester combined test and simple blood count parameters. J Clin Diagn Res 2015; 9: QC20-3.
6. Isık H, Aynıoglu O, Sahbaz A, et al. Can plateletcrit, an underestimated platelet parameter, be related with preterm labour? J Obstet Gynaecol 2015; 35: 676-80.
7. Sahbaz A, Cicekler H, Aynioglu O, et al. Comparison of the predictive value of plateletcrit with various other blood parameters in gestational diabetes development. J Obstet Gynaecol 2016; 36: 589-93.
8. Yayla CA, Ozkaya E, Tayyar A, et al. Predictive value of complete blood count parameters for placental invasion anomalies. J Matern Fetal Neonatal Med 2017; in press Doi: 10.1080/14767058.2017.1306051.
9. Aynıoglu O, Isık H, Sahbaz A, et al. Can plateletcrit be a marker for recurrent pregnancy loss? Clin Appl Thromb Hemost 2016; 22: 447-52.
10. Serin S, Avcı F, Ercan O, et al. Is neutrophil/lymphocyte ratio a useful marker to predict the severity of pre-eclampsia? Pregnancy Hypertens 2016; 6: 22-5.
11. Acharya G, Wilsgaard T, Berntsen GK, et al. Reference ranges for serial measurements of umblical artery Doppler indices in the second half of pregnancy. Am J Obstet Gynecol 2005; 192: 937-44.
12. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology 1991; 181: 129-33.
13. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016; 48: 333-9.
14. Şener T, Atar Gürel S, Gürel H, et al. Fetal gelişmenin değerlendirilmesinde kullanılan kendi popülasyonumuza ait doğum ağırlığı standart eğrileri [Birth weight reference ranges of fetal growth in our population]. Zeynep Kamil Tıp Bulteni 1992; 24: 230-6 [Turkish].
15. Chauhan SP, Dahlke JD, Magann EF, et al. Isolated IUGR:a survey of central association of obstetricians Gynecologists (ACOG) members. J Matern Fetal Neonatal Med 2013; 26: 497-502.
16. Khong TY, De Wolf F, Robertson WB, et al. Inadequate maternal vascular to placentation in pregnancies complicated by preeclampsia and by small-for-gestational age infants. BJOG 1986; 93: 1049-59.
17. Rebelo I, Carvalho-Guerra F, Pereira-Leite L, et al. Comparative study of lactoferrin and other blood markers of inflammatory stress between preeclamptic and normal pregnancies. Eur J Obstet Gynecol Reprod Biol 1996; 64: 167-73.
18. Tsukimori K, Maeda H, Ishida K, et al. The superoxide generation of neutrophils in normal and preeclamptic pregnancies. Obstet Gynecol 1993; 81: 536-40.
19. Sabatier F, Bretelle F, d'Ercole C, et al. Neutrophil activation in preeclampsia and isolated intrauterine growth restriction. Am J Obstet Gynecol 2000; 183: 1558-63.
20. von Dadalszen P, Watson RWG, Noorwali F, et al. Maternal neutrophil apoptosis in normal pregnancy, preeclampsia and normotensive intrauterine growth restriction. Am J Obstet Gynecol 1999; 181: 408-14.
21. Gelber SE, Brent E, Redecha P, et al. Prevention of defective placentation and pregnancy loss by blocking innate immune pathways in a syngeneic model of placental insufficiency. J Immunol 2015; 195: 1129-38.
22. Xiong F, Tong Y, You Y, et al. Prospective cohort study about the lymphocyte subpopulations's change and impact on the pregnancy outcome in fetal growth restriction. J Matern Fetal Neonatal Med 2012; 25: 2773-7.
23. Bartha JL, Comino-Delgado R. Lymphocyte subpopulations in intrauterine growth retardation in women with or without previous pregnancies. Eur J Obstet Gynecol Reprod Biol 1999; 82: 23-7.
24. Budak YU, Polat M, Huysal K. The use of platelet indices, plateletcrit, mean platelet volume and platelet distribution width in emergency non-traumatic abdominal surgery: a systematic review. Biochem Med 2016; 26: 178-93.
25. Naljayan MV, Karumanchi SA. New developments in the pathogenesis of preeclampsia. Adv Chronic Kidney Dis 2013; 20: 265-70.
26. Palei AC, Spradley FT, Warrington JP. Pathophysiology of hypertension in pre-eclampsia: a lesson in integrative physiology. Acta Physiol (Oxf) 2013; 208: 224-33.
27. Gagnon R. Placental insufficiency and its consequences. Eur J Obstet Gynecol Reprod Biol 2003; 110: S99-107.
28. Bryan SM, Hindmarsh PC. Normal and abnormal fetal growth. Hor Res 2006; 65 (Suppl. 3): 19-27.
29. Sankaran S, Kyle PM. Aetiology and pathogenesis of IUGR. Best Pract Res Clin Obstet Gynaecol 2009; 23: 765-77.

30. Piazze J, Gioia S, Maranghi L, et al. Mean platelet and red blood cell volume measurements to estimate the severity of hypertension in pregnancy. J Perinat Med 2006; 34: 246-7.
31. Ceyhan T, Beyan C, Baser I, et al. The effect of pre-eclampsia on complete blood count, platelet count and mean platelet volume. Ann Hematol 2006; 85: 320-2.
32. Altinbas S, Toğrul C, Orhan A, et al. Increased MPV is not a significant predictor for preeclampsia during pregnancy. J Clin Lab Anal 2012; 26: 403-6.
33. Jaremo P, Lindahl TL, Lennmarken C, et al. The use of platelet density and volume measurements to estimate the severity of preeclampsia. Eur J Clin Invest 2000; 30: 1113-8.
34. Kanat-Pektas M, Yesildager U, Tuncer N, et al. Could mean platelet volume in late first trimester of pregnancy predict intrauterine growth restriction and pre-eclampsia? J Obstet Gynaecol Res 2014; 40: 1840-5.
35. Kashanian M, Hajjaran M, Khatami E, et al. Evaluation of the value of the first and third trimester maternal mean platelet volume (MPV) for prediction of preeclampsia. Pregnancy Hypertens 2013; 3: 222-6.
36. Chandrashekar V. Plateletcrit as a screening tool for detection of platelet quantitative disorders. J Hematol 2013; 2: 22-6.
37. Giacomini A, Legovini P, Gessoni G, et al. Platelet count and parameters determined by the BAYER ADVIA 120 in reference subjects and patients. Clin Lab Haematol 2001; 23: 181-6.
38. Adibi P, Faghih Imani E, Talaei M, et al. Population-based platelet reference values for an Iranian population. Int J Lab Hematol 2007; 29: 195-9.
39. Karateke A, Kurt RK, Baloglu A, et al. Relation of platelet distribution width (PDW) and platelet crit (PCT) to pre-eclampsia. Ginekol Pol 2015; 86: 372-5.