Original Article

موضوع أُصيل

EVALUATION OF PLATELETS COUNT, NEUTROPHIL TO LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO IN SYRIAN PREGNANT WOMEN WITH PREECLAMPSIA

تقييم تعداد الصفيحات، نسبة العدلات للمفاويات ونسبة الصفيحات للمفاويات

في حالات ما قبل الارتعاج عند النساء الحوامل في سورية

Faihaa Hkima Abou Fakher, MD

د. فيحاء حكيمة أبو فخر

ملخص البحث

هدف البحث: تقييم تعداد الصفيحات، نسبة العدلات للمفاويات NLR ونسبة الصفيحات للمفاويات PLR لدى الحوامل المصابات بحالة ما قبل الارتعاج مقارنةً مع النساء الحوامل المصابات بارتفاع ضغط الدم والنساء الحوامل السليمات، وذلك لتقييم وجود علاقة بين هذه الواسمات وحالة ما قبل الارتعاج.

طرق البحث: تم تقييم 49 من النساء الحوامل بحالة ما قبل الارتعاج، بالإضافة إلى 22 امرأة حامل مع ارتفاع ضغط الدم و50 حامل سليمة من المراجعات لمستشفى التوليد وأمراض النساء في دمشق. تمت مقارنة المجموعات من حيث الخصائص السريرية والواسمات الدموية.

النتائج: لوحظ انخفاض كبير في تعداد الصفيحات (182.29±64.97 ألف/ملم³، قيمة p=0.01) عند مريضات حالة ما قبل الارتعاج بالمقارنة مع مجموعة الشاهد (215.86±66.50 ألف/ملم³)، بينما لم يلاحظ فارق بين هذه المجموعة الأخيرة ومجموعة النساء بحالة ارتفاع ضغط الدم (209.09±51.13 ألف/ملم³، قيمة p=0.67). كان تعداد الكريات البيضاء أعلى بكثير عند النساء الحوامل بحالة ما قبل الارتعاج (p<0.01)، في حين لم يلاحظ وجود فارق هام عند النساء الحوامل بحالة ارتفاع ضغط الدم (p=0.31) مقارنةً مع مجموعة الشاهد. لم يلاحظ فارق هام في تعداد العدلات، اللمفاويات، قيمة NLR، PLR بين مجموعات الدراسة، على الرغم من وجود ارتفاع في تعداد الكريات البيضاء لدى الحوامل بحالة ما قبل الارتعاج.

الاستنتاجات: لم يلاحظ اختلاف في قيم NLR و PLR بين المجموعات المعتمدة في الدراسة، في حين انخفض تعداد الصفيحات لدى المريضات بحالة ما قبل الارتعاج مقارنة بالحوامل السليمات. قد يشكل تعداد الصفيحات الدموية واسماً مناسباً في رصد الحوامل اللواتي يعانين من حالة ما قبل الارتعاج.

ABSTRACT

Objective: *To assess the platelets count, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with preeclampsia (PE), compared with pregnant women with hypertension and normal pregnant women in order to evaluate the association between preeclampsia and these parameters.*

Methods: *Forty nine pregnant women with preeclampsia, 22 pregnant women with hypertension and 50 healthy controls from an Obstetrics and Gynecology hospital in Damascus were prospectively*

*Faihaa Hkima Abou Fakher, MD, Professor of Immunology (PhD), Department of Laboratory Medicine, Faculty of Medicine, Damascus University, Damascus, Syria. Faihaa_aboufakher@yahoo.fr

evaluated. The groups were compared in terms of clinical characteristics and hematological parameters.

Results: Platelets count decreased significantly (182.29±64.97x10⁹/L, p=0.01) in patients with preeclampsia as compared to the control group (215.86±66.50 x10⁹/L), while no difference of platelets count was observed between the control group and pregnant women with hypertension (209.09±51.13 x10⁹/L, p=0.67). WBC count was significantly higher in pregnant women with preeclampsia (p<0.01), while no significant difference was observed in women with hypertension (p=0.31) compared with the healthy pregnant women. No significant difference of the value of neutrophils, lymphocytes, NLR, and PLR was seen, whereas WBC count was high in women with preeclampsia.

Conclusions: NLR and PLR were not different between groups, while platelets count decreased in preeclampsia compared to normal pregnancy. Platelets count may be a suitable marker in suspecting subjects with preeclampsia.

INTRODUCTION

Numerous etiological factors have been proposed to explain the pathological changes in preeclampsia (PE), but the exact underlying pathology is not yet completely understood. The alteration in coagulation, vascular endothelial function and the altered immune response causing excessive maternal inflammation, have been among the proposed mechanisms.[1,2]

Many different markers of inflammation, such as C-reactive protein, erythrocyte sedimentation rate (ESR), interferons and interleukin-6, have been used to assess inflammation. Recently, platelets (PLT), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) provoked significant interest as systemic inflammatory response markers in various clinical circumstances. PLT form aggregates with leukocytes and form bridges between leukocytes and endothelium. Through their interaction, platelets are an important coordinator of inflammation as well as both innate and adaptive immune response.[3]

NLR and PLR have recently been investigated as new prognostic indicators for several malignancies.[4,5] Moreover, studies from recent years have shown them to be associated with morbidity and mortality in many chronic diseases, such as heart failure. NLR and PLR are also predictors of heart failure,[6] acute coronary syndrome[7] and hypertension.[8-10] Inflammation may be a hidden factor that explains the correlation between the two ratios and these diseases. However; to date, data about their association with inflammation are still insufficient for patients with preeclampsia. Therefore, this study aims to evaluate some hematological markers as PLT, NLR, and PLR in pregnant women with preeclampsia.

METHODS

This case-control study was carried out at Obstetrics and Gynecology hospital in Damascus, between November 2014 to December 2016. Ethical approvals of the study were obtained from the local committees of the hospital. Exclusion criteria were as follows: pregnant with chronic hypertension, secondary hypertension, infectious diseases diagnosed during pregnancy, active labor, premature rupture of membrane, systemic inflammatory disease, diabetes mellitus and renal or hepatic dysfunction. Written informed consent was taken from all participants.

The diagnosis of preeclampsia was made in accordance with the American College of Obstetrics and Gynecology criteria.[11] Cases were divided into severe preeclampsia defined as a blood pressure of at least 160/110 mmHg on two occasions each 6 hours apart, accompanied by proteinuria of at least 3+ on dip stick testing. Mild preeclampsia is defined as a blood pressure of at least 140/90 mmHg on two occasions each 6 hours apart accompanied by proteinuria of at least 1+ on dip stick testing.

The second group of patients was pregnant women with hypertension during pregnancy without proteinuria. The control group included healthy pregnant women with no known medical or obstetric complications. A questionnaire was used to gather data from each woman in cases and control groups. The women's age, parity, and gestational age were recorded. Weight and height

were measured, and body mass index (BMI) was calculated. All participants underwent blood collection via antecubital vein puncture. Hematological parameters were measured by using an automated hematology analyzer (Medonic, Sweed).

Statistical analysis: All statistical analyses were performed using GraphPad prism software. Descriptive statistics were represented as means ± standard deviations (SD). A student's t test was used to compare the pregnant women with hypertension or preeclampsia with the control group, and to compare pregnant women with hypertension with pregnant women with preeclampsia. Severe and mild preeclampsia subgroups were compared as well. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of population study: Table 1 depicts the characteristics of pregnant women with preeclampsia compared to the hypertension and healthy pregnant women with normotensive pressure as control group. A total of 121 pregnant women were included in the study with age ranged between 16-42 years. Forty nine women with preeclampsia (mean age: 27.57±8.04 years), 22 pregnant women with hypertension (mean age: 29.25±6.79 years) and 50 healthy pregnant women (mean age: 25.64±7.05 years). No significant difference between the groups in mean age and parity. BMI was significantly higher in preeclampsia and hypertension groups comparing with the control group, (p=0.001 and 0.007, respectively).

Mean value of WBCs was significantly different (p=0.01) between patients with PE and control group, while there was no difference concerning women with hypertension (p=0.31) comparing with normotensive pregnant women. Despite this increase of WBCs in women with PE, the absolute count of neutrophils or lymphocytes was not significantly different. Calculating NLR showed no significant difference too.

Mean platelets count of PE group was (182.29±64.97 x10⁹/L), while in control group it was (215.86±66.50 x10⁹/L), which yielded to a statistically significant

difference (p=0.01). No difference was observed in hypertension group compared with control group (p=0.67). PLR was not different between the control group and the both other groups. The comparison between hypertension and PE group showed no differences as well.

It is observed that the mean duration of pregnancy was significantly higher in control group (38.78±1.97 weeks), which means most of them were full term deliveries, whereas the duration of pregnancy was reduced in patients with hypertension (36.46±3.80 weeks, p=0.001), and in pregnant women with preeclampsia (34.59±4.13 weeks, p=0.0001), thereby suggesting early delivery as prompt treatment of the disease and preventing complications.

The average birth weight of patients in control group was (2976.47±567.31 g), and it revealed no statistically significant difference when tested against hypertension group (2741.18±787.45 g, p=0.16), however; in preeclampsia group it was highly significant (2342.5±1030.03 g, p=0.002), Table 1.

Comparison between mild and severe preeclampsia subgroups: The participants of our study consisted of 24 women in mild preeclampsia group (26.38±7.35 years), and 25 in severe preeclampsia group (28.72±8.64 years), as showed in Table 2.

There was no significant difference between the two groups in mean age, parity, BMI and gestational age at delivery. Insignificant difference (p>0.05) was discovered in the number of WBC, neutrophils, lymphocytes, platelets, NLR and PLR.

DISCUSSION

Preeclampsia is the most important cause of maternal death and perinatal mortality. Many theories suggested that abnormal placentation is one of the initial events in the pathogenesis of preeclampsia. Altered immune response, excessive maternal inflammation, and immune maladaptation are also among the proposed etiological factors. Sacks et al, demonstrated a massive influx of pro-inflammatory cells in the first trimester as early as 4 weeks of gestation.[12]

	CT	HT	PE	CT/HT	CT/PE	HT/PE
Number	50	22	49			
	Mean±SD	Mean±SD	Mean±SD	p-value	p-value	p-value
Age (years)	25.64±7.05	29.25±6.79	27.57±8.04	0.05	0.21	0.35
Multiparty	2.56±1.86	3.01±2.22	2.86±2.01	0.37	0.44	0.78
Gestational age at delivery (weeks)	38.78±1.97	36.46±3.80	34.59±4.13	0.001	0.0001	0.07
Birth weight (g)	2976.47±567.31	2741.18±787.45	2342.5±1030.03	0.16	0.002	0.11
BMI (kg/m^2)	27.55±3.77	31.64±5.84	30.36±4.66	0.007	0.001	0.33
WBCs (x10^9/l)	11960±2476.91	12740.91±3973.9	13681.63±4137.62	0.31	0.01	0.37
Neutrophils (x10^9/l)	9620±2440.79	9904.55±3933.19	10881.83±4072	0.71	0.06	0.35
Lymphocytes (x10^9/l)	1854±972.17	2377.27±1289.49	1944.90±922.42	0.06	0.63	0.11
Platelets (x10^9/l)	215.86±66.50	209.09±51.13	182.29.±64.97	0.67	0.01	0.09
NLR	6.44±3.67	5.03±3.01	6.78±3.95	0.18	0.65	0.06
PLR	134.09±67.43	106.71±52.86	109.94±54.29	0.09	0.05	0.93

SD: Standard deviation, CT: Control group, PE: Preeclampsia group, HT: Hypertension group, WBCs: White Blood Cells, NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, p-value is significant if <0.05.

Table 1. Characteristics of population study and their hematological markers.

	Mild preeclampsia	Severe preeclampsia	p-value
Number	24	25	
	Mean±SD	Mean±SD	
Age (years)	26.38±7.35	28.72±8.64	0.3
Gestational age at delivery (weeks)	35.55±4.08	33.66±4.03	0.1
BMI (kg/m^2)	128.95±4.06	130.85±4.70	0.1
WBCs (x10^9/l)	13150±4452.7	14192±3832.09	0.38
Neutrophils (x10^9/l)	10221±4190	11516±3934.64	0.27
Lymphocytes (x10^9/l)	2133.33±1090.54	1764±701.71	0.16
Platelets (x10^9/l)	180±52.7	182.29.±64.97	0.89
NLR	5.85±3.43	7.66±4.28	0.11
PLR	103.63±56.13	112.07±47.19	0.57

SD: Standard deviation, WBC: white blood cells, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelets to Lymphocyte Ratio, p-value is significant if <0.05.

Table 2. Comparison between mild and severe preeclampsia.

The initiation of preeclampsia might be predicted by assessing the values of platelets count, NLR and PLR, which are systemic inflammatory markers. The present study found that mean platelets count in the pregnant women with preeclampsia was lower than normal group (p=0.01). This result was consistent with several studies,[13-19] however; a study of Tzur et al, reported high first-trimester platelet counts in preeclampsia patients.[20]

This decrease of platelets count was not correlated with the severity of preeclampsia. No difference was observed between mild and severe preeclampsia

patients (p=0.89), contrary to other studies that found a relationship between platelets count and their indices and severity of preeclampsia.[16]

High NLR and PLR have been found to be associated with increased inflammation. These markers were studied as new predictors for various illnesses, and high PLR value is used as a marker for long term mortality. The results of this study on preeclampsia showed that NLR and PLR level were comparable between PE and normal pregnant women, and between mild and severe PE. Consistent with this study, two recent studies reported that NLR and PLR were not significantly different between preeclampsia and control groups.[21,22] That contradicts with what Gezer C et al, showed when they mentioned that high NLR and PLR during the first trimester are independent predictors of susceptible preeclampsia.[23] Furthermore, Yavuzcan A et al, showed that NLR alone had a statistically significant difference between preeclampsia and healthy pregnant women.[24]

CONCLUSIONS

In the present study, patients with PE are more likely to have significant decrease in platelets count. Thus, it is suggested that the pregnant women with low platelets count during the first trimester of pregnancy should be monitored closely for signs of preeclampsia, such as hypertension and proteinuria. PLR and NLR were found to be not associated with PE. The relation of PLR and NLR with the preeclampsia is contradictory in medical literature, that is why further research is required to elucidate their relationship to preeclampsia.

ACKNOWLEDGMENTS

REFERENCES

1. Pijnenborg R, Bland JM, Robertson WB. Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. Placenta 1983;4:397-413.
2. Lyall F, Greer IA. Pre-eclampsia: a multifaceted vascular disorder of pregnancy. J Hypertens 1994;12:1339-45.
3. Thomas MR, Storey RF. The role platelets in inflammation. Thromb Haemost 2015;114(3):449-58.
4. Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23(7):1204-12.
5. Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Nat Cancer Inst 2014;106(6).
6. Durmus E, Kivrak T, Gerin F, et al. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are predictors of heart failure. Arq Bras Cardiol 2015;105(6):606-13.
7. Tamhane UU, Aneja S, Montgomery D, et al. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol 2008;102: 653-7.
8. Balta S, Ozturk C, Yildirim A, et al. The relation between neutrophil-lymphocyte ratio and hypertension. Am J Hypertens 2015;28(11):1386.
9. Belen E, Sungur A, Sungur M, et al. Increased neutrophil to lymphocyte ratio in patients with resistant hypertension. J Clin Hypertens 2015;17.
10. Liu X, Zhang Q, Wu H, et al. Blood neutrophil to lymphocyte ratio as a predictor of hypertension. Am J Hypertens 2015;28(11):1339-46.
11. American College of Obstetricians and Gynecologists: ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Int J Gynaecol Obstet 2002;77:67-75.
12. Sacks GP, Seyani L, Lavery S, et al. Maternal C-reactive protein levels are raised at 4 weeks of gestation. Hum Reprod 2004;19:1025-30.
13. AlSheeha MA, Alaboudi RS, Alghasham MA, et al. Platelets count and platelet indices in women with preeclampsia. Vasc Health Risk Manag 2016;12:477-80.
14. Biva RM, Debatosh P, Tuhin S, et al. Assessment of

platelet count and platelet indices in pre-eclampsia and eclampsia. *Am J Innov Res Appl Sci* 2015;1(3):80-4.

15. Annam V, Srinivasa K, Yatnatti SK, et al. *Evaluation of platelet indices and platelet counts and their significance in preeclampsia and eclampsia. Int J Biol Med Res* 2011;2(1):425-8.

16. Wael A, Ezzat KA, Moharam AH, et al. *Evaluation of platelet indices and their significance in Preeclampsia. Nature Sci* 2014;12(3).

17. Monteiro G, Subbalakshmi NK, Sheila RP. *Relevance of measurement of hematological parameters in subjects with pregnancy induced hypertension. NUJHS* 2014;4.

18. Biva RM, Debatosh P, Tuhin S, et al. *Assessment of platelet count and platelet indices in preeclampsia and eclampsia. Am J Innov Res App Sci* 2014:80-4.

19. Vinodhini R, Kumari L. *Evaluation of platelet count as a prognostic index in eclampsia and preeclampsia. Int J Modn Res Revs* 2014;(2):447-52.

20.   Tzur T, Sheiner E. *Is there an association between platelet count during the first trimester and preeclampsia or other obstetric complications later in pregnancy? Hypertens Preg* 2013;32(1):74-82.

21.   Yücel B, Ustun B. *Pregnancy hypertension. Int J Women Cardiovasc Health* 2017;7:29-32.

22. Toptasa M, Asikb H, Kalyoncuogluc M, et al. *Are neutrophil/lymphocyte ratio and platelet/lymphocyte ratio predictors for severity of preeclampsia? J Clin Gynecol Obstet* 2016;5(1):27-31.

23. Gezer C, Ekin A, Ertas IE, et al. *High first-trimester neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are indicators for early diagnosis of preeclampsia. Ginekol Pol* 2016;87: 431-5.

24. Yavuzcan A, Cağlar M, Ustün Y, et al. *Mean platelets volume, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in severe preeclampsia. Ginekol Pol* 2014;85(3):197-203.