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Neutrophil-Lymphocyte Ratio as a Screening Test for Preeclampsia in the First and Early-Third Trimesters of Pregnancy: A Cohort Study

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Abstract

Background: Preeclampsia (PEC), affecting 5-10% of all pregnancies, is a multisystem disease diagnosed by hypertension (HTN) and protein in the urine or multi-organ problems without signs of proteinuria occurring after 20 weeks of gestation. PEC is the most common cause of maternal death and can lead to premature delivery. The current study aimed to investigate the accuracy of neutrophil-lymphocyte ratio (NLR) for predicting PEC in the first and early-third trimesters of pregnancy in a normal population in the south of Iran. **Materials and Methods:** A large-scale cohort study was performed from early pregnancy onward during November 2018-2019 in a normal population from Fars province, Southwest Iran. Four hundred forty-nine pregnant women were followed prospectively, and normal blood pressure (normotensive), gestational HTN, and PEC groups were compared in terms of white blood cells (WBC) count, neutrophil, lymphocyte, and NLR. **Results:** The serum levels of WBC count, neutrophil, and NLR significantly increased from the first to the early-third trimesters of pregnancy ($P<0.05$); however, lymphocytes decreased ($P<0.05$). The NLR cut-off points for predicting PEC were 2.79 (sensitivity=86.7% and specificity=92.6%) in the first and 3.2 (sensitivity=90.5% and specificity=79.4%) in the early-third trimesters. **Conclusion:** Our findings revealed that NLR could be an accurate predictive factor for PEC in the first and early-third trimesters of pregnancies; however, more studies are needed to investigate the immunomodulatory drugs for the prevention of PEC.

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Keywords: Neutrophils; Lymphocytes; Preeclampsia; Gestation; Hypertension

Introduction

Preeclampsia (PEC) is a multisystem disease diagnosed by hypertension (HTN) and proteinuria or multi-organ problems without signs of proteinuria occurring after 20 weeks of gestation [1]. PEC affects approximately 5 to 10% of all pregnancies [2]. It is one of the three main causes of mortality and morbidity during pregnancy besides infection

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and bleeding [3]. Also, PEC is the most common cause of maternal death and can lead to premature delivery [2]. Hence, PEC has been considered an economic burden on the health system [4].

Although the definitive mechanism of PEC is not clear, two theories are considered. Abnormal placentation and vascular endothelial damage by oxidative stress cause endothelial dysfunction resulting in clinical manifestations of PEC [5]. Another mechanism of PEC is genetic and immunological factors [6-8]. Among the cited factors, maternal immunologic intolerance is among the full investigations.

Successful semi-allograft reaction in normal pregnancy and balance between the immune system and inflammatory responses are crucial for maintaining the pregnancy. Normal pregnancy and PEC are inflammatory states of the body in which normal pregnancy controls the inflammatory response, but PEC has an excessive systemic inflammatory response (SIR) [9].

Lipids secreted from the placenta cause activation in the leukocyte classes in the intervillous space. The leukocyte re-enters the maternal systemic circulation, resulting in vascular dysfunction in women with PEC [10]. Some hematological parameters derived from the peripheral blood cells are known as SIR markers, including the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), red cell distribution width (RDW), and mean platelet volume (MPV) [10]. To lower adverse pregnancy outcomes, timely diagnosis of high-risk women prone to developing PEC is crucial. Nowadays, the healthcare system focuses on the prevention of PEC through modifications in lifestyle, nutritional supplementation, and pharmacological therapy [11]. In the second trimester of pregnancy, the maternal serum level of angiogenic and antiangiogenic factors besides abnormal uterine artery Doppler velocimetry provide a moderate to high predictive value to determine the early-onset PEC [12]. However, a low-cost screening test that is available and easy to use is necessary.

The complete blood count (CBC), including the neutrophil, lymphocyte, and NLR could have a diagnostic value for predicting PEC [13]. Most studies have reported significant predictive values of NLR for PEC in non-prospective designs [13-19]. Though studies investigated the diagnostic value of NLR in predicting PEC, further large-scale prospective studies are required to validate its accuracy [20, 21]. Since the neutrophil, lymphocyte, and NLR are relatively inexpensive and available tests compared to other predictive tests, timely prediction, diagnosis, and management of PEC are important to lower adverse pregnancy outcomes. Hence, in a large-scale prospective cohort study, this study aimed to evaluate the predictive value of NLR for the detection of the PEC in the first and early-third trimesters of pregnancy.

Materials and Methods

Study Population and Design

A cohort study was performed on 449 healthy pregnant women from early pregnancy onward. All participants were recruited from dual centers affiliated with Shiraz University of Medical Science (SUMS) as the referral center in the south of Iran from November 2018 to November 2019.

The inclusion criteria were singleton pregnancy up to 30 weeks of gestational age with the live fetus, clear gestational age, and natural conception. The exclusion criteria were diabetes mellitus, heart failures, liver disorders, renal failures, chromosomal abnormalities, inherited metabolic diseases, thyroid disease, chronic hypertensive disorders, any disease that directly affects the WBC count (such as all rheumatologic diseases, vascular disorders, infections, and immunosuppression conditions), drug-induced immunosuppression, malignancies, and active allergic reaction [22].

All the participants were followed to the end of the pregnancy, and their blood pressures were checked during each visit. At the end of pregnancy, they were divided into two groups; patients with hypertensive pregnancy disorders (HPD), including gestational HTN and PEC, and patients without HTN (normotensive). Cases of PEC were considered severe if they had at least one of the following symptoms:

a systolic blood pressure ≥160 mmHg, a diastolic blood pressure ≥110 mmHg, proteinuria of 5 g/24 hours, proteinuria of 3+ or more, oliguria, pulmonary edema, or convulsions/eclampsia. All other cases were considered mild [23].

Sample Size Calculation

Considering α=0.05 a d the prevalence of PEC=0.05, we used the Buderer formula for diagnostic tests:

$$\text{Sample size}: n \geq \frac{z_{\frac{\alpha}{2}}^2 * sensitivity * (1 - sensitivity)}{d^2 * prevalence}$$

Where α=0.05, $z_{\frac{\alpha}{2}} = 1.96$

Using the information of NLR sensitivity equal to 73.4% from the previous article [24], a minimum of 400 participants were needed.

CBC Analysis

K2-EDTA anticoagulated venous blood samples were taken after eight-hour overnight fasting from all the participants at the first (0-14 gestational weeks) and early-third trimesters (24-30 gestational weeks) of pregnancy to evaluate the levels of the WBC, neutrophil, lymphocyte, and NLR using the Sysmex XS-800i analyzer (Sysmex Corporation, Japan).

Follow-up and Data Collections

All the participants completed a brief checklist about the maternal age, height, weight, parity, gravida, history of abortion, and gestational age at the time of entering the study. All women were followed-up during the whole pregnancy period. Also, one visit was done at weeks 6-12 postpartum to check the blood pressure. Any sign of HTN and PEC was evaluated precisely. Patients with rapid weight gain, edema, headache, blurred vision, epigastric pain, and unexplained nausea and/or vomiting were referred to the primatologists for further evaluation to detect any case of gestational HTN and PEC.

Ethical Considerations

This study was approved by the Ethics Committee of SUMS (approval code: IR.SUMS.MED.REC.1397.446). Consent forms were taken from all participants, the process of the work was completely anonymous, and the results were reported to them.

Statistical Analysis

Median±interquartile range (IQR=Q3-Q1) was used to describe variables quantitatively, and frequency (proportional frequency) was used to describe variables qualitatively. Kolmogorov-Smirnov normality, Chi-square, Fisher Exact, Mann-Whitney U, Wilcoxon rank, and Generalized Linear Models, as well as receiver operating characteristic (ROC) analysis with Uden index=sensitivity+specificity-1 (to determine cut-offs), were used. In addition, the positive predictive value (PPV) and negative predictive value (NPV) were calculated. All the analyses were done by SPSS Statistics for Windows (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA). The significance level was considered at P=0.05

Results

Maternal features of pregnant women are presented in Table-1. In this study, 449 pregnant women were followed prospectively; of them, 408 (90.9%), 11 (2.4%), and 30 (6.7%) women were normotensive, gestational HTN, and PEC, respectively. Also, 70% and 30% of the PEC women had mild and severe PEC, respectively. Age, body mass index (BMI), and parity were not significantly different among normotensive, gestational HTN, and PEC groups (P>0.05, Table-1). Also, there were no significant differences between mild and severe PEC groups regarding age, BMI, and parity (P>0.05, Table-1).

Regarding Table-2, the WBC count, neutrophil, and NLR of all groups significantly increased from the first to the early-third trimesters (P<0.001); however, the lymphocyte significantly decreased (P<0.001). Also, there were no significant differences in terms of WBC count, neutrophil, lymphocyte, and NLR between normotensive and gestational HTN groups in both the first and early-third trimesters (P>0.05).

As mentioned in Table-3, the neutrophil, WBC, and NLR were significantly higher

Table 1. Maternal Features of Pregnant Women

Variables		Total (n=449)	HPD			P-value	PEC groups		P-value
			Normotensive (n=408)	Gestational HTN (n=11)	PEC (n=30)		Mild (n=21)	Severe (n=9)	
Age, y	16-24	78 (17.4)	73 (17.9)	0 (0)	5 (16.7)	0.9	4 (19.05)	1 (11.1)	0.86
	25-34	269 (59.9)	243 (59.6)	7 (63.6)	19 (63.3)		13 (61.9)	6 (66.7)	
	35	102 (22.7)	92 (22.5)	4 (36.4)	6 (20)		4 (19.05)	2 (22.2)	
BMI	≤18.5	17 (3.8)	17 (4.2)	0 (0)	0 (0)	0.86	0 (0)	0 (0)	0.3
	18.5-24.9	93 (20.7)	85 (20.8)	0 (0)	8 (26.7)		4 (19)	4 (44.4)	
	≥25	339 (75.5)	306 (75)	11 (100)	22 (73.3)		17 (81)	5 (55.6)	
Parity	Null	192 (42.8)	177 (43.4)	3 (27.3)	12 (40)	0.24	9 (42.9)	3 (33.3)	0.62
	Multi	257 (57.2)	231 (56.6)	8 (72.7)	18 (60)		12 (57.1)	6 (66.7)	

HPD: Hypertension pregnancy disorder; **BMI**: Body mass index; **PEC**: Preeclampsia
*Data presented as n (%)

Table 2. White Blood Cells, Neutrophil, Lymphocyte, and Neutrophil-Lymphocyte Ratios in the First and Early-Third Trimesters of Pregnancy among 449 Pregnant Women

Parameters		Groups (Median±IQR)			
		Normotensive	Gestational HTN	Mild PEC	Sever PEC
First trimester	WBC	7500±1900	7000±900	*8100±1250	7500±2010
	Neutrophil (%)	64±6	69±4	$^{*\&}$71±2	$^{*\&}$71±2
	Lymphocyte (%)	29±6	28±7	$^{*\&}$24±3	$^{*\&}$23±2
	NLR	2.21±0.62	2.3±0.91	$^{*\&}$2.96±0.4	$^{*\&}$3.13±0.25
Early-third trimester	WBC	†9200±1500	†70±4	$^{*\&\dagger}$9900±3150	*†9700±2600
	Neutrophil (%)	†69±5	†24±6	$^{*\&\dagger}$76±4	$^{*\&\dagger}$75±2
	Lymphocyte (%)	†25±5	†3.12±0. 94	$^{*\&\dagger}$20±4.5	$^{*\&\dagger}$18±5
	NLR	†2.77±0.69	†70±4	$^{*\&\dagger}$3.8±1.14	$^{*\&\dagger}$4.1±1

WBC: White blood cells; **NLR**: Neutrophil-lymphocyte ratio; **HTN**: Hypertension; **PEC**: Preeclampsia; **IQR**: Inter quartile range
* Significant difference vs. normotensive group
$^{\&}$ Significant difference vs. gestational HTN group
† Significant difference vs. first trimester

in the mild PEC group compared to the normotensive group in the first and early-third trimesters (P<0.05); however, the lymphocyte was significantly lower in the first and early-third trimesters (P<0.05). Also, the strongest associations were for NLR in the first and early-third trimesters (odds ratio [OR]=1.18 and 1.3, respectively).

The neutrophil and NLR were significantly higher in the severe PEC group compared to the normotensive group in the first and early-third trimesters (P<0.05, Table-3); however, the lymphocyte was significantly lower (P<0.05); despite no significant difference in WBC count in the first trimester (P>0.05), it was significantly higher in the early-third trimester (P<0.05, Table-3). The strongest associations were for NLR in the first and early-third trimesters (OR=1.09 and 1.07, respectively).

The neutrophil and NLR were significantly higher in the mild PEC group compared to the gestational HTN group in both the first and early-third trimesters (P<0.05, Table-3); however, the lymphocyte was significantly lower (P<0.05). Although there was no association for WBC in the first trimester (P>0.05), it was significantly higher in the

early-third trimester (P<0.05, Table-3); the strongest associations were for NLR in the first and early-third trimesters (OR=1.69 and 1.16, respectively).

The neutrophil and NLR were significantly higher in the severe PEC group compared to the gestational HTN group in the first and early-third trimesters (P<0.05, Table-3); however, the lymphocyte was significantly lower (P<0.05); also, WBC count did not differ in the first and early-third trimesters (P>0.05). The strongest associations were for NLR in the first and early-third trimesters (OR=1.67 and 1.67), respectively.

The cut-off points of the neutrophil and NLR in the first and early-third trimesters of pregnancy for PEC, mild PEC, and severe PEC are shown in Table 4. The neutrophil of more than 69.5% and 72.5% in the first and early-third trimesters could validly predict PEC, mild PEC, and severe PEC, respectively (Table-4). Also, the NLR of more than 2.79 and 3.2 could predict PEC, mild PEC, and severe PEC in the first and early-third

Table 3. Associations between Various Groups of Pregnant Women in the Terms of White Blood Cells, Neutrophil, Lymphocyte, and Neutrophil-Lymphocyte Ratios in the First and Early-Third Trimesters of Pregnancy

Parameters		Normotensive vs.		Gestational HTN vs.	
		Mild PECOR (95% CI)	Severe PECOR (95% CI)	Mild PECOR (95% CI)	Severe PECOR (95% CI)
First trimester	WBC	1.001 (1-1.001)	1 (1-1)	1(1-1)	1(1-1)
	Neutrophil (%)	1.017 (1.013-1.021)	1.008 (1.005-1.01)	1.08(1.06-1.11)	1.07(1.04-1.1)
	Lymphocyte (%)	0.987 (0.983-0.992)	0.993 (0.99-0.998)	0.94(0.91-0.98)	0.93(0.89-0.98)
	NLR	1.18 (1.13-1.23)	1.09 (1.06-1.12)	1.69(1.33-2.15)	1.67(1.35-2.07)
Early-third trimester	WBC	1.001 (1-1.001)	1.001 (1-1.003)	1(1-1.001)	1(1-1)
	Neutrophil (%)	1.021 (1.01-1.025)	1.008(1.005-1.01)	1.07(1.04-1.09)	1.11(1.06-1.15)
	Lymphocyte (%)	0.985 (0.98-0.989)	0.992 (0.98-0.996)	0.95(0.92-0.98)	0.92(0.88-0.96)
	NLR	1.3 (1.11-1.17)	1.07 (1.04-1.09)	1.16(1.04-1.29)	1.67(1.34-2.07)

WBC: White blood cells; **NLR**: Neutrophil-lymphocyte ratio; **HTN**: Hypertension; **PEC**: Preeclampsia; **OR**: Odds ratio; **CI**: Confidence interval

Table 4. Cut-off Point Values of the Neutrophil Percent and Neutrophil-Lymphocyte Ratio for Prediction of Preeclampsia among Pregnant Women Based on the First and Early-Third Trimesters of Pregnancy

Parameters			Cut-off point	AUR	Sensitivity	Specificity	PPV (%)	NPV (%)
First trimester	Neutrophil (%)	PEC	69.5	0.98	100	97.6	45.4	100
		Mild PEC	69.5	0.97	100	0.96	98.5	48.4
		Sever PEC	69.5	0.97	100	0.96	98.5	100
	NLR	PEC	2.79	0.93	86.7	92.6	49.2	89
		Mild PEC	2.79	0.92	85	90.9	96.5	38.8
		Sever PEC	2.79	0.95	85.7	90.9	96.5	67.9
Early-third trimester	Neutrophil (%)	PEC	72.5	0.96	96.7	86.9	49.2	89
		Mild PEC	72.5	0.95	95.2	85	96.5	38.8
		Sever PEC	72.5	0.93	95.2	85	96.5	97.5
	NLR	PEC	3.2	0.91	90.5	79.4	92.9	70.8
		Mild PEC	3.2	0.92	90.51	79.4	92.9	38.1
		Sever PEC	3.2	0.91	90.5	79.4	92.9	73.5

PEC: Preeclampsia; **NLR**: Neutrophil-lymphocyte ratio; **AUR**: Area under ROC; **PPV**: Positive predictive value; **NPV**: Negative predictive value

trimesters, respectively (Table-4).

Discussion

Totally, 449 pregnant women were followed prospectively, of whom 90.9%, 2.4%, and 6.7% had normal hypertension, gestational HTN, and PEC, respectively. Maternal age, BMI, and parity did not differ among the normotensive, PEC, and gestational HTN groups. The serum levels of the WBC count, neutrophil, and NLR increased significantly from the first to the early-third trimesters of pregnancy; however, the lymphocyte decreased. The WBC count, neutrophil, and NLR were significantly higher in the PEC group compared to the normotensive group in the first and early-third trimesters; however, the lymphocyte was lower. The NLR and neutrophil cut-off points for predicting PEC were 2.79 and 69.5% in the first, and 3.2 and 72.5% in the early-third trimesters, respectively.

NLR is proven as a marker of the SIR and is reported in some diseases, including appendicitis, advanced stages of cancer, acute myocardial infarction, acute pulmonary embolism, and ulcerative colitis [25-28].

Various studies have shown that WBC types, e.g., neutrophils, are associated with inflammatory responses, namely atherogenesis and atheroma thrombosis [29]. Maternal leukocytes are activated during pregnancy as well as PEC [29, 30]. Kurt *et al*. reported higher neutrophils in patients with PEC, indicating an increased inflammatory status [31].

In PEC, hyper-activation of the inflammatory cell and immunological responses are the causes of releasing inflammatory cytokines, antibodies, and oxidative agents, resulting in endothelial dysfunction [15]. PEC is associated with impaired regulation of TH_1 and TH_2 as inflammatory responses and consequently increased NLR [14-17, 19].

Yavuzcan *et al*. reported that, though not statistically significant, NLR was higher in PEC women than normal women [32]; however, several authors have reported a statistically significant positive association, suggesting that NLR could predict PEC and its severity [33-35].

Kang *et al*. showed that the amount of NLR was higher in patients with PEC, especially in severe cases [15]. While Kurt *et al*. reported that NLR was not significantly different between PEC and normal groups, but the neutrophil was significantly higher in the group with PEC [31]. However, recently published articles have reported that NLR was significantly higher in PEC women [36, 37]. Also, in the current study, the neutrophil showed a more accurate predictive value for PEC in both the first and early-third trimesters. In other words, the sensitivity and specificity of the neutrophil were more than those of NLR. In line with our study, Canzoneri *et al*. showed that neutrophils increased in PEC [38]. Also, they reported leukocytosis in PEC patients, which is associated with the severity and degree of thrombocytopenia in Hemolysis, Elevated Liver enzymes, and Low Platelets syndrome [38, 39].

Although we performed this study with a large sample size and prospective design, an underestimation in reporting the prevalence of HPD due to excluding the high-risk women from the study should be considered as the main limitation of our study.

Conclusion

Regarding routine CBC checking in the first trimester and 24-28 weeks of pregnancy, measured NLR and neutrophil in the first and early-third trimesters of pregnancy could be accurate predictions of PEC in a normal population.

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Conflict of Interest

The authors declared no competing interest in the study.

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