ORIGINAL RESEARCH

Diagnostic performance of hematological indices in early and late preeclampsia

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Abstract

To evaluate diagnostic performance of Neutrophil/lymphocyte ratio (NLR), Platelet to lymphocyte ratio (PLR) and platelecrit in the first and third trimester in preeclampsia. This was a single center case control study conducted between January 2015 and January 2021. Patients diagnosed with preeclampsia were assigned as study population. The preeclamptic patients were assigned into two groups based on gestational weeks at diagnosis. Patients diagnosed before 34th gestational weeks were categorized as early preeclampsia and whereas patients diagnosed after 34th gestational weeks as late preeclampsia. Receiver operating characteristics curve was used to assess diagnostic value of first and third trimester NLR, PLR and platelecrit in preeclampsia. Detection rate of each variable was assessed for a 10% false positive rate. NLR in the first trimester have highest sensitivity of 30 % at a 90 % specificity to detect early preeclampsia. The area under curve (AUC) for NLR was 0.742 respectively. The best cut off for 1st trimester NLR was 4.98. PLR and platelecrit yielded low diagnostic performance. NLR in the first trimester has a moderate predictive performance for early preeclampsia. PLR was not different in preeclamptic cases and controls and platelecrit yielded a low diagnostic performance for preeclampsia.

Keywords: Diagnostic performance, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, platelecrit, preeclampsia

Introduction

Preeclampsia is one of the leading causes of fetal and maternal morbidity and mortality. It is a pregnancy-specific disorder and affects approximately 3% of all pregnancies [1]. Although the underlying pathophysiological changes of preeclampsia become evident in the second half of pregnancy, it is thought to begin in the first weeks of pregnancy during the placentation period [1]. Once preeclampsia has been diagnosed, there is no treatment other than delivery. However, studies have shown that starting 150 mg of aspirin before week 16 can prevent almost half of early preeclampsia. However, routine aspirin treatment in every pregnancy will increase the rate of unnecessary treatment, and it also brings various risks such as postpartum hemorrhage [2]. For this reason, many studies have focused on identifying

patients at risk of preeclampsia in the early stages of pregnancy [3, 4]. However, so far, no marker with optimal predictive value was found [3, 4]. The American College of Obstetricians and Gynecologists (ACOG) currently recommends starting aspirin in patients considered high risk based on their preeclampsia history and medical condition. However, most patients with preeclampsia do not have any risk factors [5]. Nicolaides et al. developed a risk calculation method using maternal uterine artery Doppler pulsatility index (UA PI), placental growth factor (PLGF), mean arterial pressure and maternal characteristics [2]. This method can identify 90% of early preeclampsia with a 10% false positive rate; however, this method requires first trimester biochemical markers such as PLGF, which are not available in many centers.

It is thought that defective placentation plays a central role in the development of preeclampsia. Insufficient trophoblastic invasion of spiral arterioles causes placental release of inflammatory mediators [4,6-8]. These mediators subsequently create response in mother which include increase in neutrophil count, increased production of superoxide compared with nitric oxide [4,9]. Endothelial damage and dysfunction, which are especially evident in late gestation, causes platelet activation, low platelet number,

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high platelet mean platelet volume (MPV) [9]. Previous studies have shown alteration of neutrophil to lymphocyte ratio (NLR) and platelet indices in preeclampsia [3].

The primary aim of this study was to evaluate both diagnostic and predictive value of the systemic inflammatory markers including NLR and platelet to lymphocyte ratio (PLR), in preeclampsia. We also investigated predictive and diagnostic potential of platelet indices including mean platelet volume (MPV), Plateletcrit (Pct) in preeclampsia.

Materials and Methods

This was a single center case control study conducted at Etlik Zübeyde Hanım Maternity hospital between January 2015 and January 2021. Patients diagnosed with preeclampsia were assigned as the study population. Patients who do not have first trimester results available for evaluation or patients with chronic systemic disease that may affect any parameter investigated in the present study were excluded. Accordingly, patients with HELLP syndrome, diabetes mellitus, chronic hypertension, collagen vascular disease, acute or chronic liver disease, renal insufficiency, ischemic heart disease, hypothyroidism or hyperthyroidism, fewer, rupture of membranes were excluded from further analysis. Patients with multiple pregnancies were also excluded (Figure 1).
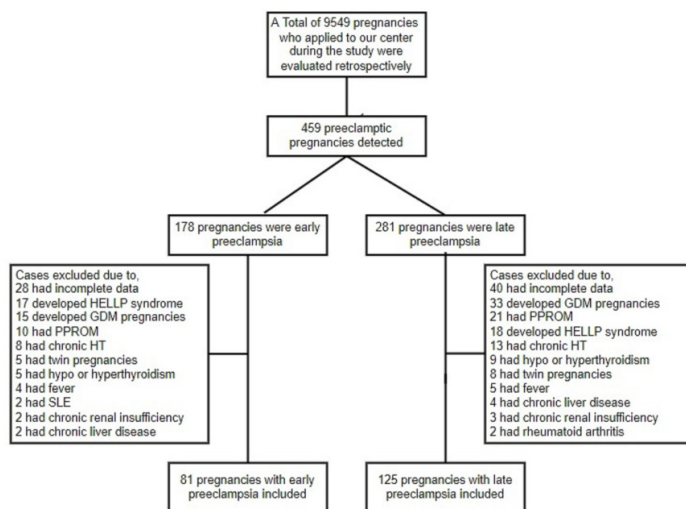

Figure 1. Study flow chart

The preeclamptic patients were assigned into two groups based on gestational weeks at diagnosis. Patients diagnosed before 34th gestational weeks were categorized as early preeclampsia and whereas patients diagnosed after 34th gestational weeks as late preeclampsia. The control group consisted of 200 healthy patients without preeclampsia and without systemic disease that may interfere with any of the investigated parameters.

The following data were obtained by hospital database; maternal age, body mass index (BMI), method of conception, gravidity, parity, smoking, first trimester biomarkers including PAPP-A and B-HCG, first and third trimester, white blood cell (WBC), platelet, MPV, Pct, neutrophil, lymphocyte, albumin, bilirubin, AST, ALT, urea, creatinine. Pct is the volume occupied by platelets in the blood as a percentage. Serum samples were obtained in the first trimester between 8–14 weeks. Third trimester samples were obtained at hospital admission. The following pregnancy data were

obtained; gestational age at delivery, presence of preterm delivery and intrauterine growth retardation (IUGR). The fetal outcomes including 1. And 5. APGAR scores, admission to the neonatal intensive care unit, fetal sex and weight were also retrieved.

The NLR was calculated by dividing the number of neutrophils to lymphocytes, the PLR was calculated by dividing the number of platelets to lymphocytes. The diagnosis of preeclampsia was done if blood pressure elevation $\geq 140/90$ mm Hg on two occasions 4 hours apart and proteinuria ≥ 300 mg/dl in 24 hours urine or $\geq +2$ using dipstick test in spot urine [6]. Preterm delivery was defined as deliveries that occurred before 37th gestational weeks.

The present study was approved by the Etlik Zübeyde Hanım Ethics Committee for Non-interventional Studies at 19.11.2020 (ID: 17). Statistical analysis was performed using SPSS version 26 (Statistical Package for the Social Sciences, Chicago, IL). The Kolmogorov-Smirnov test was used to assess whether the data were distributed normally. Normally distributed parametric variables were compared with one way analysis of variance. Parametric variables with abnormal distribution were compared using Kruskal- Wallis test. Chi-square test was used to compare categorical variables between independent groups. Receiver operating characteristics (ROC) curve was used to evaluate diagnostic value of NLR, PLR and in the first and third trimester. The detection rate of each variable was assessed for a 10% false positive rate. A p-value <0.05 was considered significant. Multivariable logistic regression model was performed to define relationship between first and third trimester NLR, first and third trimester PLR, first and third trimester Pct, Age, BMI, parity and early onset preeclampsia

Results

Among 459 pregnancies with preeclampsia 205 who met the study criteria were included in the study. Of these, there were 80 early preeclampsia, 125 late preeclampsia. The maternal age of early preeclampsia and late preeclampsia group were similar (p=0.137), but preeclamptic patients (group1 and 2) were older than control group (p<0.01). The BMI of early preeclampsia and late preeclampsia groups were similar (p=0.06), but both were higher than the control group (p<0.01). Parity and previous miscarriage were similar in both groups (p>0.05). Both groups were similar regarding the rate of pregnancies conceived by assisted reproductive technology (ART) and fetal sex (p>0.05 for each comparison). There was no differences between all groups regard to the first trimester free B-HCG and PAPP-A (p>0.05 for each comparison). [Table 1.]

Gestational weeks at delivery of early preeclamsia group were lower than late preeclampsia and control group (35.4±2.9, 38.0 1.5 and, 39.2±1.3 respectively, p<0.001 Please delete this part of sentence). Delivery before 37 weeks and delivery before 34 weeks were higher in early preeclamptic patients than late preeclampsia and control groups (p<0.001 for all comparisons). The neonatal birth weight was lower in early preeclampsia group than late preeclampsia and control group (2538±793 gr, 3109±518 gr and 3222 410 gr, respectively, p<0.001 for early vs late preeclampsia and p<0.001 for early preeclampsia vs control). Low birth weight infants was also significantly higher in early preeclamptic patients than late preeclampsia and control group (30

(37.5%), 12 (9.6%), 11 (5.5%) respectively, p<0.001 for pairwise comparisons between late preeclampsia and control group vs early preeclamptic patients). There was no difference regard to neonatal intensive care unit between late preeclampsia group and control groups (p>0.05) however both were lower compared to early preeclampsia group (p<0.001 for early vs late preeclampsia and p<0.001 for early preeclampsia vs control). IUGR was more frequent in early preeclampsia compared to late preeclampsia and control group (p<0.001 for early vs late preeclampsia and p<0.001 for early preeclampsia vs control). But this was not valid for late preeclampsia (p>0.05) [Table 2].

Table 3. shows some inflammatory markers, platelet indices of groups. The first and third trimester NLR in first trimester and third trimester were higher in early pregnancy group than late preeclampsia and control group (p<0.05 for early vs late preeclampsia and for early preeclampsia vs control). However, there was not a statistically significant difference in NLR between late preeclampsia and control group (p>0.05 for early vs late preeclampsia and for early preeclampsia vs control). The platelet count of all groups was similar (p>0.05). Pct were similar between preeclamptic groups in first and third trimester. However both early and late preeclamptic patients had higher Pct values in the first trimester and lower Pct values in the third trimester than control group (p<0.05 for late preeclampsia vs control and for early preeclampsia vs control). First trimester PLR was similar in both groups. The third trimester PLR in early preeclampsia group was significantly lower than late preeclampsia and control groups (p<0.05 for early vs late preeclampsia and for early preeclampsia vs control), but there were no differences between late preeclampsia and control group according to PLR (P>0.05). The third trimester MPW and Pct in early preeclampsia and late preeclampsia were similar (p>0.05). Pct was significantly higher at 1st trimester and was significantly lower than control group in both group of patients with preeclampsia (p<0.05 for late preeclampsia vs control and for early preeclampsia vs control).

The diagnostic performances of PLR, NLR, Pct, for the detection of early preeclampsia was evaluated by ROC analysis. Among them NLR in the 1st trimester have highest sensitivity of 30% at a 90% specificity to detect early preeclampsia. The area under curve (AUC) for NLR was 0.742 (p<0.001). The best cut off for 1st trimester NLR was 4.98. [Table 4], (Figure 2-4). The AUC for 1st and 3rd trimester Pct was 0.638 and 0.613 respectively (p<0.001 and p: 0.003 respectively)
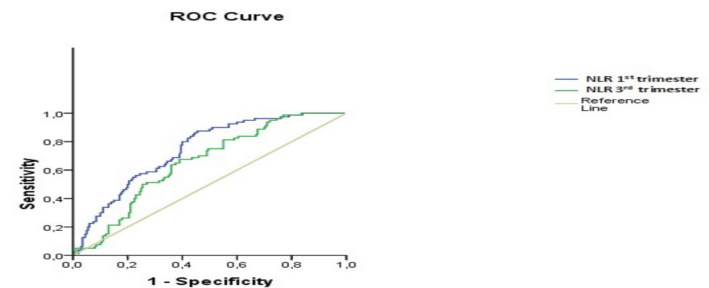

Figure 2. Diagnostic performance of NLR in first and second trimesters
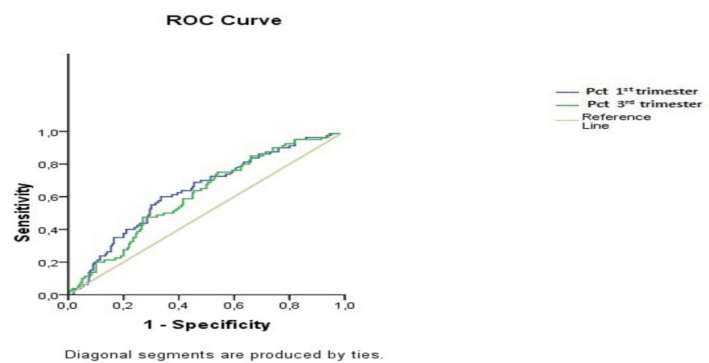

Figure 3. Diagnostic performance of Pct in first and second trimesters

Table 1. Patients' characteristics and first trimester biomarkers of groups

Characteristics	Early PE (n=80)	Late PE (n=125)	p 1 vs 2	Control (n=200)	p 1 vs 3	p 2 vs 3
Age±SD, (years)	32.4±6	30.6±6.4	0.137	27.5±6	<.001	<.001
BMI±SD (kg/m²)	29.8±5.3	28.2±5	0.062	24.8±3.9	<.001	<.001
Parity						
0(%)	31(38.8%)	42 (33.6 %)		75(37.5%)		
1-3(%)	44(55%)	76(60.8 %)	0.098	123(61.5%)	0.098	0.098
>3(%)	5 (6.3%)	7(5.6 %)		2(1%)		
Previous miscarriage						
0(%)	57(71.3%)	90(72 %)		148(74%)		
1(%)	17(21.3%)	19(15.2 %)	0.224	40(20%)	0.224	0.224
≥2(%)	6(7.5%)	16(12.8 %)		12(6%)		
Smoking (%)	17(21.3%)	14(11.2)	<.001	7(3.5%)	<.001	0.006
PAPP-A Median (MoM) (min-max)	0.91	0.88	.900	1.02	.020	.011
Free β HCG Median (MoM) (min - max)	0.85	0.79	.489	0.94	.158	.012
ART (%)	2(2.5%)	4(3.2%)	0.923	5(2.5%)	0.923	0.923
Fetal gender						
Female (%)	46(57.5%)	57(45.6%)	0.226	105(52.5%)	0.226	0.226
Male (%)	34(42.5%)	68(54.4%)		95(47.5%)		

P<0.05 considered as significance; PE, preeclampsia; SD, standard deviation; BMI, body mass index; MoM, multiple of median; PAPP-A pregnancy associated plasma protein; B-HCG, beta human chorionic gonadotropin; ART, assisted reproductive technology

Table 2. Comparison of obstetric and fetal characteristics of groups

Characteristics	Early PE (n=80)	Late PE (n=125)	p 1 vs 2	Control (n=200)	p 1 vs 3	p 2 vs 3
Gestational age at delivery (weeks ±SD)	35.4±2.9	38.0±1.5	<0.001	39.2±1.3	<0.001	<0.001
Delivery <37 weeks	47(58.8%)	27(21.6%)	<0.001	11(5.5%)	<0.001	<0.001
Delivery <34 weeks	19(23.8%)	0	<0.001	0	<0.001	1
Severe preeclampsia	27(33.8%)	16(12.8%)	<0.001	-	-	-
IUGR	25(31.3%)	6(4.8%)	<0.001	5 (2.5%)	<0.001	0.346
Neonatal birth weight (grams ± (SD))	2538±793	3109±518	<0.001	3222±410	<0.001	0.185
Fetal W. <2500 grams	30(37.5%)	12(9.6%)	<0.001	11(5.5%)	<0.001	0.161
Fetal W. <1500 grams	12(15%)	0	<0.001	0	<0.001	1
NICU admission	6(7.5 %)	1(0.8%)	<0.001	3(1.5%)	0.001	1

PE, preeclampsia; IUGR, Intrauterine growth restriction, SD, standard deviation; W, weight; NICU, neonatal intensive care unit. P<0.05 considered as significance

Table 3. Hematological and parameters in study population

Characteristics	Early PE (n=80)	Late PE (n=125)	p 1 vs 2	Control (n=200)	p 1 vs 3	p 2 vs 3
NLR						
1st trimester	4.7±1.6	3.7±1.4	< 0.001	3.6±1.7	<0.001	0.973
3rd trimester	4.9±1.4	4.3±1.6	0.029	4.3±1.6	0.007	0.947
Platelet (103/µl) (mean ± SD)						
1st trimester	276±65	270±74	0.841	258±62	0.112	0.238
3rd trimester	247±74	258±73	0.615	249±79	0.985	0.584
PLR (mean ± SD)						
1st trimester	149±54	148±51	.078	161±58	.078	.078
3rd trimester	130±54	150±57	.006	143±73	.011	.375
MPV (fL) (mean ± SD)						
1st trimester	8.1±1.0	8.2±0.9	0.842	7.9±0.7	.055	.024
3rd trimester	8.8±1.1	8.8±1.1	.863	9.8±1.5	<0.001	<0.001
Platelocrit (%)(mean ± SD)						
1st trimester	0.22±0.04	0.22±0.05	1	0.20±0.05	<0.001	<0.001
3rd trimester	0.21±0.06	0.22±0.05	.179	0.24±0.07	0.006	0.002

P<0.05 considered as significant; SD, standard deviation; PE, preeclampsia; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MPW, mean platelet volume

Table 4. Diagnostic performance of NLR, PLR, Platelocrit, 1st and 3rd Trimester for prediction of early onset preeclampsia

	AUC	95 % Confidence interval	p	Cutoff	Sensitivity	Specificity
NLR 1st trimester	0.742	0.68 – 0.80	< 0.001	4.98	30 %	90 %
NLR 3rd trimester	0.652	0.59 – 0.71	< 0.001	6.48	10 %	90 %
PLR 1st trimester	0.572	0.496 – 0.65	0.06	-	-	-
PLR 3rd trimester	0.535	0.46 – 0.61	0.363	-	-	-
Platelocrit 1st trimester	0.638	0.57 – 0.71	< 0.001	0.26	20 %	90 %
Platelocrit 3rd trimester	0.613	0.54 – 0.68	0.003	0.23	21%	90 %

Table 5. Multivariate logistic regression model of maternal factors and NLR, PLR, Platelocrit in 1st and 3rd Trimester for prediction of early onset preeclampsia

	Cut-off	Odds Ratio	95 % Confidence interval	p
NLR 1st trimester	4.98	4.04	1.97–8.33	< 0.001
NLR 3rd trimester	6.48	0.88	0.34–2.32	0.803
PLR 1st trimester	220	1.14	0.39–3.30	0.809
PLR 3rd trimester	234	0.72	0.24–2.14	0.554
Platelocrit 1st trimester	0.26	2.69	0.87–6.54	0.087
Platelocrit 3rd trimester	0.23	0.54	0.28 –1.05	0.068
Age	> 35	4.24	2.12 – 8.50	< 0.001
BMI	> 30	5.69	2.93 - 11.05	< 0.001
Parity	> 0	0.84	0.44 – 1.60	0.601
Assisted reproduction	-	1.14	0.11 – 2.96	0.785

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; BMI Body mass index
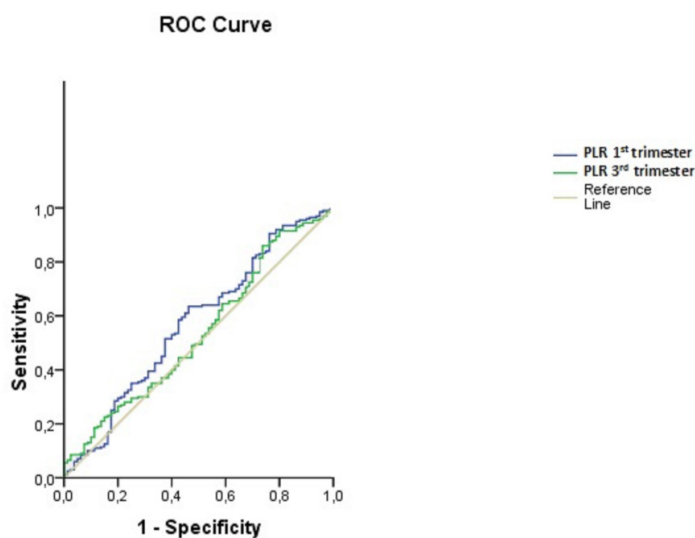
Figure 4. Diagnostic performance of PLR in first and second trimesters

In the multivariate model NLR in the 1st trimester was associated with an increased risk of early onset preeclampsia (Odds ratio 4.04, 95% confidence interval: 1.97–8.33). Among maternal factors age>35 and BMI>30 was associated with increased risk of early onset preeclampsia. NLR in the 3rd trimester was not predictive of early onset preeclampsia. PLR and Pct 1st or 3rd trimester was not predictive of early onset preeclampsia [Table 5].

Discussion

In the present study, 1st trimester NLR was found to be higher in early preeclamptic pregnant women compared to late preeclamptic patients and control group. However, there was no significant difference between the late preeclamptic patients and the control group. Similarly, NLR in the 3rd trimester were significantly higher in early preeclamptic patients compared to late preeclamptic patients and control group. NLR was similar in late preeclamptic patients and in the control group. The cut off values for NLR was 4.98 in the first trimester and 6.48 in the third trimester for a 10 % false positive rate. In the multivariate model, the only parameter that predicted early onset preeclampsia was 1st trimester NLR.The findings of this study are generally in agreement with previous

studies [3, 10]. Many case-control studies have evaluated the diagnostic value of NLR in preeclampsia [3, 10-13]. In a meta-analysis evaluating the data of 11 of these studies, it was reported that NLR increased significantly in severe and mild preeclampsia compared to the control group [14]. In some of the studies included in this meta-analysis [10, 12, 13], NLR rates were found to be similar in mild preeclampsia, severe preeclampsia and control groups. Exclusion criteria were similar in the majority of studies [14]. Chronic diseases that could affect NLR rates were excluded. However, the gestational age in which the NLR assessment is performed is quite heterogeneous. Some studies evaluated NLR in the first trimester [10, 11, and 15], others have calculated NLR in the second or third trimester or on admission [12, 13, and 16]. Only Mannerts et al. looked at NLR in the 1st and 3rd trimesters, but there were only 28 patients in this study [17]. Another important point to be addressed is the differences in diagnostic performance and cut off values of NLR. Different cut off values have been reported in different studies. These cut off values range from 3.08 to 4.1 [15, 18]. In the first trimester NLR cut off 3.08 was suggested to predict preeclampsia in one study with moderate predictive accuracy (sensitivity 74.6% specificity 71.8%, AUC 0.716) [15]. In another study NLR in the 3rd trimester performed poorly in the prediction of severe preeclampsia (AUC 0.635,p>0.005) [12]. Mannaerts et al, however reported that NLR before delivery had a high diagnostic accuracy with an AUC of 0.863 and they reported an optimal cut off of 3.92 [17]. However NLR was similar in preeclamptic patients and control group prior to 20 weeks in their study. In this study, the 1st trimester cut off was found to be 3.53 for the prediction of early onset preeclampsia. The third trimester cut off for early preeclampsia was determined as 3.86. The diagnostic power of 1st trimester NLR was better than 3rd trimester NLR. As discussed above there are many methodological differences between studies. Some have aimed to evaluate NLR to predict preeclampsia in the first trimester while others have aimed to diagnose severe preeclampsia or just preeclampsia on admission [11, 12, 17, and 18]. Therefore some of the findings of these studies are not clinically relevant as prediction of mild preeclampsia by 1st trimester NLR or diagnosis of preeclampsia without severe features by 3rd trimester NLR would not be of therapeutic value.

In the present study, the 1st and 3rd trimester PLR ratios did not

have any diagnostic or predictive value for early preeclampsia. Gezer et al. reported that high PLR in the first trimester predicted preeclampsia [15]. The findings of this study contradict with those of Gezer et al. Kim et al. reported that low PLR rates in the 3rd trimester predicted severe preeclampsia [19]. The present study study is in keeping with Kim et al. Since the 3rd trimester PLR was lower in pregnant women with early-onset preeclampsia. However this difference did not have sufficient diagnostic power. Another thrombocyte index, Pct in the 3rd trimester were found to be mildly lower in both group of patients with preeclampsia than control group. This finding was in agreement with previous studies which have consistently reported lowered Pct in preeclampsia [20-21]. However Pct had a low diagnostic yield at each trimester with detection rate around 20% for 10% false positive rate.In the multivariate model however neither PLR nor Pct was not predictive of early onset preeclampsia in 1st or 3rd trimester [Table 5].

Conclusion

The present study has some limitations; Due to its retrospective nature, the relationship between NLR and PLR with other first trimester parameters such as UA PI, PLGF could not be examined. However the present study is among the few studies that compared both first trimester and third trimester values with a relatively large sample size. In conclusion, 1st trimester NLR has moderate predictive value for preeclampsia. No other parameters were able to predict early onset preeclampsia independently in multivariate model. The clinical importance of the present study is its large sample size as well as incorporation of multivariate analysis. Future studies should aim to combine one or more of these ratios to reveal the maximum predictive or diagnostic value associated with these tests. In addition, it seems that the use multiples of median values rather than cut-off values for these parameters may increase their clinical use.

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