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Can systemic immune inflammation index measured in the first trimester predict later occurring isolated oligohydramnios?

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Abstract

The aim of our study is to determine whether the first trimester systemic immune inflammation index (SII) and other hematological markers can be useful as new markers of isolated oligohydramnios that may develop later. Two main groups were formed in this retrospective study. In the first group, 57 pregnant women with isolated oligohydramnios in their third trimester (between 28-40 weeks) were included. The control group consisted of 137 healthy pregnant women with a normal amniotic index (AFI) in the third trimester. First trimester and delivery hemogram values and newborn results of all pregnant women in both groups included in the study were noted for statistical comparison. Platelet (261.895+8.04), which is the hematological marker that best predicts IO in the first trimester, was found to be higher than the healthy group (244.390±4.79) (p=0.03). PLR was the best predictor of oligohydramnios in the third trimester. The PLR level was determined as 113,288, and the cut-off value was 64.91%, the upper limit was 95% CI, the specificity was 51.09%, the positive predictive value was 35.58%, and the negative predictive value was 77.78%. The platelet count in the first trimester and the progressive increase in the number of PLR in the third trimester are significantly related in the prediction of oligohydromnus. SII, NLR and PLR measured in the first trimester are useless in predicting isolated oligohydramnios that may develop in the future.

Keywords: First trimester, NLR, Isolated oligohydroamnios, PLR, SII

Introduction

Oligohydramnios is a condition detected at routine obstetric examination in which the amniotic fluid index (AFI) calculated by examining four quadrants at ultrasound is ≤ 5 cm or in which the longest vertical pocket length measured at ultrasound is ≤2 cm. The condition is seen in 5% of term pregnancies and is associated with poor obstetric outcomes [1]. Isolated oligohydramnios (IO) is defined as insufficient amniotic fluid (AFI≤5) in pregnant women without maternal or fetal disease. It can be seen in approximately 0.5-5% of pregnancies [2]. Oligohydramnios can result in increased mortality and morbidity, either in association with the etiology, or else as a result of a decrease in amniotic fluid [3]. Several authors have thought that the development of oligohydramnios may be a sign of uteroplacental failure or chronic fetal stress [4]. In addition, various physiological changes occurring for adaption to pregnancy in the maternal hematological system may give rise to a mild inflammatory state [5]. Pathological deviations from these physiological adaptations can be detected by examining peripheral blood specimens collected from expectant mothers during routine pregnancy follow-ups. Several indices have recently been

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developed from hematological parameters investigated in peripheral blood for showing systemic inflammation. Two such indices, the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR), are simple biomarkers widely employed for the detection of systemic inflammation [6]. Both NLR and PLR have been shown to be correlated with cancer and several inflammatory diseases, and have begun being regarded as likely inflammatory markers [6-7]. The system immune-inflammation index (SII), used as a novel inflammatory biomarker in recent years, has been shown to be associated with adverse obstetric outcomes such as placental pathologies [8-9]. To the best of our knowledge, there have been no reports to date of the importance of the SII in women with IO in the first trimester. The purpose of this study was therefore to investigate SII levels in addition to NLR and PLR for predicting the development and progression of IO among women in the first trimester.

Material and Methods

This study was planned and completed in accordance with the Declaration of Helsinki and was approved by the university ethical committee (no. 05/26 dated 29.04.2020). The research was designed as a retrospective case-controlled study at the Mengücek Gazi Training and Research Hospital (MEAH), Turkey, a tertiary institution. A total of 194 women were included in the study, 57 with oligohydramnios and 137 healthy pregnant women followed-up at the MEAH between January 2018 and January 2021. Pregnant women aged 18-40 years with gestational ages ≥28 weeks with IO and with available first trimester complete blood count results were included in the study. Women with pre-eclampsia, eclampsia, and hypertensive disease, with gestational diabetes mellitus, with anomalies determined during pregnancy follow-ups, or who smoked or used alcohol during pregnancy were excluded. In addition, all patients included in the study underwent the AmniSure(R) test, and those in whom early membrane rupture was detected were also excluded. Women with high WBC and CRP values were similarly not included. Two main groups were established in this retrospective study. The first consisted of 57 women with IO whose amniotic fluid was <2 cm in the deepest pocket or ≤5 cm in total in four quadrants at ultrasonography performed between gestational weeks 28 and 40. The control group consisted of 137 healthy pregnant women with normal amniotic index (AFI) values in the 28-40th weeks of pregnancy. The same protocols for the induction of labor were applied to both groups. Oxytocin for induction was administered by infusion at 0.002 IU/min. Additionally, women with Bishop scores <6 received 10 mg dinoprostone by the intravaginal route for cervical maturation [10]. Fetal biophysical scoring was performed and closely monitored twice weekly for fetal well-being in patients with IO in whom labor was not immediately induced. Routine hourly blood pressure, heart beat, urine output, and vaginal bleeding checks were performed postpartum to determine postpartum bleeding. Complete blood count values in both groups in the first trimester and at the time of delivery, and neonatal results were recorded.

Statistical analysis

The study data were analyzed on SPSS version 20.00 software and were expressed as mean±standard deviation or percentage values. Normality of distribution was examined using the Kolmogorov Smirnov test. One-Way ANOVA and Tukey's HSD test post hoc were used in the evaluation of hematological parameters test. Logistic regression analysis was applied to determine whether maternal PLR, WBC, and lymphocyte values measured during presentation for labor predict oligohydramnios. Receiver operating characteristic (ROC) analysis was performed to determine the platelet cut-off point for predicting oligohydramnios in the first trimester of pregnancy. ROC analysis was also applied to determine PLR, WBC, and lymphocyte cut-off points for predicting oligohydramnios in the third trimester. p values <0.05 were regarded as significant for all analyses.

Results

The records of patients diagnosed with oligohydramnios and followed-up at the MEAH between September 2010 and April 2022 were examine retrospectively and included in the study. The demographic characteristics of the study groups are shown in Table 1. The median age of the patients included was 27.21 (±5.39) years. The mean week of gestation was 26.30±4.87 for the oligohydramnios group and 28.29± 5.50 for the healthy group, and there was no statistical difference between the groups (p : 0.53). Mean birth week was 38.33±1.776 for the oligohydramnios group and 38.84±1.88 in the healthy control group, and this was statistically significant (p:0.03). Gravidity and parity values were higher in the healthy group compared to the IO group (p:0.011 and p:0.023, respectively). The rate of cesarean delivery was higher in the IO group (p:0.002). In terms of hematological parameters investigated in the first trimester, no statistically significant differences were observed between the groups' WBC, hemoglobin, neutrophil, or lymphocyte counts (p : 0.89, p : 0.95, p :0.51, and p : 0.13, respectively). Platelet counts in the first trimester were significantly higher in the IO group (261.895+8.04) than in the healthy control group (244.390±4.79) (p:0.03). No significant differences were observed between the groups in the terms of RDW, MPV, NLR, PLR, or SII values in the first trimester (p:0.13, p :0.99, p :0.35, p: 0.49, and p: 0.21, respectively) (Table 2). However, significant differences between the groups were observed in terms of the hematological parameters of WBC and lymphocyte counts investigated in the third trimester (p: 0.014 and p:0.03, respectively) (Table 3). No significant differences were observed in terms of RDW, MPV, NLR, or SII in the third trimester (p: 0.13, p: 0.99, p: 0.35, p: 0.49, and p:0.21, respectively) (Table 3). Only PLR values were significantly higher in the oligohydramnios group compared to the healthy control group (p:0.01). As shown in Table 4, first trimester the serum platelet level that best predicted oligohydramnios was 240,500. This cut-off value exhibited 63.1% sensitivity, 50.3% specificity, a positive predictive value (PPV) of 34.6% and a negative predictive value (NPV) of 76.6% with a 95% upper confidence interval (CI) (Figure 1). PLR was

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the hematological index that best predicted oligohydramnios in the third trimester. A PLR level of 113,288 was determined. This cut-off value exhibited 64.91% sensitivity, 51.09% specificity, 35.58 PPV, and 77.78% NPV with a 95% upper confidence interval (Figure 1). The third trimester WBC value that best predicted oligohydramnios was 10.35, which exhibited 68.4% sensitivity, 47.40% specificity, 34.65% PPV, and 76.34% NPV with a 95% upper confidence interval (Figure 2). The third trimester serum lymphocyte level that best predicted oligohydramnios was 1.95. This cut-off value exhibited 68.42% sensitivity, 52.55% specificity, 37.50% PPV, and 80% NPV with a 95% upper confidence interval (Figure 2). As shown in terms of the neonatal results in Table 5, there was no difference between the groups in female/male fetal gender (p=0.44). Fetal weight was higher in the healthy group (3194±470.34) than in the oligohydramnios group (3046±519.02) (p:0.046). Similarly, low birth weight fetus delivery was observed in eight cases (14%) in the oligohydramnios group compared to two (1.5%) in the healthy group. The probability of low birth weight fetal delivery was significantly higher in the oligohydramnios group (p:0.002). There was no difference between the groups in terms of premature birth (p:0.92). APGAR scores at 1 and 5 min during delivery were higher in the healthy group than in the oligohydramnios group (p:0.001 and p:0.001, respectively). Fetal length was also similar between the healthy (49.68±0.14 cm) and oligohydramnios (49.21±0.25 cm) groups (p:0.120). Incubation requirements in the NICU were also similar in the two groups (p:0.162).

Table 1. Characteristics of pregnant women with and without oligohydramnios

Parameters	Oligohydramnios (n = 57)	Healthy Pregnant (n = 137)	p-value
Age [year]	26.30± 4.87(18-40)		0,53
Pregnancy; weeks	38.33±1.776	38.84+1.88	0.039*
Gravidity	2,04±1.295	2.53±1.36	0.011*
Parity	0.88±1.18	1.23 ±1.16	0.023*
Type of delivery			
Vaginal	36(63.2%)	114 (83.8%)	0.002*
Cesarean	21 (36.8%)	22 (16.2%)	

Cesarean delivery rates were given as number of percentage, and other values were given as mean ± standard deviation. *p<0.05 was considered statistically significant

Table 2. Comparison of the hematological test results measured in the first trimester of pregnant women with and without oligohydramnios between the groups

Parameters	Oligohydramnios (n = 57)	Healthy Pregnant (n = 137)	p-value
WBC (×10³/l)	8.78±0.29	8.79±0.20	0.89
Hemoglobin, g/L	12.37±0.19	12.31±0.13	0,95
Platelets (×10³ /L)	261.895+8.04	244.390±4.79	0.03*
Neutrophils (×10³ /L)	6.17+0.25	6.05±0.16	0.51
Lymphocytes (×10³ /L)	2.01±0.06	2.08±0.05	0.73
RDW	14.02+0.24	13.91±0.13	0.99
MPV	10.55±0.13	10.33±0.07	0.13
NLR	3.25±0.16	3.15±0.11	0.35
PLR	134.08±5.37	129.77±3.92	0.49
SII	817.82±50.13	775.86±32.47	0.21

*p<0.05 was considered statistically significant

Abbreviations: WBC:white blood cells; RDW=:red blood cell distribution width; MPV=mean platelet volume (MPV); NLR=Neutrophil to lymphocyte ratio; PLR= Platelet to lymphocyte ratio; SII= systemic immune inflammation index

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Table 3. Comparison of the 3rd trimester haematological test results of pregnant women with and without oligohydramnios between the groups

Parameters	Oligohydramnios (n = 57)	Healthy Pregnant (n = 137)	p-value
WBC	10.06±0.36	11.41±0.30	0.01*
Hemoglobin, g/L	11.75±0.17	11.69±0.09	0.60
Platelets (×10³ /L)	232.02±6.76	225.10±5.47	0.14
Neutrophils (×10³ /L)	7.61±0.32	8.57+0.28	0.11
Lymphocytes (×10³ /L)	1.93.01±0.10	2.12±0.079	0.03*
RDW	14.56±0.27	14.65±0.22	0.49
MPV	10.66±0.12	10.56±0.84	0.76
NLR	4.35±0.29	4.72±0.26	0.81
PLR	129.82±5.21	117.70±4.13	0.01*
SII	1022.47±85.04	1063.60±72.99	0.52

*p<0.05 was considered statistically significant
Abbreviations: Wbc: white blood cells; RDW: red blood cell distribution width; MPV: mean platelet volume (MPV); NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: systemic immune inflammation index

Table 4. Diagnostic sensitivity and specificity of serum markers in study groups

Parameters	Cutoff	Sensitivity(%)	Specificity (%)	PPD (%)	NPD (%)
Plt 1	≥240.500	63.16	50.36	34.62	76.67
PLR 2	≥113.288	64.91	51.09	35.58	77.78
WBC 2	≤10.35	68.40	47.40	34.65	76.34
Lymphocytes 2	≤1.95	68.42	52.55	37.50	80.00

%: Percentage;
Abbreviations: PPD: Positive predictive value; NPD: Negative predictive value. WBC2: white blood cells(third trimester; Plt1: Platelet count in the first trimester ,PLR2 — Platelet lymphocyte ratio(third trimester); Lymphocytes 2: Lymphocytes (third trimester)

Table 5. Neonatal outcomes in pregnant women with and without oligohydraomnios.

Parameters	Oligohydramnios (n = 57)	Healthy Pregnant (n = 137)	p-value
Fetal Gender			0.442
Female	28(49.1%)	59(43.1%)	
Male	29(50.9%)	78(56.1%)	
Birth weight [grams]	3046±519.02	3194±470.34	0.032*
Low Brith Weight			
<2500 gr	8 (14%)	2 (1.5%)	0.002*
Gestational age at birth (weeks)			0.92
<37 week	4(7.0%)	10(7.3%)	
>37 week	53(93%)	127(92.7%)	
Apgar score			
1st minute	7.86±0.06	7.90±0.39	0.001*
5st minute	8.89±041	8.92±0.35	0.001*
Fetal length	49.21±0.25	49.68±0.14	0.120
Need of NICU	5(8.8%)	5(3.6%)	0.162

NICU;newborn intensive care unit, %: Percentage *p<0.05 was considered statistically significant

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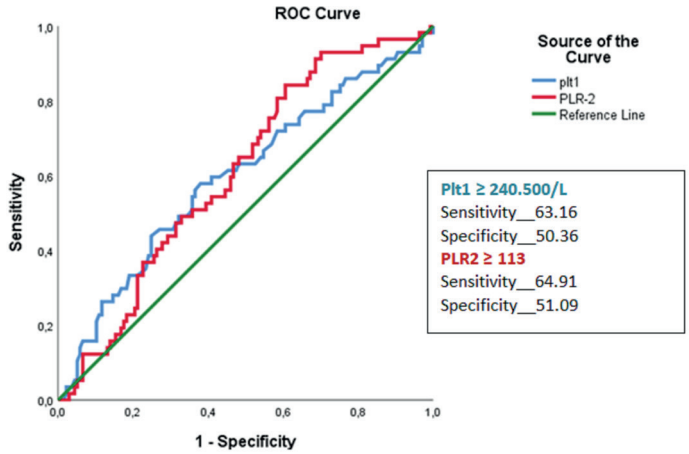

Figure 1. ROC curve of first trimester platelet and third trimester PLR

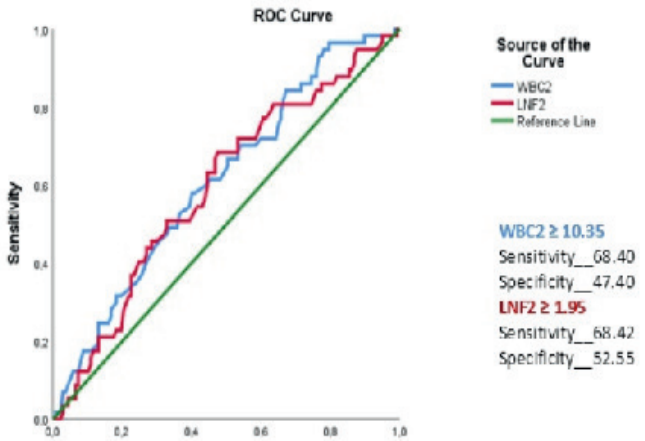

Figure 2. ROC curve of third trimester WBC and lymphocyte count

Discussion

Studies showing that poor obstetric outcomes may be a result of inflammatory processes are available in the literature [2,5,7,8]. Based on this information, in our current study, we investigated whether there is a relationship between hematological parameters measured in the first trimester and oligohydramnis that may develop later. To the best of our knowledge, this is the first study to compare women with oligohydramnios and healthy women in terms of SII, NLR, and PLR values in the first trimester. The findings showed that platelet levels, one of the serum biomarkers investigated in the first trimester, were associated with higher IO rates in the subsequent weeks of pregnancy. Additionally, they showed that WBC, PLR, and lymphocyte values investigated in the third trimester may be associated with higher IO rates.

The clinical importance of oligohydramnios derives from its exacerbation of the risk of fetal and neonatal morbidity and mortality. These poor obstetric outcomes associated with oligohydramnios are thought to be related to placental insufficiency [11]. Additionally, a progressive decrease in uteroplacental flow causes activation of neutrophils in the fetus in the subsequent stages of pregnancy and increased chemokine release by resulting in chronic hypoxia [7]. Similar to neutrophils, platelets contribute both to the initiation of inflammation by increasing the secretion of cytokines and to the continuation of inflammation by increasing the production of neutrophils and platelets. [12]. All these inflammatory processes suggest that an inflammatory process plays a role in the pathogenesis of IO [7]. Previous studies have also investigated whether hematological parameters investigated in the first trimester can predict poor obstetric outcomes [13-16]. First trimester a platelet cut-off value of ≥240,500 (62% sensitivity and 73.6% specificity) best predicted the subsequent development of IO. To the best of our knowledge, this is the first study to show an association between platelet counts in the first trimester and IO. In contrast, hematological indices such as WBC, hemoglobin, neutrophil, lymphocyte, RDW, MPV, NLR, PLR, and SII values investigated in the first trimester yielded no significant findings in terms of predicting IO. One study involving 11,415 patients reported no significant difference in PLR and NLR values investigated in the first trimester between high-risk pregnancies and healthy pregnancies [17]. Similarly to those results, no relationship was also determined between either NLR or PLR investigated in the first trimester and IO in the present study. Consistent with the present research, a previous study from Turkey also reported no relationship between hematological indices in the first trimester and SGA or oligohydramnios [18]. In the present study, serum WBC value of 10.35 (68.4% sensitivity and 47.4% specificity) best predicted the development of IO in the third trimester. The hematological index that best predicted IO in the third trimester was PLR. The optimal cut-off value for PLR was 113,288 (64.9% sensitivity and 51.0% specificity). In agreement with our PLR findings, Erten O et al. reported significantly higher cystatin C, hs-CRP, and PLR values in the third trimester in an oligohydramnios group compared to a control group. However, again similarly to the present research, that study found no significant difference in NLR values between the two groups [7]. Smiliary to present study, another study comparing high-risk pregnant women and the normal population in the third trimester also reported no association between NLR values and adverse obstetric outcomes [18]. Higher adverse neonatal outcomes were also observed in the oligohydramnios group in the present study. More than one study has shown that increasing proinflammatory cytokine production may be associated with adverse pregnancy outcome such as uterine activation and prematurity [19-20]. It is unclear whether IO reflects an underlying pathological condition, for which reason the management of IO is still controversial. Smiliary to present study, several studies have shown that a higher cesarean section rate in patients with IO compared to healthy groups [21-22]. Effects on neonatal outcomes are also uncertain; some authors showed no adverse effects [23]. while others showed higher neonatal intensive care unit (NICU) admission rates and higher rates of meconium aspiration syndrome [16]; however, only some studies showed low APGAR scores, which is consistent with our

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current study [24]. In terms of cesarean delivery rates, a meta-analysis of 12 studies in which 35,999 pregnant women were included significantly higher labor induction and cesarean rates in patients with IO, a finding consistent with the present study [16]. However, the higher rates of admission to the NICU in that meta-analysis [16] were inconsistent with our findings. In a study by Manzanares, S. et al., the cesarean delivery rate was found to be higher in the oligohydramnios group than in the control group, which was consistent with our study results. However, the demonstration that there was no difference between the groups in terms of neonatal outcomes or perinatal morbidity or mortality was not compatible with our study results [25].

Conclusion

In conclusion, this retrospective study is the first to show an association between SII values investigated in the first trimester and oligohydramnios that may develop subsequently. This study also showed an association between maternal platelet counts investigated in the first trimester and WBC, PLR, and lymphocyte values in the third trimester and oligohydramnios. However, no relationship between SII, NLR and PLR values in the first trimester and IO. We think that IO can be identified early and neonatal morbidity and mortality reduced to a minimum by evaluating women's platelet values in the first trimester and PLR, WBC, and lymphocyte values in the third trimester. However, further prospective studies with more participants are now needed to determine whether these parameters can be used to detect a pregnant woman at risk of IO and to predict whether this will lead to adverse perinatal outcomes.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

Our study was approved by the ethics committee of the university (Ethics Committee Date: 29.04.2020, Number: 05/26).

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