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İlk Trimesterde Monosit Sayısı ve Monosit Bazlı Kan Hücre İndekslerinin Gebeliğin İntrahepatik Kolestazı Gelişimi, Şiddeti ve Prognozunu Öngörmedeki Rolü

The Role of Monocyte Count and Monocyte Based Complete Blood Cell Indexes in Predicting the Development, Severity and Prognosis of Intrahepatic Cholestasis of Pregnancy in the First Trimester

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ÖZ

Amaç: İlk trimesterde gebeliğin intrahepatik kolestazının (GİK) öngörüsünde monosit sayısı ve monosit bazlı kan hücre indekslerinin etkisini değerlendirmek.

Gereçler ve Yöntem: Bu çalışmaya 01/01/2021 ile 01/10/2022 tarihleri arasında Sağlık Bakanlığı Ankara Şehir Hastanesi Perinatoloji kliniğinde değerlendirilen GİK tanılı hasta grubu (n=65) ve kontrol grubu (n=107) dahil edildi. Her iki grubun laboratuvar testleri retrospektif olarak incelendi. Grupların maternal demografik özellikleri, ilk trimester monosit sayıları ile lenfosit-monosit oranı (LMO), platelet-monosit oranı (PMO), bazofil-monosit oranı (BMO), nötrofil-monosit oranı (NMO) indeksleri karşılaştırıldı. GİK grubunda monosit sayıları ve monosit bazlı kan hücre indeksleri ile açlık safra asidi düzeyleri arasındaki ilişki değerlendirildi. GİK'i öngörmede ilk trimester monosit sayısı ve monosit bazlı kan hücre indeksleri için eşik değeri belirlendi.

Bulgular: GİK grubunda doğum haftası, doğum ağırlığı daha düşük ve yenidoğan yoğun bakım ihtiyacı daha yüksek ve istatistiksel olarak anlamlıydı ($p < 0.05$). GİK grubunda monosit sayısı daha yüksek (p=0.002), trombosit sayısı daha düşük (p=0.002) ve monosit bazlı tam kan hücre indeksleri sırasıyla NMO, LMO, PMO daha düşük ve istatistiksel olarak anlamlıydı (sırasıyla p=0.005, p=0.001, p<0.001).

Sonuç: Sonuç olarak, gebeliğin ilk trimesterinde daha yüksek monosit sayıları ve düşük monosit bazlı tam kan hücre indeks değerleri GİK ile ilişkili görünmektedir. Bu yeni indeksler, GİK'in ve bunun olumsuz perinatal sonuçlarının tahmininde kullanılabilir.

Anahtar Kelimeler: Gebelik, intrahepatik kolestaz, monosit, serum safra asidi

ABSTRACT

Aim: To evaluate the effect of monocyte count and monocyte-based whole blood cell indices in the prediction of intrahepatic cholestasis of pregnancy (ICP) in the first trimester.

Materials and Method: The clinical data of patients who presented to the Perinatology Clinic of the Turkish Ministry of Health Ankara City Hosiptal with ICP between January 1, 2021, and October 1, 2022, were evaluated retrospectively. Maternal demographic parameters, gestational age at birth, fetal birth weight, first-trimester white blood cell, neutrophil, platelet, monocyte, lymphocyte, and basophil counts, lymphocyte-to-monocyte ratio (LMR), platelet-to-monocyte ratio (PMR), neutrophil-to-monocyte ratio (NMR), and basophil-to-monocyte ratio (BMR) were recorded. These parameters were compared between the ICP and control groups. The relationship between monocyte count, monocyte-based blood cell indices, and fasting bile acid levels was evaluated in the ICP group. The cut-off values of the first-trimester monocyte count and monocyte-based blood cell indices for the prediction of ICP were determined.

Results: Gestational week at birth and fetal birth weight were significantly lower, and the neonatal intensive care requirement was significantly higher in the ICP group ($p<0.05$) compared to the control group. The ICP group had a significantly higher monocyte count (p=0.002), a significantly lower platelet count (p=0.002), and significantly lower values for monocyte-based complete blood cell indices (NMR, LMR, and PMR) compared to the control group (p=0.005, p=0.001, and p<0.001, respectively).

Conclusion: A high monocyte count and low monocyte-based inflammatory indices measured in the first trimester of pregnancy seem to be associated with ICP. These novel indices can be used in the prediction of ICP and its adverse perinatal outcomes.

Keywords: Pregnancy, intrahepatic cholestasis, monocytes, serum bile acid

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease and is characterized by elevated serum aminotransferase levels. It develops during the second or third trimester of pregnancy and usually presents with itching and high bile acid levels. ICP resolves spontaneously within a few weeks after delivery (1, 2). In clinical practice, ICP may have a late diagnosis, resulting in delays in treatment.

Persistently high bile acid levels can lead to significant vasospasm of the placental villus surface, reduce the blood flow from the intervillous region of the placenta, and result in complications in both the mother and the fetus (3, 4).Therefore, the early diagnosis and treatment of ICP are very important. The pathogenesis of ICP is complex, and inflammation may play an important role. In the pathogenesis of ICP, an increase in the pathological concentration of bile acid can induce many inflammatory responses to in hepatocyte cells, leading to the production of many agents (5, 6).

Complete blood cell analysis is a simple and inexpensive test that is widely used to evaluate inflammatory processes and diagnose many diseases. During inflammation, the number of circulating monocytes increases, and most of these cells migrate to the site of inflammation and differentiate into exudate macrophages. Monocytes are circulating leukocytes that are important for innate and adaptive immunity and the functioning of immune defense, and are involved in inflammation and tissue remodeling. ICP is a multifactorial pregnancy-specific disease that includes many risk factors, such as genetic predisposition, chronic liver disease, and excessive inflammation. Therefore, increased inflammation in the first trimester of pregnancy may be associated with a higher ICP rate. Various studies have investigated the relationship between complete blood cell indices and obstetric complications, and such indices have been employed to predict the course and adverse outcomes of numerous diseases in other branches of medicine (7-9).

This study aimed to evaluate the role of the first-trimester monocyte count and monocyte-based complete blood cell indices in predicting the development, severity, and prognosis of ICP and determine whether these indices were correlated with the severity of the disease.

MATERIALS AND METHOD

The clinical data of patients who presented to the Perinatology Clinic of the Turkish Ministry of Health Ankara City Hospital with ICP between January 1, 2021, and October 1, 2022, were evaluated retrospectively. The study protocol was approved by the institutional ethics committee in terms of conformance to the principles of the Declaration of Helsinki, and approval was obtained from the clinical ethics committee of Ankara City Hospital (approval number: E2-22-2850).

A diagnosis of ICP was made based on the presence of unexplained, generalized pruritus,abnormal liver function test results serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >40 U/l), and a fasting serum bile acid level of above 10 mmol/l in pregnant women in the second or third trimester (10). In all cases, abdominal and hepatobiliary ultrasonographic imaging findings were normal, and viral hepatitis serology was negative for hepatitis. Pregnant women with systemic diseases, such as diabetes, hypertension, and kidney disease; smokers; women with multiple pregnancies; and pregnant women with fetal anomalies were excluded from the study. Maternal demographic parameters, gestational age at birth, fetal birth weight, first-trimester white blood cell, neutrophil, platelet, monocyte, lymphocyte, and basophil counts, lymphocyte-to-monocyte ratio (LMR), platelet-to-monocyte ratio (PMR), neutrophil-to-monocyte ratio (NMR),and basophil-to-monocyte ratio (BMR) were recorded. These parameters were compared between the ICP and control groups. First- and fifth-minute Apgar scores and neonatal intensive care requirements were also noted.

Statistical analysis

According to the analysis performed with ClinCalc, a total of 96 patients, 48 in each group, were required to achieve 95% power , p value of 0.05 (11). Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS v. 22, IBM, SPSS for Windows, NY: IBM Corp.). Descriptive statistics were presented as median and interquartile range values for non-normally distributed variables. Median values were compared using the Mann–Whitney U-test for non-normally distributed data and Student's t-test used for normally distributed variables.

Finally, receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off value of the investigated parameters for the prediction of ICP. A p value of <0.05 was regarded as statistically significant.

RESULTS

The study included a total of 172 pregnant women (18-44 years), of whom 65 had ICP and 107 were healthy controls. There

was no statistically significant difference between the two groups in terms of maternal age, fetal birth weight, gravidity, parity, body mass index (BMI), or first- and fifth-minute Apgar scores ($p > 0.05$). In the ICP group, gestational week at birth and fetal birth weight were significantly lower, and the neonatal intensive care requirement was significantly higher compared to the control group ($p < 0.05$) (Table 1).

Table 1: Maternal Demographic Parameters and Fetal and Neonatal Measurements

	ICP group (n = 65)	**Control group (n=107)**	**p value**
Maternal age	27(8)	28 (7)	0.766
Gravidity	2 (2)	2 (2)	0.878
Parity	0 (1)	1 (1)	0.845
BMI	27 (7)	28 (9)	0.103
Gestational week at birth	37 (1)	38 (2)	<0.001*
Fetal birth weight	2,750(570)	3,025 (630)	0.016*
First-minute Apgar score	7(1)	7 (1)	0.132
Fifth-minute Apgar score	9(1)	9(0)	0.799
NICU requirement	24(36%)	12(11%)	0.009*

Note: Data given as median and interquartile range

Abbreviations: ICP, intrahepatic cholestasis of pregnancy; NICU, neonatal intensive care unit; BMI, body mass index.

White blood cell, neutrophil, lymphocyte, and basophil counts and the BMR did not statistically significantly differ between the two groups ($p > 0.05$).The ICP group had a significantly higher monocyte count ($p=0.002$), a significantly lower platelet count ($p=0.002$), and significantly lower values for monocyte-based complete blood cell indices compared to the control group ($p=0.005$, $p=0.001$, and $p=0.000$, respectively) (Table 2).

Table 2: Comparison of First-Trimester Maternal Blood Parameters and Indices Between the Study Groups

	ICP group (n =65)	**Control group (n =107)**	**p value**
WBC count	9.68 (3.98)	9.63 (2.56)	0.436
Neutrophil count	6.96 (3.74)	7.19 (2.83)	0.726
Lymphocyte count	1.83 (0.86)	1.87 (0.74)	0.903
Monocyte count	0.54 (0.26)	0.44 (0.23)	0.002*
Basophil count	0.020 (0.03)	0.020 (0.03)	0.509
Platelet count	233 (73)	262 (97)	0.002*
LMR	3.1818 (1.51)	4.2222 (2.15)	0.001*
NMR	12.9048 (5.07)	14.5686 (6.67)	0.005*
PMR	418.1818 (234.53)	571.4286 (334.39)	<0.001*
BMR	0.50 (0.60)	0.513 (0.05)	0.798

Note: Data given as median and interquartile range

Abbreviations: ICP, intrahepatic cholestasis of pregnancy; WBC,white blood cell; LMR, lymphocyte-to-monocyte ratio;PMR, platelet-to-monocyte ratio;NMR,neutrophil-to-monocyte ratio;BMR,basophil-to-monocyte ratio.

In the ICP group, the patients with a serum bile acid level of ≥40 mmol/L had a higher monocyte count and lower monocyte-based complete blood cell indices than those with a serum bile acid level of < 40 mmol/L, but the differences between these two groups were not statistically significant (p> 0.05) (Table 3).

Table 3: Relationship Between Serum Bile Acid Levels and First-Trimester Maternal Blood Parameters in the ICP Group

	Bile acid <40 mmol (n=52)	**Bile acid ≥40 mmol (n=13)**	**p value**
MONOCYTE	0.515 (0.3)	0.59 (0.23)	0.310
LMR	3.3537 (1.51)	2.9683 (1.45)	0.335
NMR	13.2562 (6.41)	12.1224 (3.99)	0.318
PMR	448.9044 (239.26)	367.1165 (276.18)	0.180

Note: Data given as median and interquartile range

Abbreviations: ICP, intrahepatic cholestasis of pregnancy; LMR, lymphocyte-to-monocyte ratio; PMR, platelet-to-monocyte ratio; NMR,neutrophil-to-monocyte ratio.

Table 4 and Figures 1 and 2 present the results of the ROC analysis performed to determine the optimal cut-off values of first-trimester monocyte count and monocyte-based complete blood cell indices for the prediction of ICP.

Table 4: Results of the ROC Curve Analysis on the Performance of the First-Trimester Monocytes Count and Monocyte-Based Inflammatory Indices in Predicting ICP.

	Cut-off value	**Sensitivity**	**Specificity**	***p* value**
Monocyte count (AUC: 0.640, 95% CI: .553-.728)	0.485	62%	62%	0.002*
LMR (AUC: 0.647, 95% CI: .563-.731)	3.7190	63%	64%	0.001*
PMR (AUC: 0.692, 95% CI: .612-.772)	481.2466	65%	66%	<0.001*
NMR(AUC: 0.629, 95% CI: .552-.716)	13.6098	63%	65%	0.005*

Abbreviations: ROC, receiver operating characteristic; ICP, intrahepatic cholestasis of pregnancy; LMR, lymphocyte-to-monocyte ratio;PMR, platelet-to-monocyte ratio;NMR,neutrophil-to-monocyte ratio;AUC, area under the curve; CI, confidence interval.

Figure 1: Receiver Operating Characteristic (ROC) Curve Showing the Performance of the First-Trimester Monocyte Count in Predicting Intrahepatic Cholestasis of Pregnancy.

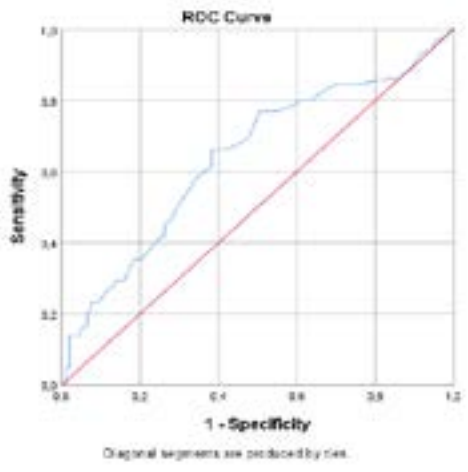
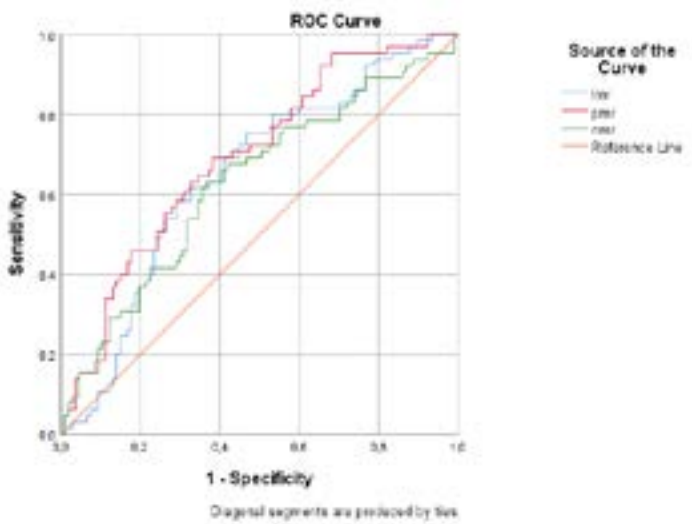


Figure 2: Receiver Operating Characteristic (ROC) Curve Showing the Performance of the First-Trimester Monocyte-Based Inflammatory Indices in Predicting Intrahepatic Cholestasis of Pregnancy.



DISCUSSION

In this study, we investigated the first-trimester maternal monocyte count and monocyte-based complete blood cell indices in patients with ICP and compared the results to a control group consisting of healthy pregnancies. When compared to the healthy control group, we found a significantly higher monocyte count and significantly lower values of monocyte-based complete blood cell indexes in patients with ICP, the most common liver disease that develops in pregnancy and has an inflammatory basis.

ICP complicates approximately 0.35–0.65% of pregnancies worldwide (12). Although the etiology of ICP has not yet been fully understood, it has been suggested that environmental effects, ethnic, genetic, and familial factors, geographic variations, activation of inflammatory cells, hormonal factors, and placental pathologies contribute to its pathogenesis (13, 14). Prediction and prevention of pregnancy-related complications are of great importance (15). It is known that there is an increased risk of preterm birth, an increased need for neonatal intensive care (NICU),and stillbirth in ICP, and these conditions increase as the maternal acid level increases (16).

In our study, the neonatal intensive care requirement was found to be statistically higher in the ICP group, as expected in newborns of pregnant women with cholestasis. However, no difference was found between the ICP and control groups in terms of Apgar scores. Numerous algorithms and guidelines have been proposed for the management of risk factors in ICP, and early diagnosis, treatment, and observation may help reduce fetal and maternal complication rates (17, 18).

According to previous studies, monocyte-based blood cell indices are relatively stable biomarkers of systemic inflammation (19). The traditional view on monocyte function is that monocytes are precursors to macrophages that extravasate into tissues and differentiate into professional antigen-presenting cells, where they are then able to resolve inflammation (20, 21).The depletion of monocytes at different stages of inflammation suggests that these cells play a critical role in mediating the resolution of the response (22, 23). Studies have shown that ICP is also an inflammatory process and that there is a relationship between inflammation markers and the severity of ICP. Recent studies indicate an association between complete blood cell indices and perinatal outcomes (24).

Increased bile acids are considered to cause fetal death by causing fetal arrhythmia and sudden vasospasm in placental chorionic vessels (25). A meta-analysis reported that as the serum bile acid level increased, the rate of adverse perinatal outcomes also increased (26). Other studies have shown that pregnancies presenting with a maternal serum bile acid concentration of 40 μmol/L or higher are more likely to be complicated by spontaneous preterm birth, meconium amniotic fluid, fetal asphyxia, and fetal death, and there is a relationship between the maternal high serum bile acid concentration and stillbirth (27-29). Similarly, in a systematic review, the fetal death rates were found to be 0.4, 0.3, and 6.8% in pregnancies in which the total maternal bile acid concentrations were <40 mmol/L, 40-99 mmol/L, and ≥100 mmol/L, respectively (30).

The degree of inflammation can be assessed using complete blood cell parameters and indices. In this study, we determined the cut-off values of monocyte-based complete blood cell indices and monocyte count in predicting patients with ICP. We also evaluated the relationship of the bile acid level with monocyte count and monocyte-based complete blood cell indexes in the ICP group. Although monocyte count was higher and monocyte-based complete blood cell indices were lower in the ICP subgroup with a serum bile acid level of ≥40 mmol/L, this did not reach a statistically significant level. In the ICP subgroup with a high bile acid level (≥40 mmol/L), lower monocyte-based blood cell indices and a higher monocyte count are expected in terms of the relationship between ICP and adverse perinatal outcomes, and these findings are consistent with the literature (31, 32).

In liver biopsies of women with ICP, pathological findings, such as biliary plugs containing hepatocytes and canaliculi without dilatation or injury, as well as centrilobular cholestasis, have been detected, suggesting that ICP is a reversible disease (6, 33). Dal-Secco et al. showed that during sterile injury to the liver, proinflammatory monocytes were transformed into reparative monocytes at the injury site (34). Other researchers have, proposed that the risk of liver, biliary tract, pancreatic diseases, and hepatobiliary cancer increases in women with a history of ICP (35). Circulating monocytes may promote tumor growth and help tumor cells escape immune surveillance (36). Derived from circulating monocytes, tumor-associated macrophages have been reported to be able to infiltrate into the hepatocellular carcinoma matrix and promote proliferation, metastasis, and angiogenesis (37-39). However, long-term cohort studies are needed to establish a relationship between the risk of hepatobiliary disease or malignancy with high monocyte levels and

low monocyte-based complete blood cell indices during pregnancy. The increased incidence of hepatobiliary malignancies in women with a history of ICP, the proliferation of monocytes in hepatic malignancies, and the support of angiogenesis suggest that there may be a relationship between ICP and monocytes.

The gold standard for the diagnosis of ICP is the fasting serum bile acid level. However, not all healthcare institutions perform this measurement, and there is a relatively long turn-around time for those that do. Therefore, alternative indexes, especially those that are easy to access and cost-effective and facilitate the timely evaluation of tests performed in almost every healthcare facility,may have significant clinical value for the evaluation of ICP.

To the best of our knowledge, this is the first study to investigate the role of the first-trimester monocyte count and monocyte-based inflammatory indices in ICP. We consider that our results will contribute to the literature. However, the relatively small number of patients, the single-center design, and the absence of long-term perinatal outcomes are the main limitations of this study. In this context, there is a need for randomized, controlled studies with a larger number of participants.

CONCLUSION

A high monocyte count and low monocyte-based inflammatory indices measured in the first trimester of pregnancy seem to be associated with ICP. These novel indices can be used in the prediction of ICP and its adverse perinatal outcomes.

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